# Stability and bifurcation for a haematopoietic stem cell transplantation model with HIV virus-to-cell infection

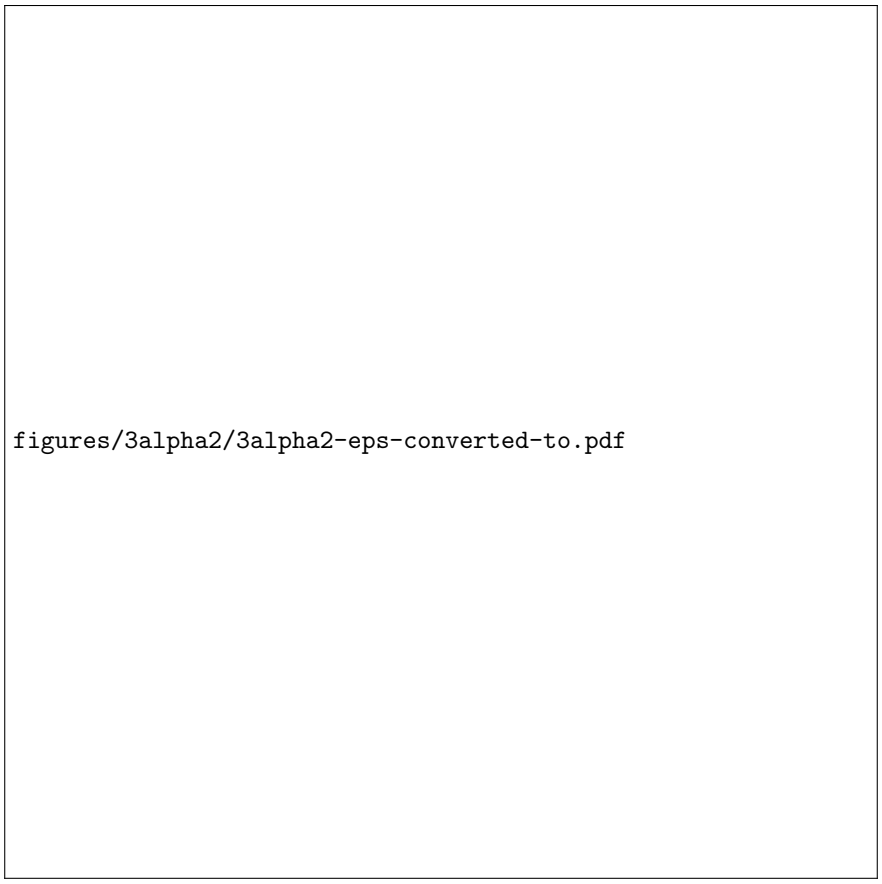
Wencong Wang[1], Long Zhang[1], Hong-Li Li[1], and Zhidong Teng[2]

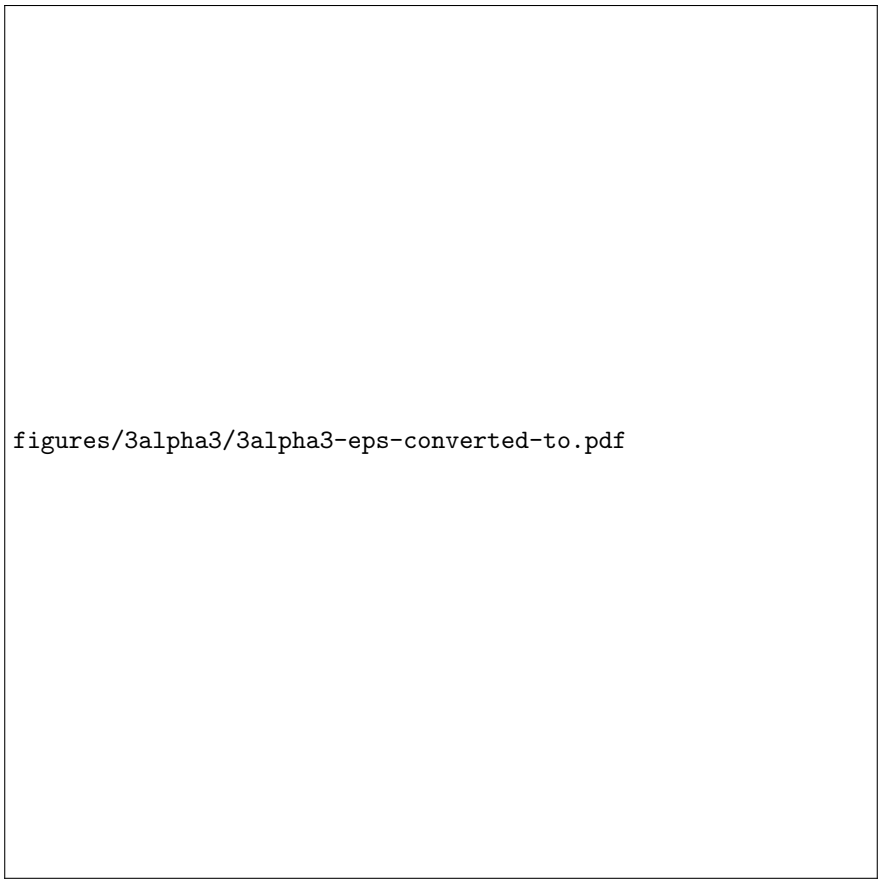
[1]Xinjiang University
[2]Xinjiang Medical University

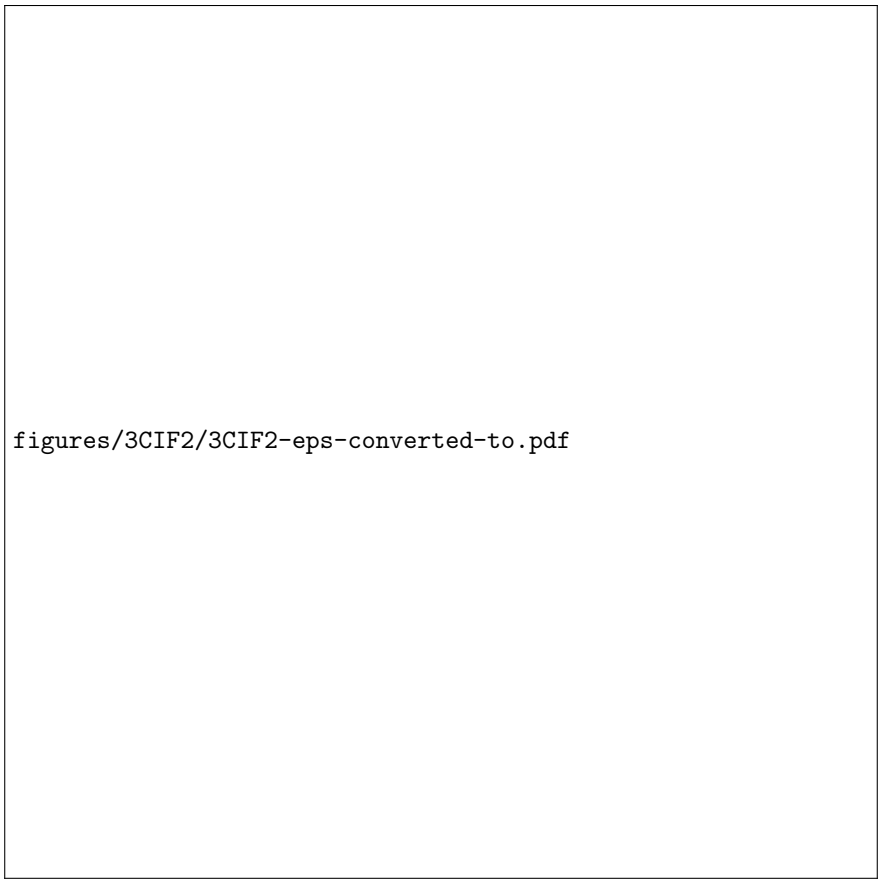
January 09, 2025

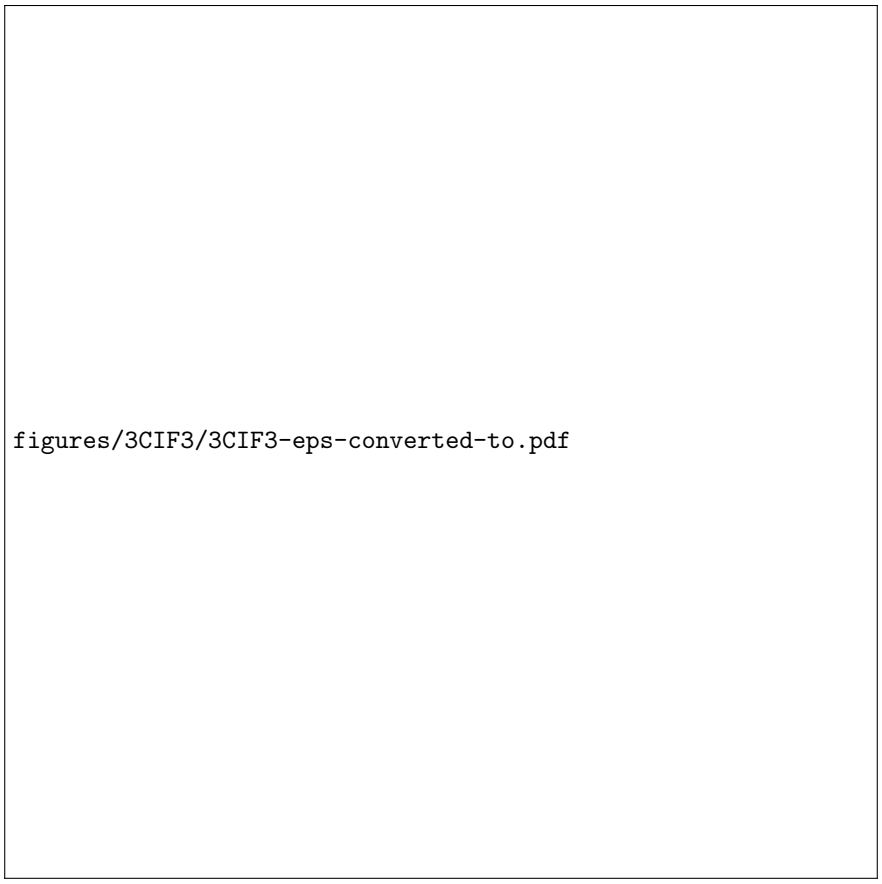
**Abstract**

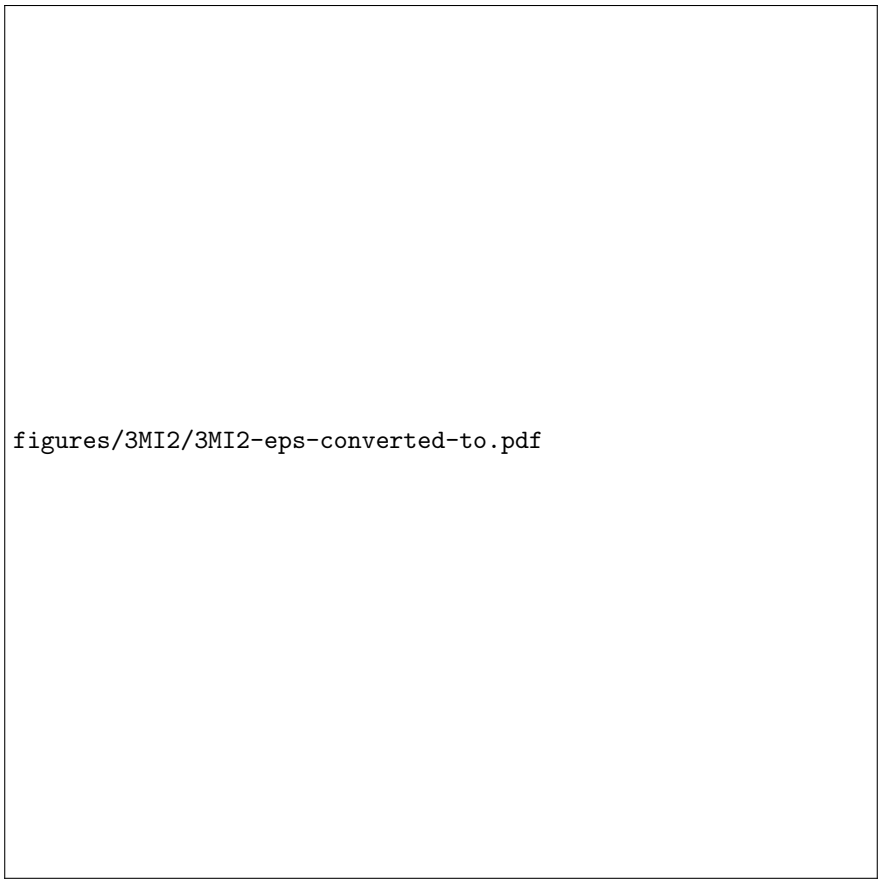
In this paper, a class of hematopoietic stem cell transplantation model with virus-to-cell HIV infection is proposed to characterize the competitive exclusion and coexistence between the host CD4+T cells and donor CD4+T cells. First, the positivity and boundedness of solutions as well as the basic reproduction number R are obtained. Second, criteria on the locally and globally asymptotical stability of all feasiable equilibria are established. Furthermore, bifurcation analysis is performed on the mixed chimerism infection equilibrium. Finally, the theoretical results are illustrated by numerical simulation, we find that chimerism is an important indicator of model stability, and AIDS may be cured when chimerism reaches a certain threshold.

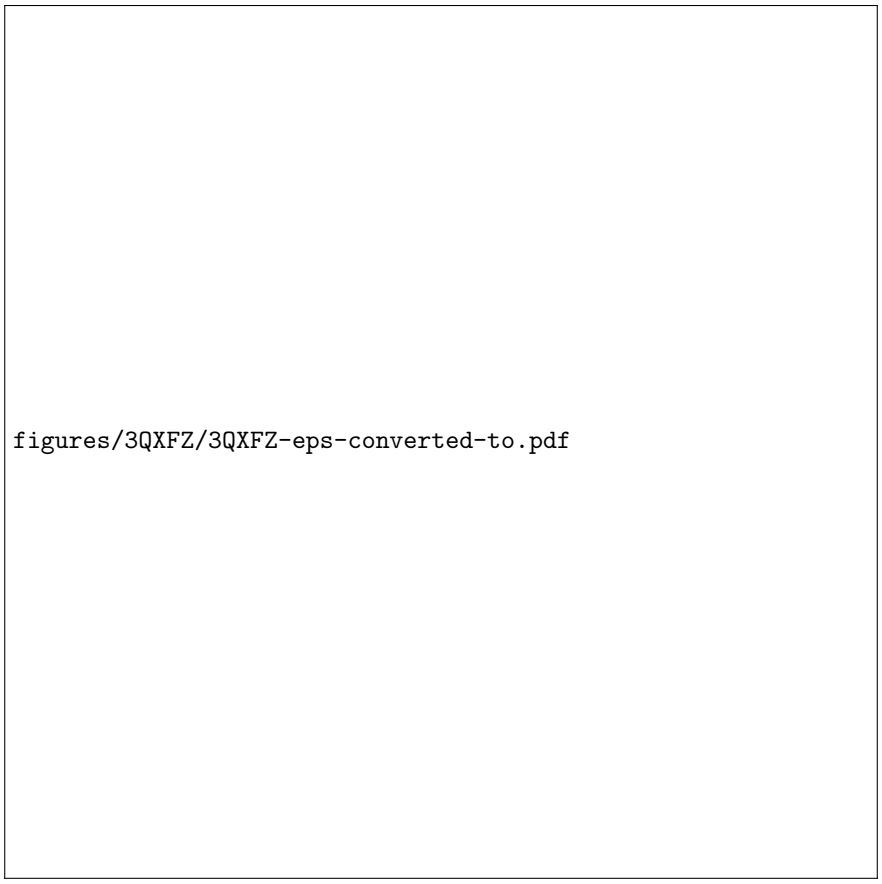


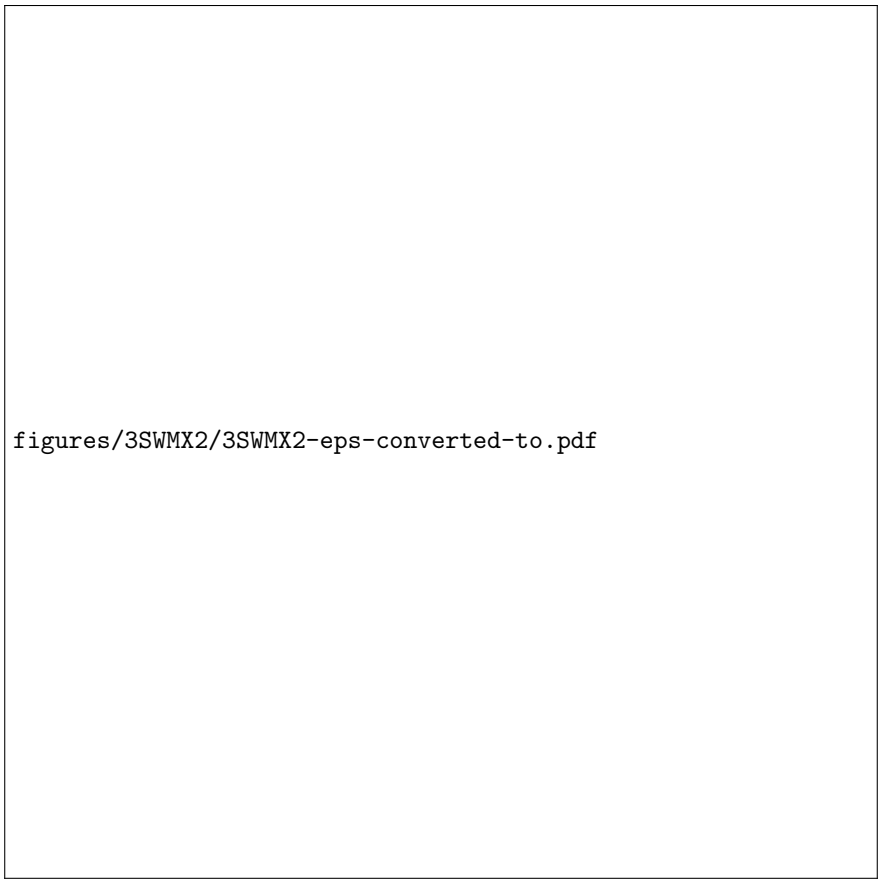


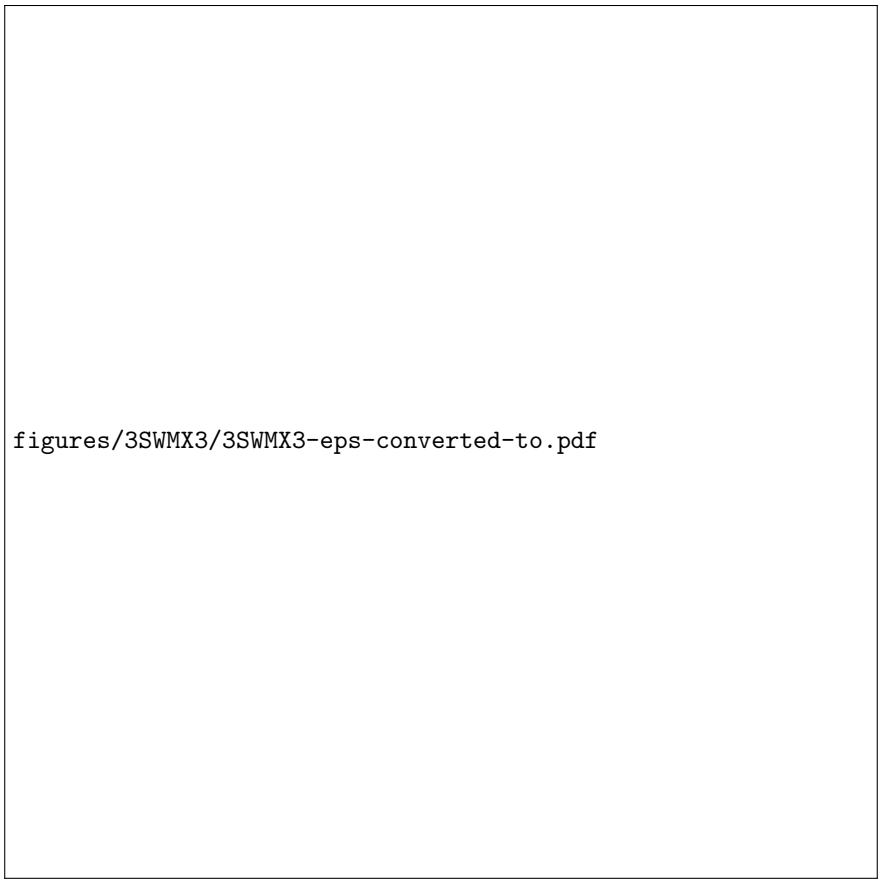


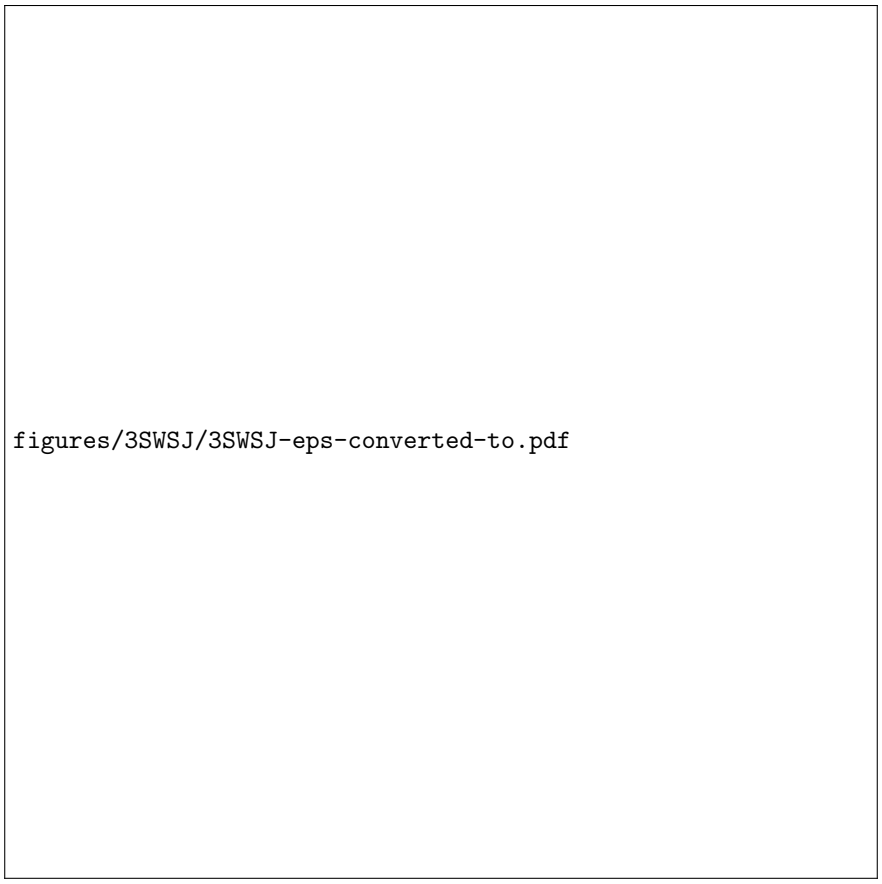


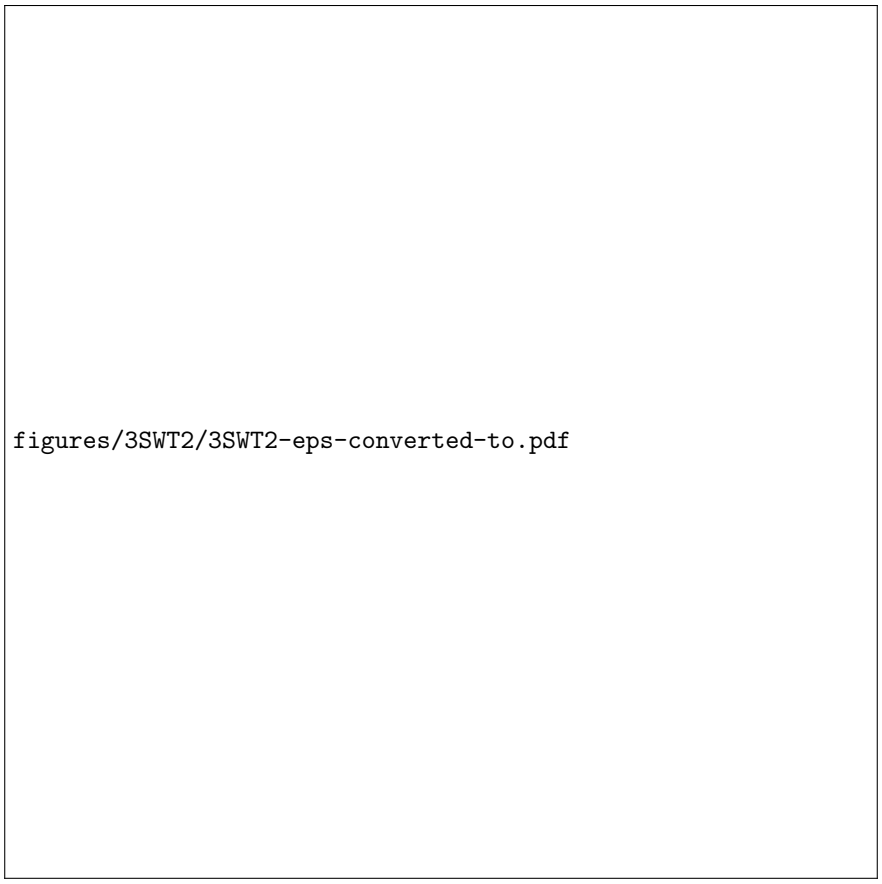


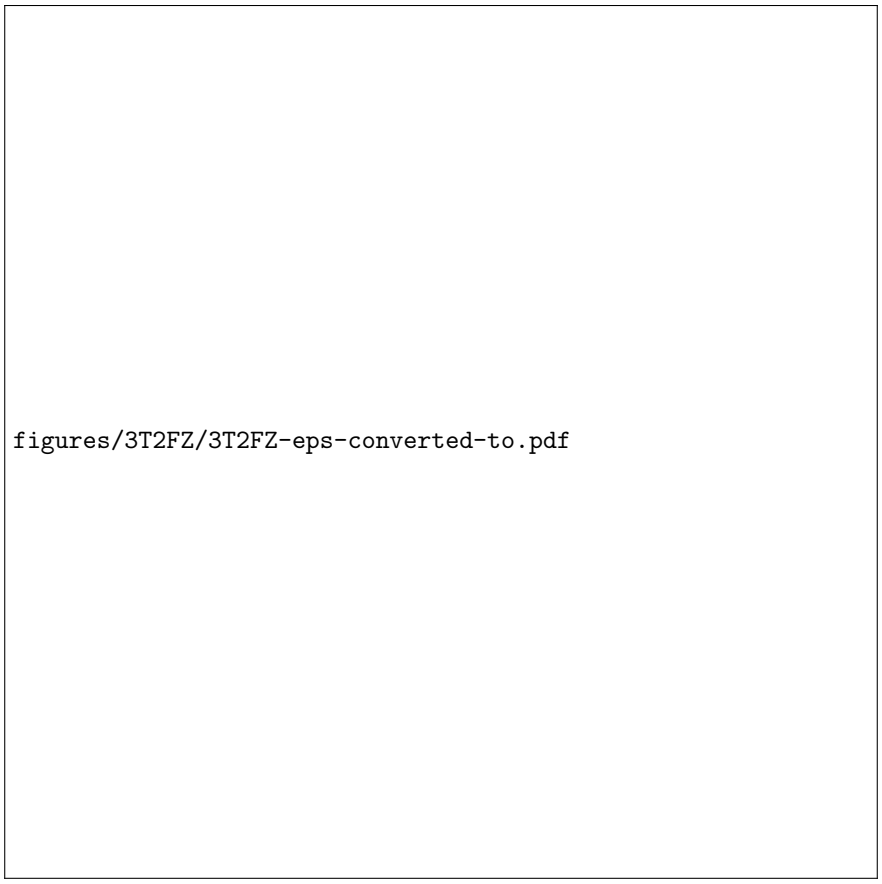


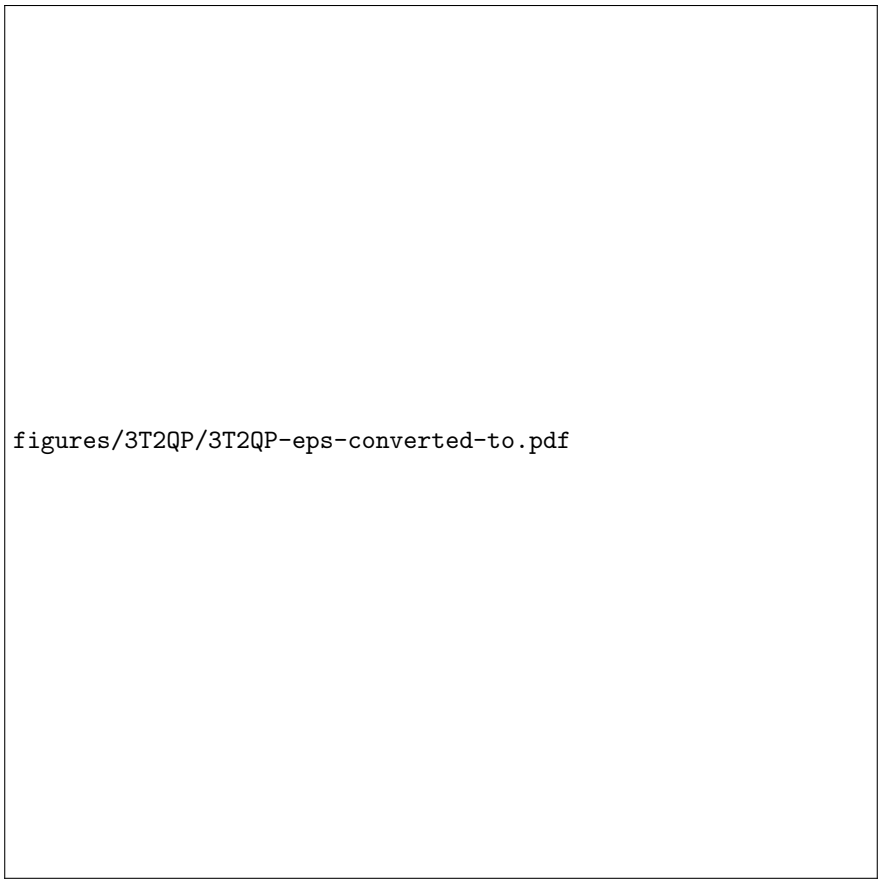


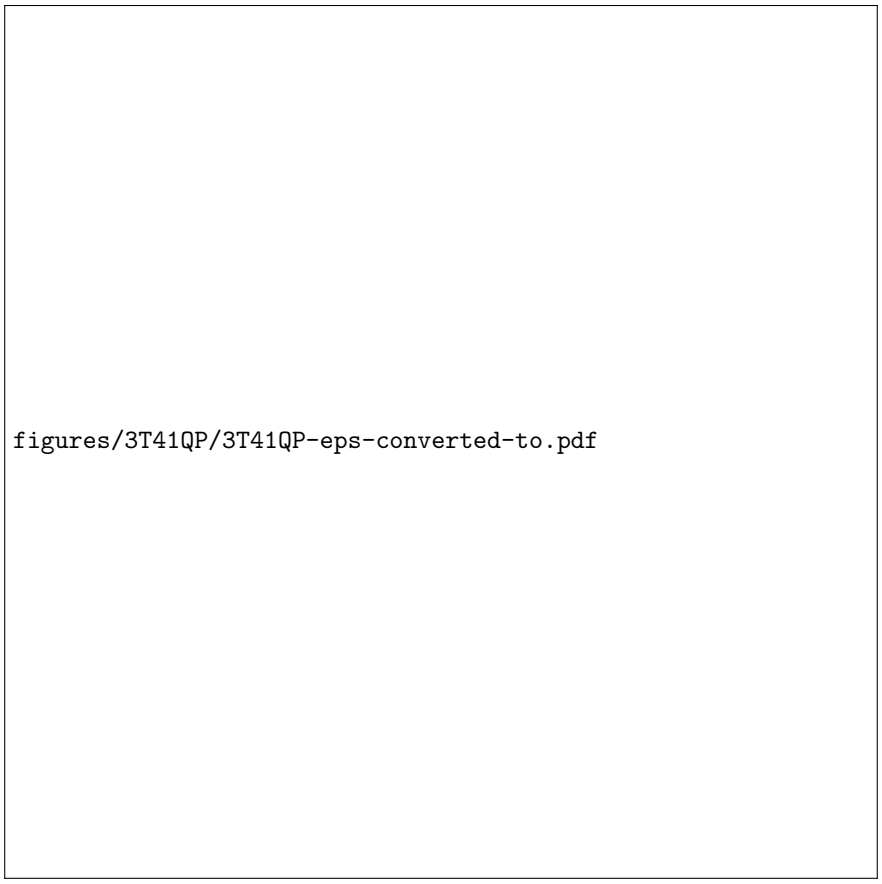


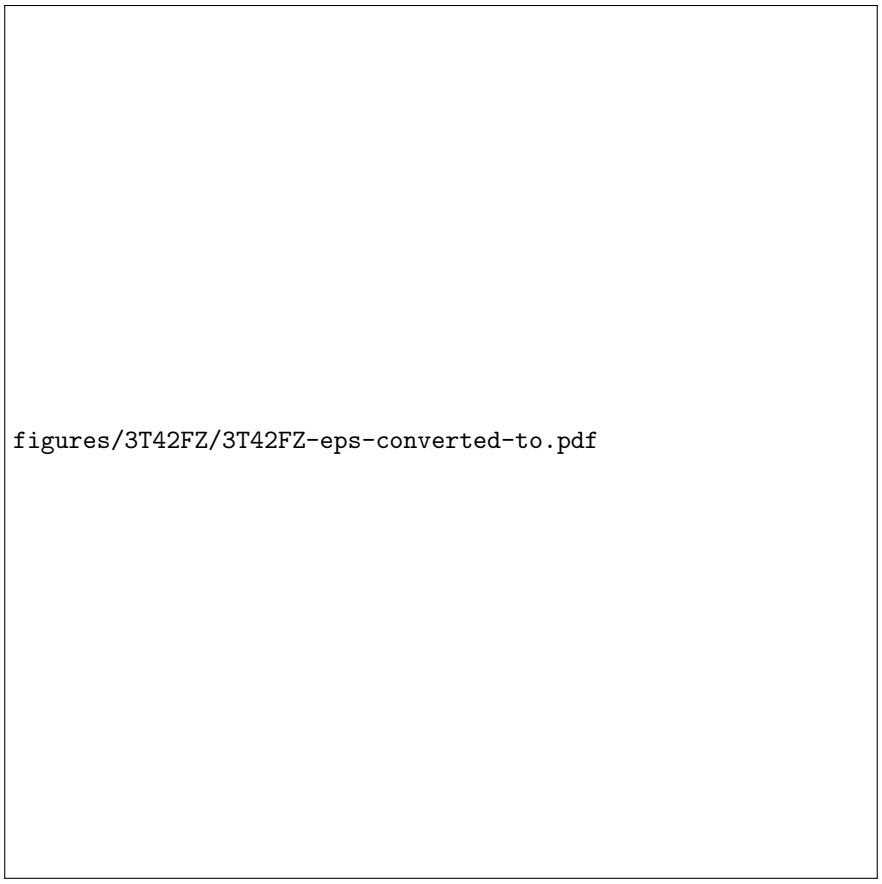


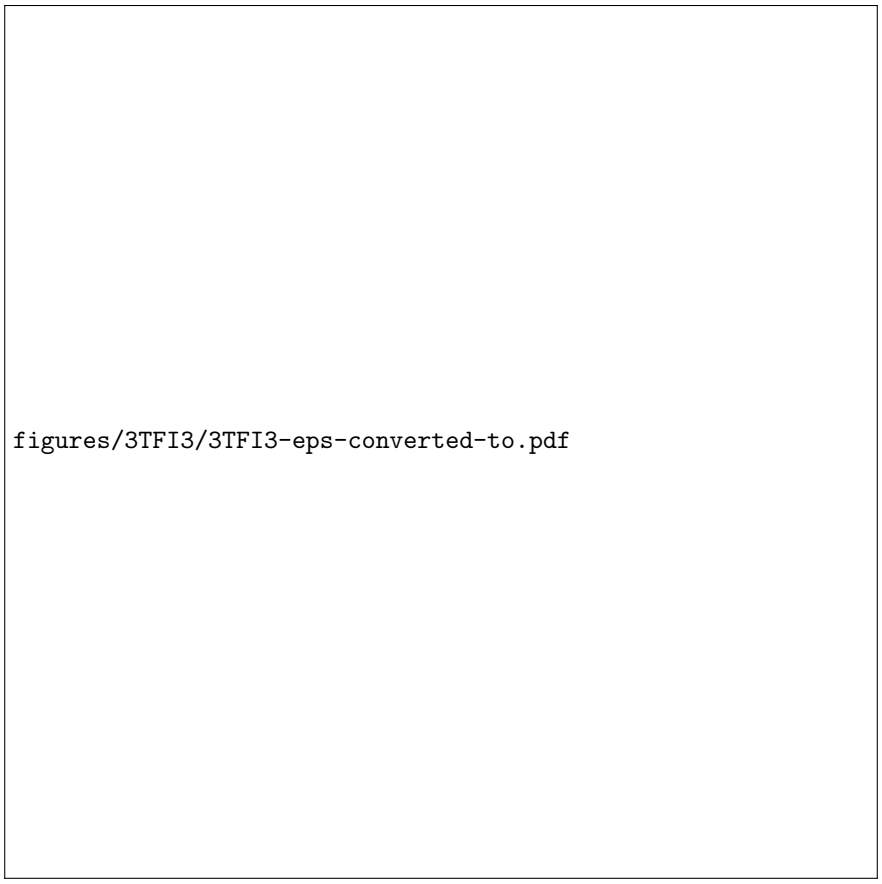


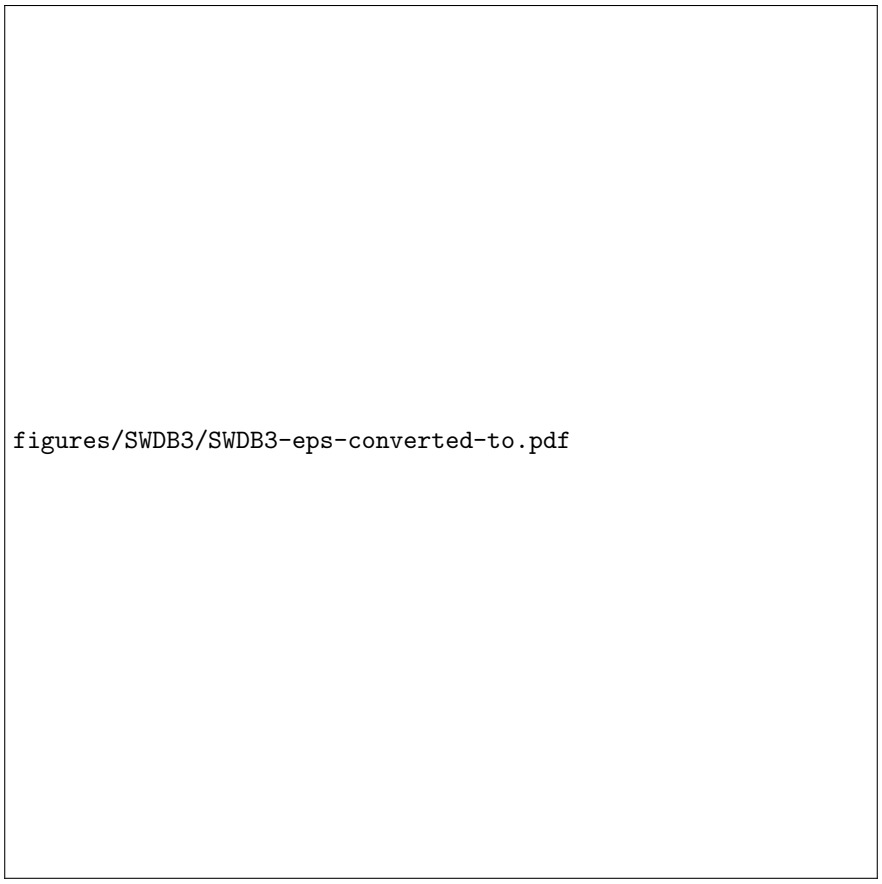












Received: Added at production | Revised: Added at production | Accepted: Added at production

DOI: xxx/xxxx

ARTICLE TYPE

# Stability and bifurcation for a haematopoietic stem cell transplantation model with HIV virus-to-cell infection

**Wencong Wang**[1] | **Long Zhang**[1,2] | **Hong-Li Li**[1,2] | **Zhidong Teng**[3]

[1]College of Mathematics and Systems Science, Xinjiang University, Urumqi, China

[2]The Key Laboratory of Applied Mathematics of Xinjiang Uygur Autonomous Region, Xinjiang University, Urumqi, China

[3]College of Medical Engineering and Technology, Xinjiang Medical University, Urumqi, China

**Correspondence**
Long Zhang,
Email: longzhang_xj@sohu.com

**Present address**
Xinjiang University, Urumqi, China.

## Abstract

In this paper, a class of hematopoietic stem cell transplantation model with virus-to-cell HIV infection is proposed to characterize the competitive exclusion and coexistence between the host CD4+T cells and donor CD4+T cells. First, the positivity and boundedness of solutions as well as the basic reproduction number $\mathcal{R}$ are obtained. Second, criteria on the locally and globally asymptotical stability of all feasiable equilibria are established. Furthermore, bifurcation analysis is performed on the mixed chimerism infection equilibrium. Finally, the theoretical results are illustrated by numerical simulation, we find that chimerism is an important indicator of model stability, and AIDS may be cured when chimerism reaches a certain threshold.

**KEYWORDS**

HIV infection, Stability, Competition exclusion, Haematopoietic stem cell transplantation, Hopf bifurcation

## 1 | INTRODUCTION

As we all knows, AIDS caused by the human immunodeficiency virus (HIV) infection is one of the most fatal infectious diseases in human history, which has infected more than 75 million people[1]. By the end of 2022, there were 760,000 new cases of HIV infection, with approximately 39 million people living with HIV, around 630,000 people dying from AIDS-related diseases[2]. HIV invades human body mainly by means of blood, sexual contact, and mother-to-child transmission (vertical transmission)[2], which primarily attacks the human immune system, including CD4+T lymphocytes, monocyte-macrophages, and dendritic cells. The main manifestation of HIV infection is a continuous decrease in the number of CD4+T lymphocytes, ultimately leads to cellular immune deficiency and various opportunistic infections and tumors[2].

Usually, the process of HIV infection in human cells includes adsorption, membrane fusion and entry; reverse transcription, nuclear entry and integration; transcription and translation; assembly, budding and maturation[3]. Currently, ART is the most common treatment method, which could prevent HIV from entering human cells, block HIV replication within cells, or inhibit the activity of enzymes required for integrating HIV gene material into human DNA. Among all HIV-infected individuals, 76% are receiving antiretroviral therapy[?], it could reduce plasma viral levels, prevents viral evolution, and slows disease progression. However, the effectiveness of ART would significantly decrease as HIV drug resistance becomes increasingly prevalent[4]. Additionally, due to the existence of persistent latent reservoirs of HIV-1, ART cannot completely eradicate HIV from the patient's body[5].

Chemokines are small cytokines or signaling proteins with the ability to induce directed chemotaxis in nearby cells. CCR5 is a chemokine receptor on the surface of CD4+T cells[6]. In 1996, multiple research indicated that CCR5 is the preferred chemokine receptor necessary for HIV to enter lymphocytes[7,8,9,10]. The CCR5$\Delta$32/$\Delta$32 homozygous mutation could efficiently prevent HIV from invading CD4+T cells[11,12], which greatly enhance the chance of full HIV cure.

In 2006, a hospital in Berlin, treated a patient named Timothy Brown (the Berlin Patient) who was suffering from both AML and AIDS. To treat the acute myeloid leukemia, the doctors chose a bone marrow transplant from a donor with the

**Abbreviations:** ART, antiretroviral therapy; AML, acute myeloid leukemia; HSCT, hematopoietic stem cell transplantation.

CCR5Δ32/Δ32 mutation. After transplantation, both AML and AIDS were cured, even several years after stopping ART, no HIV was detected in his body. In 2011, scientists re-examined Brown's blood and confirmed that his HIV viral load do not rebounded, officially named Timothy Brown as "the first person in the world to be completely cured of AIDS"[13]. In 2020, the second cured person of HIV, "the London Patient" emerged[14]. In February 2022, researchers from the United States reported the third "cured" AIDS patient, "the New York Patient"[15]. In July 2022, "the City of Hope Patient" was reported; in February 2023, "the Düsseldorf Patient" was reported[16]. These cured AIDS patients are similar to the Berlin Patient in that they all recovered after HSCT. Several studies indicated that allogeneic HSCT is currently the only medical means to completely cure AIDS[17,18,19,20].

Usually, HSCT is primarily used for blood system diseases, lymphomas, and many other conditions[21]. Chimerism status is an important indicator for assessing transplantation status, referring to the proportion of donor and host hematopoietic cells in the host's body. Complete chimerism indicates that donor cells make up more than 95% of the host's bone marrow or peripheral blood, while mixed chimerism indicates that donor cells make up between 5% and 95% of the host's bone marrow or peripheral blood[22]. Transplant failure is divided into primary transplant failure and secondary transplant failure. Primary transplant failure refers that achieve engraftment 28 days after peripheral blood stem cell or bone marrow stem cell transplantation or 42 days after umbilical cord blood stem cell transplantation; secondary transplant failure refers to the decline or loss of at least two blood cell lines after initially meeting the criteria for successful engraftment, or the loss of donor-host chimerism[23,24].

In 1997, Bonhoeffer et al.[25] proposed the following HIV virus-to-cell model.

$$\begin{cases} \dot{x} = \lambda - dx - \beta xv, \\ \dot{y} = \beta xv - ay, \\ \dot{v} = ky - uv, \end{cases} \tag{1}$$

where $x, y, v$ refer to the density of susceptible, infected CD4+T cells, and free virus, respectively. $\lambda$ is the rate of healthy cell production, $d$ is the natural death rate of healthy cells, the infected cells are produced from the uninfected cells and free virus at a rate of $\beta$, dying at a rate of $ny$, free virus are produced at a rate of $ky$, and die at a rate of $uv$.

Shinji et al.[26] initially established a mathematical model for HSCT treatment of leukemia, established the theoretical conditions for successful transplantation. Precup et al.[27] proposed the following allogeneic bone marrow transplantation model to discuss cell evolution after stem cell transplantation.

$$\begin{cases} \dot{x} = \dfrac{a}{1 + b(x + y + z)} \dfrac{x + y + \varepsilon}{x + y + \varepsilon + gz} x - cx, \\ \dot{y} = \dfrac{A}{1 + B(x + y + z)} \dfrac{x + y + \varepsilon}{x + y + \varepsilon + Gz} y - Cy, \\ \dot{z} = \dfrac{a}{1 + b(x + y + z)} \dfrac{z + \varepsilon}{z + \varepsilon + h(x + y)} z - cz, \end{cases} \tag{2}$$

where $x, y, z$ represent the normal cells, leukemia cells and donor cells. They found that the model has two asymptotically stable equilibria. Meanwhile, when the initial concentration of host cells is known, a successful measure of the cells needed for transplantation could be calculated.

In recent years, HSCT treatment for AIDS has gained great attention, and many related models have been proposed[28,29,30]. Alison et al.[28] proposed a stochastic model to study the impact of chimerism on AIDS treatment. They concluded that the probability of lifelong remission(cure) is 98% at 80% chimerism, while the probability of lifelong remission is greater than 99% at 90% chimerism. Kallel et al.[29] proposed a type of model to study the effects of stem cell transplantation on AIDS patients. Manar et al.[30] proposed the following mathematical model for HSCT treatment of AIDS:

$$\begin{cases} \dot{S} = (k(\alpha_S - \alpha_D) - \delta_s) S, \\ \dot{T} = \lambda_T - d_T T + (2\alpha_D + \alpha_A) kAS - k_T TV, \\ \dot{T}_i = k_T TV - \rho_{Ti} T_i, \\ \dot{V} = \pi_{T_i} T_i - c_v V, \end{cases} \tag{3}$$

where $S, T, T_i$ and $V$ represent the concentrations of hematopoietic stem cells, uninfected CD4+T cells, infected CD4+T cells, and free virus, respectively. $k$ is the stem cell division rate, $\alpha_s, \alpha_A, \alpha_D$ are the probabilities of a stem cell dividing into two undifferentiated cells, one undifferentiated cell and one differentiated cell, two differentiated cells, respectively. $\delta_s, d_T, \rho_{Ti}, c_v$ are the death rates of stem cells, uninfected CD4+T cells, infected CD4+T cells, and free virus, respectively. $\lambda_T$ is the production

rate of uninfected CD4+T cells, $k$ is the stem cell division rate, $A$ is the amplification factor, $k_T$ is the infection rate of CD4+T cells, and $\pi_{Ti}$ is the virus production rate. They found that stem cells offer hope for a cure for HIV-1 infection by increasing the number of CD4+T cells in the blood immune system of HIV-1 patients

The model (3) characterized the process of hematopoietic stem cell differentiation but did not reflect the replacement process between host and donor hematopoietic stem cells. According to [13,14,15,16,17,18,19,20], the reason why AIDS can be cured through HSCT is that the selected donor hematopoietic stem cells are all pure for the CCR5$\Delta$32/$\Delta$32 mutation and could fully replacement the CD4+T cells of host. Therefore, taking donor and host CD4+T cells as two separate compartments is more consistent with the actual background. Additionally, hosts are prone to immune exclusion led by CD4+T cells after HSCT as well as competitive exclusion between the two types of CD4+T cells in host and donor after HSCT [31].

Based on above consideration, we propose the following haematopoietic stem cell transplantation model with HIV virus-to-cell infection

$$\begin{cases} \dot{T_{41}} = \dfrac{\alpha_1 T_{41}}{\alpha_1 T_{41} + \alpha_2 T_2}\Lambda - \mu_{41} T_{41} - \beta V T_{41} - k_1 T_{41} T_2, \\ \dot{T_{42}} = \beta V T_{41} - \mu_{42} T_{42}, \\ \dot{V} = N\mu_{42} T_{42} - \mu_V V, \\ \dot{T_2} = \dfrac{\alpha_2 T_2}{\alpha_1 T_{41} + \alpha_2 T_2}\Lambda - \mu_2 T_2 - k_2 T_{41} T_2, \end{cases} \tag{4}$$

where $T_{41}, T_{42}, V, T_2$ represent the number of uninfected CD4+T cells of the host, infected CD4+T cells of the host, free virus particles, and CD4+T cells from the donor in the host's body after HSCT at time $t$, respectively. In addition, $k_1, k_2$ represents the competitive exclusion rates between $T_{41}$ and $T_2$. $\frac{\alpha_1 T_{41}}{\alpha_1 T_{41}+\alpha_2 T_2}\Lambda$ , $\frac{\alpha_2 T_2}{\alpha_1 T_{41}+\alpha_2 T_2}\Lambda$ reflect the recruitment rates that two types of CD4+T cells competing in body, where $\alpha_1$ represents the ratio of hematopoietic stem cell chimerism and $\alpha_2$ represents the ratio of donor CD4+ T cells, satisfying $\alpha_1 + \alpha_2 = 1$. The specific parameters are shown in the following table and are all positive constants.

**TABLE 1** Biological significance of variables and parameters.

| parameters | Description | parameters | Description |
|---|---|---|---|
| $k_1(k_2)$ | Donor (Receptor )CD4+T cell immune exclusion rate | $\mu_V$ | Death rate of free viruses |
| $\mu_{41}$ | Death rate of receptor healthy CD4+T cells | $\mu_{42}$ | Death rate of receptor infected CD4+T cells |
| $\alpha_1(\alpha_2)$ | The proportion of CD4+T cells in the receptor (donor) | $\mu_2$ | Death rate of donor healthy CD4+T cells |
| $\beta$ | Infection rate of receptor healthy CD4+T cells | $\Lambda$ | Recruitment rate |
| $N$ | Number of new viruses produced per infected cell | | |

The rest of the paper is organized as follows: In Section 2, the basic properties of model (4), i.e., positivity and ultimate boundedness are obtained. In Section 3, the existence and stability of all feasible equilibria of model (4) are established. In Section 4, criteria on the bifurcation of model (4) are established. In Section 5, the main theoretical results are illustrated by numerical simulations. Finally, a brief conclusion is given in section 6.

## 2 | BASIC PROPERTIES

Denote $R^4_+ = \{(x_1, x_2, \cdots, x_4) \in R^4 : x_i \geq 0, i = 1, 2, \cdots, 4\}$. The initial condition for any solution of model (4) is as follows

$$(T_{41}(0), T_{42}(0), V(0), T_2(0)) = (T_{410}, T_{420}, V_0, T_{20}) \in R^4_+. \tag{5}$$

For the positivity and boundedness of solutions of model (4), we have the following result.

**Theorem 1.** *The solution* $(T_{41}(t), T_{42}(t), V(t), T_2(t))$ *of model* (4) *with initial condition* (5) *is nonnegative and ultimately bounded for any* $t \in [\,0, +\infty)$.

*Proof.* By the existence uniqueness theorem for solutions of ordinary differential equations [32], the solution $(T_{41}(t), T_{42}(t), V(t), T_2(t))$ of model (4) under initial condition (5) exists on $[0, T)$, where $T \leq \infty$ is the maximum interval of existence of saturated solutions.

First, we prove the nonnegativity of the solutions of model (4). From the first equation of model (4) we have

$$\begin{aligned}\frac{dT_{41}}{dt} &= \frac{\alpha_1 T_{41}}{\alpha_1 T_{41} + \alpha_2 T_2}\Lambda - \mu_{41} T_{41} - \beta V T_{41} - k_1 T_{41} T_2 \\ &= -\left(\mu 41 + \beta + k_1 T_2 - \frac{\alpha_1}{\alpha_1 T_{41} + \alpha_2 T_2}\Lambda\right) T_{41}.\end{aligned}$$

Therefore

$$T_{41} = T_{410} e^{\int_{t_0}^{t} (\mu 41 + \beta + k_1 T_2 - \frac{\alpha_1}{\alpha_1 T_{41} + \alpha_2 T_2}\Lambda) T_{41}(s) ds} \geq 0.$$

Thus for $T_{41}(0) > 0$, $T_{41}(t)$ is always nonnegative at $t \in [0, T)$. Similarly we get the non-negativity of $T_2(t)$.

To obtain the nonnegativity of $(T_{42}(t), V(t))$, we denote $m(t) = \min\{T_{42}(t), V(t)\}$, thus $m(0) > 0$. Assume that there exists a $t_1 > 0$ such that $m(t_1) = 0$, and $m(t) > 0$ for all $t \in [0, t_1)$.

If $m(t_1) = T_{42}(t_1) = 0$, we have $\frac{dT_{42}}{dt}\Big|_{t=t_1} \leq 0$. From the second equation of model (4)

$$\frac{dT_{42}}{dt}\Big|_{t=t_1} = \beta V T_{41} > 0,$$

which leads to a contraction. Thus for $T_{42}(0) \geq 0$, $T_{42}(t)$ is always nonnegative in $t \in [0, T)$. Similarly we can obtain the nonnegativity of $V(t)$.

Next, we prove the boundedness of solution for model (4). Let $P = T_{41} + T_{42} + V + T_2$, from model (4) we have

$$\begin{aligned}\dot{P} &= \Lambda - \mu_{41} T_{41} - \mu_{42} T_{42} - \mu_V V - \mu_2 T_2 - N\mu_{42} T_{42} - k_1 T_{41} T_2 - k_2 T_{41} T_2 \\ &\leq \Lambda - \mu_{41} T_{41} - \mu_{42} T_{42} - \mu_V V - \mu_2 T_2 \\ &\leq \Lambda - \mu P,\end{aligned}$$

where $\mu = min\{\mu_{41}, \mu_{42}, \mu_V, \mu_2\}$. Applying the principle of comparison one has $\limsup_{t\to\infty} P(t) \leq \frac{\Lambda}{\mu}$, therefore, we can set that $T_{41}, T_{42}, V, T_2$ is bounded on $E \in [0, t)$. Thus by the extension theorem of the solution[32] we know that $T = \infty$.

Furthermore we set $\Gamma = \left\{(T_{41}, T_{42}, V, T_2) \in R_+^4 : T(t) \leq \frac{\Lambda}{\mu}\right\}$ be the positive invariant set of the system (4). □

Let $T_{42} = V = T_2 = 0$, then system (4) has transplant failure infection-free equilibrium $E^1 = (T_{41}^1, T_{42}^1, V^1, T_2^1) = (\frac{\Lambda}{\mu_{41}}, 0, 0, 0)$. From the next generation matrix[33]

$$\mathcal{F} = \begin{pmatrix} \beta V T_{41} \\ 0 \end{pmatrix}, \mathcal{V} = \begin{pmatrix} \mu_{42} T_{42} \\ \mu_V V - N\mu_{42} T_{42} \end{pmatrix}.$$

$$F = \begin{pmatrix} 0 & \beta T_{41}^0 \\ 0 & 0 \end{pmatrix}, V = \begin{pmatrix} 0 & \mu_{42} \\ -N\mu_{42} & \mu_V \end{pmatrix}.$$

Then the basic reproduction number of model (1) $\mathcal{R} = \rho\left(FV^{-1}\right) = \frac{\Lambda\beta N}{\mu_V \mu_{41}}$.

Before going into details of discussion, we summarize the conclusions obtained for HIV virus-to-cell infection. It has been proven that the dynamics of model (1) is fully dependent on the basic reproduction number $\mathcal{R}$[25], i.e., if $\mathcal{R} < 1$, the disease-free equilibrium $E_0$ of model (1) is globally asymptotically stable. While if $\mathcal{R} > 1$, the endemic equilibrium $E_*$ of model (1) is globally asymptotically stable.

*Remark 1.* The classical HIV virus-to-cell infection model (1) discusses the interaction between $\mathcal{R} \geq (<)1$ and the transmission dynamics of HIV. In reality, if HIV is extinct, i.e., $\mathcal{R} < 1$, which would be meaningless to consider HSCT. Therefore, it is only when the disease could persist, i.e., $\mathcal{R} \geq 1$, then HSCT would be constructive. Therefore, in the following discussion, we will only consider the case that the virus cannot be extinguished in vivo without HSCT, i.e., $\mathcal{R} \geq 1$.

## 3 | STABILITY ANALYSIS

In this section, we analyse the stability of all feasible equilibria of model (4).

## 3.1 | Transplant failure infection-free Equilibrium

After HSCT, with the development of HIV and transplantion of haematopoietic stem cells in body, the infected cells and viruses may be depleted, and the host CD4+T cells may exclude donor CD4+T cells, i.e., transplant failure infection-free $E^1 = (\frac{\Lambda}{\mu_{41}}, 0, 0, 0)$ of (4) would occur.

**Theorem 2.** *If $\mathcal{R} > 1$, the transplant failure infection-free equilibrium $E^1 = (\frac{\Lambda}{\mu_{41}}, 0, 0, 0)$ of (4) is unstable.*

*Proof.* The characteristic equation at $E^1$ of model (4) is as follows

$$\begin{aligned}
\left|\lambda E - J\left(E^1\right)\right| &= \begin{vmatrix} \lambda+\mu_{41} & 0 & \frac{\beta\Lambda}{\mu_{41}} & \frac{\alpha_2\mu_{41}}{\alpha_1}+\frac{k_1\Lambda}{\mu_{41}} \\ 0 & \lambda+\mu_{41} & -\frac{\beta\Lambda}{\mu_{41}} & 0 \\ 0 & -N\mu_{42} & \lambda+\mu_V & 0 \\ 0 & 0 & 0 & \lambda-\frac{\alpha_2\mu_{41}}{\alpha_1}+\mu_2+\frac{k_2\Lambda}{\mu_{41}} \end{vmatrix} \\
&= (\lambda+\mu_{41}) \begin{vmatrix} \lambda+\mu_{42} & -\frac{\beta\Lambda}{\mu_{41}} & 0 \\ -N\mu_{42} & \lambda+\mu_V & 0 \\ 0 & 0 & \lambda-\frac{\alpha_2\mu_{41}}{\alpha_1}+\mu_2+\frac{k_2\Lambda}{\mu_{41}} \end{vmatrix} \\
&= (\lambda+\mu_{41}) \left[ \left( \lambda - \frac{\alpha_2\mu_{41}}{\alpha_1} + \mu_2 + \frac{k_2\Lambda}{\mu_{41}} \right) \left( (\lambda+\mu_{42})(\lambda+\mu_2) - \frac{\beta\Lambda N\mu_{42}}{\mu_{41}} \right) \right].
\end{aligned}$$

Then the eigenvalues of $\left|\lambda E - J\left(E^1\right)\right|$ are

$$\lambda_1 = -\mu_{41} < 0,\ \lambda_2 = \frac{\alpha_2\mu_{41}}{\alpha_1} - \mu_2 - \frac{k_2\Lambda}{\mu_{41}}.$$

Where $\lambda_3, \lambda_4$ are the roots of the quadratic equation $\lambda^2 + (\mu_{42}+\mu_V)\lambda - \frac{\beta\Lambda N\mu_{42}}{\mu_{41}}$. We have

$$\begin{aligned}
\triangle_1 &= \mu_{42} + \mu_V > 0, \\
\triangle_2 &= \begin{vmatrix} \mu_{42}+\mu_V & 0 \\ 1 & -\frac{\beta\Lambda N\mu_{42}}{\mu_{41}} \end{vmatrix} = (\mu_{42}+\mu_V)\left(-\frac{\beta\Lambda N\mu_{42}}{\mu_{41}}\right) < 0.
\end{aligned}$$

According to the Hurwitz criterion[34], if $\mathcal{R} > 1$, the transplant failure infection-free equilibrium $E^1$ of model (4) is unstable. This completes the proof. □

*Remark 2.* Theorem 2 means that if HSCT successfully make the virus and infected cells remove and the donor CD4+T cells are excluded by the host CD4+T cells, then the HIV infection will not disappear. So it is impossible to remove viruses and infected cells as well as donor CD4+T cells by HSCT except the host CD4+T cell if $\mathcal{R} > 1$, which is consistent with the real circumstance.

## 3.2 | Complete donor chimerism infection-free equilibrium

After HSCT, there may be a complete replacement of host CD4+T cells by donor CD4+T cells, i.e. the complete donor chimerism infection-free equilibrium $E^2 = (0, 0, 0, \frac{\Lambda}{\mu_2})$ of (4) would occur.

We further introduce the following assumption.

$(H_1)$ $\mu_{41} + \dfrac{k_1\Lambda}{\mu_2} > \dfrac{\alpha_1\mu_2}{\alpha_2}$.

**Theorem 3.** *If $(H_1)$ holds, the complete donor chimerism infection-free equilibrium $E^2 = (0, 0, 0, \frac{\Lambda}{\mu_2})$ of model (4) is locally asymptotically stable.*

*Proof.* The characteristic equation at $E^2$ of model (4) is as follows

$$\begin{aligned}\left|\lambda E - J\left(E^2\right)\right| &= \begin{vmatrix} \lambda - \frac{\alpha_1\mu_2}{\alpha_2} + \mu_{41} + \frac{k_1\Lambda}{\mu_2} & 0 & 0 & 0 \\ 0 & \lambda + \mu_{42} & 0 & 0 \\ 0 & -N\mu_{42} & \lambda + \mu_V & 0 \\ \frac{\alpha_1\mu_2}{\alpha_2} + \frac{k_2\Lambda}{\mu_2} & 0 & 0 & \lambda + \mu_2 \end{vmatrix} \\ &= (\lambda + \mu_2) \begin{vmatrix} \lambda - \frac{\alpha_1\mu_2}{\alpha_2} + \mu_{41} + \frac{k_1\Lambda}{\mu_2} & 0 & 0 \\ 0 & \lambda + \mu_{42} & 0 \\ 0 & -N\mu_{42} & \lambda + \mu_V \end{vmatrix} \\ &= (\lambda + \mu_2)\left[\left(\lambda - \frac{\alpha_1\mu_2}{\alpha_2} + \mu_{41} + \frac{k_1\Lambda}{\mu_2}\right)(\lambda + \mu_{42})(\lambda + \mu_V)\right].\end{aligned}$$

Then the eigenvalues of $\left|\lambda E - J\left(E^2\right)\right|$ are

$$\lambda_1 = -\mu_2 < 0,\ \lambda_2 = -\mu_{42} < 0,\ \lambda_3 = -\mu_V < 0,\ \lambda_4 = \frac{\alpha_1\mu_2}{\alpha_2} - \mu_{41} - \frac{k_1\Lambda}{\mu_2}.$$

If $(H_1)$ holds, then $\lambda_4 < 0$. Thus the equilibrium $E^2$ of model (4) is locally asymptotically stable. This completes the proof. □

*Remark 3.* After a successful HSCT, there would be no more host CD4+T cells except the donor CD4+T cells in the body, since HIV cannot attack donor CD4+T cells, which means the HIV would disappear. Therefore, the stability of $E^2$ is no longer related to the basic reproduction number $\mathcal{R}$ if a successful HSCT occurs.

**Lemma 1** (Castillo-Chavez et al.[35])**.** *Consider the following differential equations of epidemic model*

$$\frac{dX}{dt} = F(X, Y),$$

$$\frac{dY}{dt} = G(X, Y), G(X, 0) = 0,$$

*where $X \in R^n$ denotes the uninfected individuals, $Y \in R^n$ denotes the infected individuals, and $U_0 = (X_0, 0)$ is the disease-free equilibrium(DFE) of the system.*

*We also assume that the following conditions hold.*

$(H_2)$ *For $\frac{dX}{dt} = F(X, 0)$, $X_0$ is globally asymptotically stable,*

$(H_3)$ $G(X, Y) = AY - \hat{G}(X, Y), \hat{G}(X, Y) \geq 0$ *for* $(X, Y) \in \Omega$,

*where $A = D_Z G(X_0, 0)$ is an M–matrix (non-diagonal elements of A are nonnegative), $\Omega$ is a biologically significant region of the system.*

*Then the DFE $U_0 = (X_0, 0)$ is globally asymptotically stable.*

For the globally asymptotical stability of $E^2$ of model (4), we have the following result.

**Theorem 4.** *If $(H_1)$ holds, the complete donor chimerism infection-free equilibrium $E^2$ of model* (4) *is globally asymptotically stable.*

*Proof.* According to the Lemma 1, we rewrite the model (4) into the following form

$$\begin{aligned}\frac{dX}{dt} &= F(X, Y), \\ \frac{dY}{dt} &= G(X, Y), G(X, 0) = 0,\end{aligned} \tag{6}$$

where $X = (T_{41}, T_2)$, $Y = (V, T_{42})$, and $U_0 = (X_0, 0)$ is the complete donor chimerism infection-free equilibrium of system (6).

In the following discussion, we verify that the system (6) satisfies the assumptions $(H_2), (H_3)$. According to model (4), we have

$$\frac{dX}{dt} = \begin{pmatrix} \frac{\alpha_1 T_{41}}{\alpha_1 T_{41} + \alpha_2 T_2}\Lambda - \mu_{41} T_{41} - \beta V T_{41} - k_1 T_{41} T_2 \\ \frac{\alpha_2 T_2}{\alpha_1 T_{41} + \alpha_2 T_2}\Lambda - \mu_2 T_2 - k_2 T_{41} T_2 \end{pmatrix}, F(X,0) = \begin{pmatrix} \Lambda - \mu_{41} T_{41} \\ 0 \end{pmatrix}.$$

$$A = \begin{pmatrix} -\mu_{42} & \beta V T_{41}^0 \\ N\mu_{42} & -\mu_V \end{pmatrix} = \begin{pmatrix} -\mu_{42} & \frac{\beta V \Lambda}{\mu_{41}} \\ N\mu_{42} & -\mu_V \end{pmatrix}.$$

$$\begin{aligned} \hat{G}(X,Z) &= AZ - G(X,Z) \\ &= \begin{pmatrix} -\mu_{42} & \beta T_{41}^0 \\ N\mu_{42} & -\mu_V \end{pmatrix} \begin{pmatrix} T_{42} \\ V \end{pmatrix} - \begin{pmatrix} \beta V T_{41} - \mu_{42} T_{42} \\ \mu_{42} T_{42} - \mu_V V \end{pmatrix} \\ &= \begin{pmatrix} -\mu_{42} T_{42} + \beta T_{41}^0 V \\ N\mu_{42} T_{42} - \mu_V V \end{pmatrix} - \begin{pmatrix} \beta V T_{41} - \mu_{42} T_{42} \\ N\mu_{42} T_{42} - \mu_V V \end{pmatrix} \\ &= \begin{pmatrix} \beta V \left( T_{41}^0 - T_{41} \right) \\ 0 \end{pmatrix} \geqslant 0. \end{aligned}$$

According to Lemma 1, we have that $E^2$ of model (4) is globally asymptotical stability. This completes the proof. □

*Remark 4.* The Theorem 4 means that after HSCT, the virus and infected cells would be eventually cleared even if $\mathcal{R} > 1$, and the donor CD4+T cells would complete replace host CD4+T cells as well, which is the ideal state of HSCT.

## 3.3 | Mixed chimerism infection-free equilibrium

After HSCT, the infected cells and viruses may be depleted and two types of CD4+T cells in host and donor may coexist, i.e., mixed chimerism infection-free equilibrium $E^3 = (T_{41}^3, 0, 0, T_2^3)$ would exist. We have the following result.

**Theorem 5.** *If* $\frac{\alpha_2}{\mu_2} + \frac{\alpha_1 \Lambda k_1}{\mu_{41}(\mu_2 \mu_{41} + \Lambda k_1)} > \frac{\alpha_{41}}{\mu_{41}}$ *holds, model* (4) *has a unique mixed chimerism infection-free equilibrium* $E^3 = (T_{41}^3, 0, 0, T_2^3)$.

*Proof.* From model (4), let

$$\begin{cases} \frac{\alpha_1 T_{41}^3}{\alpha_1 T_{41}^3 + \alpha_2 T_2^3}\Lambda - \mu_{41} T_{41}^3 - k_1 T_{41}^3 T_2^3 = 0, \\ \frac{\alpha_2 T_2^3}{\alpha_1 T_{41}^3 + \alpha_2 T_2^3}\Lambda - \mu_2 T_2^3 - k_2 T_{41}^3 T_2^3 = 0. \end{cases} \tag{7}$$

Then we get $T_2^3 = \frac{\Lambda - \mu_{41} T_{41}^3}{\mu_2 + (k_1 + k_2) T_{41}^3}$, and $T_{41}^3$ is determined by the following quadratic equation

$$a_1 (T_{41}^3)^2 + b_1 T_{41}^3 + c_1 = 0. \tag{8}$$

Where $a_1 = \alpha_1 k_1 (k_1 + k_2), b_1 = 2\alpha_1 k_2 \mu_2 + \alpha_1 k_1 \mu_2 - \alpha_2 k_2 \mu_{41}, c_1 = \mu_2^2 \alpha_1 - \mu_2 \alpha_2 \mu_{41} - \alpha_2 \Lambda k_1$. Clearly $a_1 > 0$, the roots of equation (8) are determined by the following three cases.

Case 1: $b_1 > 0, c_1 > 0$. From (8), we have

$$\begin{cases} 2\alpha_1 k_2 \mu_2 + \alpha_1 k_1 \mu_2 - \alpha_2 k_2 \mu_{41} > 0, \\ \mu_2^2 \alpha_1 - \mu_2 \alpha_2 \mu_{41} - \alpha_2 \Lambda k_1 > 0. \end{cases} \tag{9}$$

From (9) we have $\frac{\alpha_2}{\mu_2} - \frac{\alpha_{41}}{\mu_{41}} < \frac{-\alpha_1 \Lambda k_1}{\mu_{41}(\mu_2 \mu_{41} + \Lambda k_1)}$. According to the Descarte's rule of sign, the equation (9) has no positive roots.

Case 2: $b_1 < 0, c_1 > 0$. We have

$$\begin{cases} 2\alpha_1 k_2 \mu_2 + \alpha_1 k_1 \mu_2 - \alpha_2 k_2 \mu_{41} < 0, \\ \mu_2^2 \alpha_1 - \mu_2 \alpha_2 \mu_{41} - \alpha_2 \Lambda k_1 > 0. \end{cases} \tag{10}$$

From (10) we have

$$\begin{cases} \dfrac{\alpha_1}{\alpha_2} < \dfrac{k_2\mu_{41}}{2k_2\mu_2 + k_1\mu_2}, \\ \dfrac{\alpha_1}{\alpha_2} > \dfrac{\mu_2\mu_{41} + \Lambda k_1}{\mu_2^2}. \end{cases} \tag{11}$$

If (11) holds, then $-k_2\mu_2^2\mu_{41} > 2k_2\mu_2\Lambda k_1 + k_1\mu_2^2\mu_{41} + k_2^2\Lambda\mu_2$, which leads to a contradiction. Therefore, according to the Descarte's rule of the sign, the equation (8) does not have two positive roots.

Case 3: $c_1 < 0$. We have

$$\mu_2^2\alpha_1 - \mu_2\alpha_2\mu_{41} - \alpha_2\Lambda k_1 < 0. \tag{12}$$

From (12) we have $\frac{\alpha_2}{\mu_2} - \frac{\alpha_{41}}{\mu_{41}} > \frac{-\alpha_1\Lambda k_1}{\mu_{41}(\mu_2\mu_{41}+\Lambda k_1)}$. According to the Descarte's rule of sign, for case 3, the equation (8) only has one positive root, regardless of $b_1 > 0$ or $b_1 < 0$. □

**Theorem 6.** *If $\mathcal{R} > 1$ and $\frac{\alpha_2}{\mu_2} + \frac{\alpha_1\Lambda k_1}{\mu_{41}(\mu_2\mu_{41}+\Lambda k_1)} > \frac{\alpha_{41}}{\mu_{41}}$ hold, the mixed chimerism infection-free equilibrium $E^3$ of model* (4) *is unstable.*

*Proof.* The characteristic equation at $E^3$ of model (4) is as follows

$$\begin{aligned} \left|\lambda E - J\left(E^3\right)\right| &= [\lambda - B_1] \begin{vmatrix} \lambda + \mu_{42} & -\beta T_{41}^3 & 0 \\ -N\mu_{42} & \lambda + \mu_V & 0 \\ 0 & 0 & \lambda - B_2 \end{vmatrix} \\ &= |\lambda - B_1| \Big[ (\lambda + \mu_{42})(\lambda + \mu_V)(\lambda - B_2) - N\mu_{42}\beta T_{41}^3(\lambda - B_2) \Big] \\ &= (\lambda - B_1) \Big[ \lambda^3 + (\mu_{42} + \mu_V - B_2)\lambda^2 + (\mu_{42}\mu_V - \mu_{42}B_2 - \mu_V B_2 \\ &\quad - N\mu_{42}\beta T_{41}^3)\lambda - \mu_{42}\mu_V B_2 + N\mu_{42}\beta T_{41}^3 B_2 \Big], \end{aligned}$$

where

$$B_1 = \frac{\alpha_1\alpha_2 T_2^3\Lambda}{\left(\alpha_1 T_{41}^3 + \alpha_2 T_2^3\right)^2} - \mu_{41} - k_1 T_2^3, B_2 = \frac{\alpha_1\alpha_2 T_{41}^3\Lambda}{\left(\alpha_1 T_{41}^3 + \alpha_2 T_2^3\right)^2} - \mu_2 - k_2 T_{41}^3.$$

According to (7), we have

$$\lambda_1 = B_1 = \frac{\alpha_1\alpha_2 T_2^3\Lambda}{\left(\alpha_1 T_{41}^3 + \alpha_2 T_2^3\right)^2} - \mu_{41} - k_1 T_2^3 < 0.$$

$\lambda_2, \lambda_3, \lambda_4$ are determined by the following cubic equations.

$$\begin{aligned} &\lambda^3 + (\mu_{42} + \mu_V - B_2)\lambda^2 + (\mu_{42}\mu_V - \mu_{42}B_2 - \mu_V B_2 - N\mu_{42}\beta T_{41}^3)\lambda - \mu_{42}\mu_V B_2 \\ &+ N\mu_{42}\beta T_{41}^3 B_2 = 0. \end{aligned}$$

According to the Hurwitz criterion[34], we have

$$\triangle_1 = \mu_{42} + \mu_V - B_2 > 0.$$

$$\begin{aligned} \triangle_2 &= \begin{vmatrix} \mu_{42} + \mu_V - B_2 & -\mu_{42}\mu_V B_2 + N\mu_{42}\beta T_{41}^3 B_2 \\ 1 & \mu_{42}\mu_V - \mu_{42}B_2 - \mu_V B_2 - N\mu_{42}\beta T_{41}^3 \end{vmatrix} \\ &= (\mu_{42} + \mu_V)\Big[\mu_{42}\mu_V + B_2(B_2 - \mu_{42} - \mu_V) - N\mu_{42}\beta T_{41}\Big]. \end{aligned}$$

From the second inequality of (4) we have

$$B_2 < 0, B_2 - \mu_{42} - \mu_V < 0,$$

then

$$B_2(B_2 - \mu_{42} - \mu_V) > 0.$$

From $\mathcal{R} > 1$ and the boundedness of solutions we have

$$\mu_{42}\mu_V - N\mu_{42}\beta T_{41}^3 > \mu_{42}\mu_V - N\mu_{42}\beta\frac{\Lambda}{\mu_{41}} > 0,$$

hence $\triangle_2 > 0$.

$$\triangle_3 = \begin{vmatrix} \mu_{42}+\mu_V-B_2 & -\mu_{42}\mu_V B_2 + N\mu_{42}\beta T_{41}^3 B_2 & 0 \\ 1 & \mu_{42}\mu_V - \mu_{42}B_2 - \mu_V B_2 - N\mu_{42}\beta T_{41}^3 & 0 \\ 0 & \mu_{42}+\mu_V-B_2 & -\mu_{42}\mu_V B_2 + N\mu_{42}\beta T_{41}^3 B_2 \end{vmatrix}$$

$$= (-\mu_{42}\mu_V + N\mu_{42}\beta T_{41}^3)B_2\triangle_2 < 0.$$

According to the Hurwitz criterion[34], the mixed chimerism infection-free equilibrium $E^3$ is unstable when $\mathcal{R} > 1$. This completes the proof. □

*Remark 5.* After HSCT, the CD4+T cell-mediated immune exclusion would occur, it is difficult for the two types of CD4+T cells to co-exist. Therefore, the result of Theorem 6 is much consistent with the biological significance.

## 3.4 | Transplantation failure infection equilibrium

After HSCT, the infected cells and viruses may not be depleted while the donor CD4+T cells are cleared due to immune exclusion by the host CD4+T cell, i.e., the transplantation failure infection equilibrium $E^4 = (T_{41}^4, T_{42}^4, V^4, 0)$ would occur.

For simplicity of discussion, we further introduce the following assumption

$(H_4)$ $\dfrac{\alpha_2}{\mu_2} - \dfrac{\alpha_1}{\mu_{41}} < \dfrac{k_2\Lambda\alpha_1 - 2\alpha_1\mu_{41}\mu_2}{\mu_{41}^2\mu_2}$.

**Theorem 7.** *If $\mathcal{R} > 1$ model* (4) *has a unique transplantation failure infection equilibrium $E^4 = (T_{41}^4, T_{42}^4, V^4, 0)$.*

*Proof.* From model (4), we have

$$\begin{cases} \Lambda - \mu_{41}T_{41}^4 - \beta V^4 T_{41}^4 = 0, \\ \beta V^4 T_{41}^4 - \mu_{42}T_{42}^4 = 0, \\ N\mu_{42}T_{42}^4 - \mu_V V^4 = 0. \end{cases} \tag{13}$$

By solving the equations (13) we have

$$T_{41}^4 = \frac{\mu_V}{\beta N},\quad T_{42}^4 = \frac{\Lambda}{\mu_{42}} - \frac{\mu_{41}\mu_V}{\beta N\mu_{42}},\quad V^4 = \frac{\Lambda N}{\mu_V} - \frac{\mu_{41}}{\beta}.$$

It is easy to see that the equilibrium $E^4$ exists and is unique if the basic reproduction number $\mathcal{R} > 1$. □

**Theorem 8.** *If $\mathcal{R} > 1$ and $(H_4)$ hold, the transplant failure infections equilibrium $E^4$ of model* (4) *is locally asymptotically stable.*

*Proof.* The characteristic equation at the equilibrium $E^4$ of model (4) is as follows

$$\left|\lambda E - J\left(E^4\right)\right| = \begin{vmatrix} \lambda + \left(\mu_{41} + \beta V^4\right) & 0 & \beta T_{41}^4 & \frac{\alpha_2\Lambda}{\alpha_1 T_{41}^4} + k_1 T_{41}^4 \\ -\beta V^4 & \lambda + \mu_{42} & -\beta T_{41}^4 & 0 \\ 0 & -N\mu_{42} & \lambda + \mu_V & 0 \\ 0 & 0 & 0 & \lambda - \left(\frac{\alpha_2\Lambda}{\alpha_1 T_{41}^4} - \mu_2 - k_2 T_{41}^4\right) \end{vmatrix}$$

$$= \left[\lambda - \left(\frac{\alpha_2\Lambda}{\alpha_1 T_{41}^4} - \mu_2 - k_2 T_{41}^4\right)\right] \begin{vmatrix} \lambda + \mu_{41} + \beta V^4 & 0 & \beta T_{41}^4 \\ -\beta V^4 & \lambda + \mu_{42} & -\beta T_{41}^4 \\ 0 & -N\mu_{42} & \lambda + \mu_V \end{vmatrix}$$

$$= \left[\lambda - \left(\frac{\alpha_2\Lambda}{\alpha_1 T_{41}^4} - \mu_2 - k_2 T_{41}^4\right)\right] \left[\lambda^3 + \left(\mu_V + \mu_{41} + \mu_{42} + \beta V^4\right)\lambda^2 + (\mu_{41}\mu_V + \left(\mu_{41} + \beta V^4\right)\mu_V\right.$$

$$+\left(\mu_{41}+\beta V^4\right)\mu_{42}-\beta N\mu_{42}T_{41}^4)\lambda+\left(\mu_{41}+\beta V^4\right)\left(\mu_{42}\mu_V-\beta N\mu_{42}T_{41}^4\right)+\beta^2 N\mu_{42}V^4T_{41}^4\Big].$$

Similar to the discussion of Theorem 2, it is easy to obtain the locally asymptotical stability of the transplantation failure infection equilibrium $E^4$ of model (4) according to the Hurwitz criterion[34]. This completes proof. □

*Remark 6.* We observe that there exists partial overlap between the condition of Theorem 3 and Theorem 8 at $E^4$ and $E^2$ of model (4). That is, when $\mathcal{R}>1$, $\frac{-k_1\Lambda\alpha_2}{\mu_{41}\mu_2^2}<\frac{\alpha_2}{\mu_2}-\frac{\alpha_1}{\mu_{41}}<\frac{k_2\Lambda\alpha_1-2\alpha_1\mu_{41}\mu_2}{\mu_{41}^2\mu_2}$, both types of equilibrium could be locally asymptotically stable, which means that there could exists bi-stability phenomenon of model (4) .

## 3.5 | Mixed chimerism infection equilibrium

On the mixed chimerism infection equilibrium, $E^0$, i.e., coexistent equilibrium of $T_{41}$ and $T_2$ as well as $T_{42}$ and $V$ after HSCT of model (4), we have the following result.

**Theorem 9.** *If the following assumptions are satisfied*

$(H_5)$ $\alpha_2\Lambda\beta^2N^2-\alpha_1\mu_V\mu_2\beta N-\alpha_1k_2\mu_V^2>0$,

$(H_6)$ $\dfrac{\alpha_2\Lambda\beta^2N^2-\alpha_1\mu_V\mu_2\beta N-\alpha_1k_2\mu_V^2}{\alpha_2\mu_2\beta^2N^2+k_2\mu_V\beta N}-\dfrac{\beta N\Lambda-\mu_{41}\mu_V}{\mu_2\beta N+k_1\mu_V+k_2\mu_V}<0$,

*the mixed chimerism infection equilibrium $E^0=(T_{41}^0,T_{42}^0,V^0,T_2^0)$ of model* (4) *exists uniquely.*

*Proof.* Let

$$\begin{cases}\dfrac{\alpha_1T_{41}^0}{\alpha_1T_{41}^0+\alpha_2T_2^0}\Lambda-\mu_{41}T_{41}^0-\beta VT_{41}^0-k_1T_{41}^0T_2^0=0,\\ \beta VT_{41}^0-\mu_{42}T_{42}^0=0,\\ N\mu_{42}T_{42}^0-\mu_VV^0=0,\\ \dfrac{\alpha_2T_2^0}{\alpha_1T_{41}^0+\alpha_2T_2^0}\Lambda-\mu_2T_2^0-k_2T_{41}^0T_2^0=0.\end{cases}$$

Then by calculations, we have

$$T_{41}^0=\frac{\mu_V}{\beta N},\quad T_2^0=\frac{\alpha_2\Lambda\beta^2N^2-\alpha_1\mu_V\mu_2\beta N-\alpha_1k_2\mu_V^2}{\alpha_2\mu_2\beta^2N^2+k_2\mu_V\beta N},$$

$$V^0=\frac{N\Lambda}{\mu_V}-\frac{\mu_{41}}{\beta}-\left(\frac{\mu_2N}{\mu_V}+\frac{k_1}{\beta}+\frac{k_2}{\beta}\right)T_2^0,\quad T_{42}^0=\frac{\mu_V}{N\mu_{42}}V^0.$$

So the equilibrium $E^0$ exists uniquely if $(H_5),(H_6)$ hold. This completes the proof. □

**Theorem 10.** *If $(H_5),(H_6)$ hold and the following assumptions are satisfied*

$(H_7)$ $A_5>0,A_6>0,A_7>0,A_8>0$,

$(H_8)$ $(A_5A_6-A_7)A_7>(A_5)^2A_8$.

*The mixed chimerism infection equilibrium $E^0$ of model* (4) *is locally asymptotically stable. Here $A_i(i=5,6,7,8)$ is defined in the following proof.*

*Proof.* The Jacobi matrix of model (4) at $E^0$ is as follows.

$$J=\begin{pmatrix}\dfrac{\alpha_1\alpha_2T_2^0\Lambda}{\left(\alpha_1T_{41}^0+\alpha_2T_2^0\right)^2}-\mu_{41}-k_1T_2^0 & 0 & -\beta T_{41}^0 & \dfrac{-\alpha_1\alpha_2T_{41}^0\Lambda}{\left(\alpha_1T_{41}^0+\alpha_2T_2^0\right)^2}-k_1T_{41}^0\\ 0 & -\mu_{42} & \beta T_{41}^0 & 0\\ 0 & N\mu_{42} & -\mu_V & 0\\ \dfrac{-\alpha_1\alpha_2T_2^0\Lambda}{\left(\alpha_1T_{41}^0+\alpha_2T_2^0\right)^2}-k_2T_2^0 & 0 & 0 & \dfrac{\alpha_1\alpha_2T_{41}^0\Lambda}{\left(\alpha_1T_{41}^0+\alpha_2T_2^0\right)^2}-\mu_2-k_2T_{41}^0\end{pmatrix}.$$

The characteristic equation of model (4) at $E^0$ is as follows

$$\begin{aligned}\left|\lambda E - J\left(E^0\right)\right| &= \begin{vmatrix} \lambda - A_4 & 0 & \beta T_{41}^0 & A_1 \\ \beta V^0 & -\mu_{42} & \beta T_{41}^0 & 0 \\ 0 & N\mu_{42} & -\mu_V & 0 \\ A_2 & 0 & 0 & \lambda - A_3 \end{vmatrix} \\ &= -A_1\left[(\lambda+\mu_{42})(\lambda+\mu_V)A_2 - \beta N\mu_{42}T_{41}^0 A_2\right] + (\lambda - A_3)\Big[(\lambda - A_4)(\lambda+\mu_{42}) \\ &\quad (\lambda+\mu_V) + \beta^2 V^0 T_{41}^0 N\mu_{42} - N\beta\mu_{42}T_{41}^0(\lambda - A_4)\Big] \\ &= \lambda^4 + A_5\lambda^3 + A_6\lambda^2 + A_7\lambda + A_8.\end{aligned}$$

Where

$$A_1 = \frac{\alpha_1\alpha_2 T_{41}^0\Lambda}{(a_1T_{41}^0 + a_2T_2^0)^2} + k_1T_{41}^0,\ \ A_2 = \frac{\alpha_1\alpha_2 T_2^0\Lambda}{(\alpha_1T_{41}^0 + \alpha_2T_2^0)^2} + k_2T_2^0, A_5 = \mu_V + \mu_{42} - A_3 - A_4,$$

$$A_3 = \frac{\alpha_1\alpha_2 T_{41}^0\Lambda}{(\alpha_1T_{41}^0 + \alpha_2T_2^0)^2} - \mu_2 - k_2T_{41}^0,\ A_4 = \frac{\alpha_1\alpha_2 T_2^0\Lambda}{(\alpha_1T_{41}^0 + \alpha_2T_2^0)^2} - \mu_{41} - \beta V - k_1T_2^0,$$

$$A_6 = \mu_V\mu_{42} - \mu_V A_4 - A_4\mu_{42} - N\beta\mu_{42}T_{41}^0 - A_3\mu_V - A_3\mu_{42} + A_3A_4 - A_1A_2,$$

$$A_7 = -(A_3+A_4)\mu_{42}\mu_V + \beta^2 N\mu_{42}V^0T_{41}^0 + (A_3+A_4)N\beta\mu_{42}T_{41}^0 + (\mu_{42}+\mu_V)(A_3A_4 - A_1A_2),$$

$$A_8 = (A_1A_2 - A_3A_4)N\beta\mu_{42}T_{41}^0 - A_3N\beta^2\mu_{42}V^0T_{41}^0 + (A_3A_4 - A_1A_2)\mu_{42}\mu_V.$$

In order to establish the stability at the equilibrium $E^0$ of model (4), the following conditions should be satisfied

$$A_5 > 0, A_6 > 0, A_7 > 0, A_8 > 0, (A_5A_6 - A_7)A_7 > (A_5)^2A_8.$$

Therefore, by Routh-Hurwitz criterion[34], we can see that if $(H_5) - (H_8)$ hold, the $E^0$ of model (4) is locally asymptotically stable. This completes the proof. □

## 4 | BIFURCATION ANALYSIS

In this section we analyse the local bifurcation of model (4) with some specical parameters.

### 4.1 | Forward bifurcation

We see that when $\mathcal{R} = 1$, the characteristic equation of model (4) at $E^1$ has zero eigenvalue. So when $\mathcal{R} = 1$, the model (4) may undergo a transcritical bifurcation at the transplantation failure infection-free equilibrium $E^1$. In this subsection, we use the bifurcation theorem of Castillo-Chavez and Song[36] to study the forward bifurcation of the model (4) at $E^1$.

**Theorem 11.** *If* $\frac{\alpha_2\mu_{41}}{\alpha_1} - \mu_2 + \frac{k_2\Lambda}{\mu_{41}} < 0$, $\mathcal{R} = 1$, *the model* (4) *undergoes a forward bifurcation near the equilibrium* $E^1$.

*Proof.* To simplify the notation, we take $x_1 = T_{41}, x_2 = T_{42}, x_3 = V, x_4 = T_2,\ x = (x_1, x_2, x_3, x_4)^T$. The model (4) can be rewritten by $\frac{dx}{dt} = f(x)$ as follows, where $f(x) = (f_1, f_2, f_3, f_4)^T$.

$$\begin{cases} \dot{x_1} = f_1(x) = \frac{\alpha_1x_1}{\alpha_1x_1+\alpha_2x_4}\Lambda - \mu_{41}x_1 - \beta x_3x_1 - k_1x_1x_4, \\ \dot{x_2} = f_2(x) = \beta x_3x_1 - \mu_{42}x_2, \\ \dot{x_3} = f_3(x) = N\mu_{42}x_2 - \mu_V x_3, \\ \dot{x_4} = f_4(x) = \frac{\alpha_2x_4}{\alpha_1x_1+\alpha_2x_4}\Lambda - \mu_2x_4 - k_2x_1x_4. \end{cases}$$

Take $\mathcal{R} = 1$, choose $\beta$ as a bifurcation parameter. Then $\beta^* = \frac{\mu_V \mu_{41}}{\Lambda N}$. The Jacobi matrix at $E^1$ of model (4) is

$$A = \begin{pmatrix} -\mu_{41} & 0 & \frac{-\beta^*\Lambda}{\mu_{41}} & \frac{-\alpha_2\mu_{41}}{\alpha_1} \\ 0 & -\mu_{42} & \frac{\beta^*\Lambda}{\mu_{41}} & 0 \\ 0 & N\mu_{42} & -\mu_V & 0 \\ 0 & 0 & 0 & \frac{\alpha_2\mu_{41}}{\alpha_1} - \mu_2 - \frac{k_2\Lambda}{\mu_{41}} \end{pmatrix}.$$

The characteristic equation at the equilibrium $E^1$ is as follows

$$\begin{aligned} \left|\lambda E - A\right| &= \begin{vmatrix} \lambda + \mu_{41} & 0 & \frac{\beta^*\Lambda}{\mu_{41}} & \frac{\alpha_2\mu_{41}}{\alpha_1} \\ 0 & \lambda + \mu_{42} & \frac{-\beta^*\Lambda}{\mu_{41}} & 0 \\ 0 & -N\mu_{42} & \lambda + \mu_V & 0 \\ 0 & 0 & 0 & \lambda - \frac{\alpha_2\mu_{41}}{\alpha_1} + \mu_2 + \frac{k_2\Lambda}{\mu_{41}} \end{vmatrix} \\ &= (\lambda + \mu_{41}) \left( \lambda - \frac{\alpha_2\mu_{41}}{\alpha_1} + \mu_2 + \frac{k_2\Lambda}{\mu_{41}} \right) \lambda(\lambda + \mu_V + \mu_{42}). \end{aligned}$$

When

$$\frac{\alpha_2\mu_{41}}{\alpha_1} - \mu_2 + \frac{k_2\Lambda}{\mu_{41}} < 0,$$

then

$$\lambda_1 = -\mu_{41} < 0, \lambda_2 = \frac{\alpha_2\mu_{41}}{\alpha_1} - \mu_2 + \frac{k_2\Lambda}{\mu_{41}} < 0, \lambda_3 = 0, \lambda_4 = -\mu_V - \mu_{42} < 0.$$

Therefore, only $\lambda_3$ is zero eigenvalue, and the rest all have negative real parts.

Let the right eigenvector of $A$ be $W = (w_1, w_2, w_3, w_4)^T$, the left eigenvector be $U = (u_1, u_2, u_3, u_4)$, we have $W = (-\frac{1}{\mu_{41}N}, \frac{1}{N\mu_{42}}, \frac{1}{\mu_V}, 0)^T$, $U = (0, 1, \frac{1}{N}, 0)$.

By calculation, we have

$$\begin{aligned} a &= \sum_{k=1}^{4}\sum_{i=1}^{4}\sum_{j=1}^{4} u_k w_i w_j \frac{\partial^2 f_k}{\partial x_i \partial x_j}(E^0, \beta^*) \\ &= u_2 w_1 w_3 \frac{\partial^2 f_2}{\partial x_1 \partial x_3}(E^0, \beta^*) + u_2 w_3 w_1 \frac{\partial^2 f_2}{\partial x_3 \partial x_1}(E^0, \beta^*) \\ &= u_2 w_1 w_3 \beta^* + u_2 w_1 w_3 \beta^* = -\frac{2}{\Lambda N^2} < 0, \\ b &= \sum_{k=1}^{4}\sum_{i=1}^{4} u_k w_i \frac{\partial^2 f_k}{\partial x_i \partial \beta^*}(E^0, \beta^*) = u_2 w_3 \frac{\partial^2 f_2}{\partial x_3 \partial \beta^*} = \frac{\Lambda}{\mu_V \mu_{41}} > 0. \end{aligned}$$

According to the literature[36], the direction of the bifurcation of model (4) at $\beta = \beta^*$ is forward. This completes the proof. □

## 4.2 | Hopf bifurcation

This section focuses on the existence of Hopf bifurcation at the mixed chimerism infections equilibrium $E^0$ of model (4) by choosing $\alpha_2$ as the bifurcation parameter, which reflects the replacement rate of two types of CD4+T cells after HSCT. We denote the threshold value of Hopf bifurcation point as $\alpha_2 = \alpha_2^*$.

**Lemma 2** (Liu et al.[37]). *If the following assumptions hold, there will exist a Hopf bifurcation for model* (4).

(*i*) $B_8(\alpha_2^*) > 0, Q_1(\alpha_2^*) > 0, Q_2(\alpha_2^*) > 0, Q_3(\alpha_2^*) = 0$,

(*ii*) $\frac{d}{d\alpha_2}(Q_3(\alpha_2^*)) \neq 0$,

*where* $Q_1(\alpha_2^*) > 0, Q_2(\alpha_2^*) > 0, Q_3(\alpha_2^*) > 0$ *are the Hurwitz determinants at the bifurcation parameter* $\alpha_2^*$.

We assume that there is a smooth curve of equilibrium $(E(\alpha_2), \alpha_2^*)$ for the model (4), satisfying $E(\alpha_2) = \alpha_2^*$ and $(E^0, \alpha_2^*)$ being the positive equilibrium. $C(\lambda, \alpha_2^*) = \lambda^4 + A_5(\alpha_2^*)\lambda^3 + A_6(\alpha_2^*)\lambda^2 + A_7(\alpha_2^*) + A_8(\alpha_2^*)$ is the characteristic equation at $(E^0, \alpha_2^*)$

By the proof of Theorem 10, $(i)$ clearly holds, then the characteristic polynomial must have a pair of purely imaginary roots. In the following, to prove the existence of Hopf bifurcation, we derive the transversality condition $(ii)$. We assume that $\pm iw$ is a pair of purely imaginary eigenvalues, the derivative of the characteristic equation $C(\lambda, \alpha_2^*)$ with respect to $\alpha_2$ yields

$$(4\lambda^3 + 3A_5\lambda^2 + 2A_6\lambda + A_7)\frac{d\lambda}{d\alpha_2} + \lambda^3\frac{dA_5}{d\alpha_2} + \lambda^2\frac{dA_6}{d\alpha_2} + \lambda\frac{dA_7}{d\alpha_2} + \frac{dA_8}{d\alpha_2} = 0.$$

So

$$\left(\frac{d\lambda}{d\alpha_2}\right)^{-1} = -\frac{4\lambda^3 + 3A_5\lambda^2 + 2A_6\lambda + A_7}{\lambda^3\frac{dA_5}{d\alpha_2} + \lambda^2\frac{dA_6}{d\alpha_2} + \lambda\frac{dA_7}{d\alpha_2} + \frac{dA_8}{d\alpha_2}}.$$

$$sign\left[\frac{d(Re(\lambda))}{d\alpha_2}\right]_{\lambda=iw,Q_3=0} = sign\left[Re\left(\frac{d\lambda}{d\alpha_2}\right)^{-1}\right]_{\lambda=iw,Q_3=0} = sign\big[\gamma\big].$$

$$\gamma = Re\left[-\frac{-4w^3 i - 3A_5w^2 + 2A_6wi + A_7}{-w^3 i\frac{dA_5}{d\alpha_2} - \frac{dA_6}{d\alpha_2}w^2 + \frac{dA_7}{d\alpha_2}iw + \frac{dA_8}{d\alpha_2}}\right]$$

$$= Re\left[\frac{(3A_5w^2 - A_7) + i(4w^3 - 2A_6w)}{\left(-\frac{dA_6}{d\alpha_2}w^2 + \frac{dA_8}{d\alpha_2}\right) + i\left(\frac{dA_7}{d\alpha_2}w - \frac{dA_5}{d\alpha_2}w^3\right)}\right]$$

$$= \frac{M_1M_3 + M_2M_4}{M_3^2 + M_4^2}.$$

Where

$$M_1 = 3A_5w^2 - A_7,\ M_2 = 4w^3 - 2A_6w,\ M_3 = -\frac{dA_6}{d\alpha_2}w^2 + \frac{dA_8}{d\alpha_2},\ M_4 = -\frac{dA_7}{d\alpha_2}w - \frac{dA_5}{d\alpha_2}w^3.$$

$A_i (i = 5, \ldots, 8)$ is defined in Theorem 10.

If $M_1M_3 + M_2M_4 > 0$, then $sign[\frac{d(Re(\lambda))}{d\alpha_2}]_{\alpha_2=\alpha_2^*} > 0$, and the transversality condition $(ii)$ holds. We have the following result.

**Theorem 12.** *If $M_1M_3 + M_2M_4 > 0$, model (4) exists a Hopf bifurcation near $E^0$ when $\alpha_2$ crosses $\alpha_2^*$.*

## 5 | NUMERICAL SIMULATION

In this section, we first perform numerical simulation to demonstrate the stability of model (4) at equilibria $E^0$, $E^2$, $E^4$. Then we illustrate the complex dynamics of model (4) at the mixed chimerism infection equilibrium $E^0$ with the change of $\alpha_1, \alpha_2$.

### 5.1 | Numerical simulation of stability

We numerically simulate the stability of equilibria $E^0, E^2, E^4$ of model (4). Fig. 1, 2, 3 show the simulation result at the equilibria $E^0$, $E^2$, $E^4$, respectively.

The values of parameters in Fig. 1 are taken as $\Lambda = 30, \alpha_1 = 0.86, \alpha_2 = 0.14, \beta = 0.03, N = 0.76, \mu_{41} = 0.7, \mu_{42} = 0.65, \mu_V = 0.2, \mu_2 = 0.3, k_1 = 0.0002, k_2 = 0.0003$. By calculations, we have $\mathcal{R} = 4.89$. It is verified that assumptions $(H_5) - (H_8)$ hold, which means that $E^0 = (9, 16, 38, 45)$ is locally asymptotically stable, therefore, the Theorem 10 is ture.

The values of parameters in Fig. 2, 3 are taken as $\Lambda = 20, \alpha_1 = 0.2, \alpha_2 = 0.8, \beta = 0.01, N = 0.36, \mu_{41} = 0.2, \mu_{42} = 0.24, \mu_V = 0.22, \mu_2 = 0.28, k_1 = 0.0002, k_2 = 0.002$. By calculation, we have $\mathcal{R} = 1.64$. It is verified that assumption $(H_1)$ holds. According to Fig. 2, we find that the disease in model (4) is persistent. But from Fig. 3, even if the basic reproduction number $\mathcal{R} \geq 1$, the viruses would be extinct. The equilibrium $E^2 = (0, 0, 0, 70)$ is globally asymptotically stable, which means that the Theorem 4 is true.

The values of parameters in Fig. 4 are taken as $\Lambda = 10, \alpha_1 = 0.65, \alpha_2 = 0.35, \beta = 0.03, N = 0.3, \mu_{41} = 0.2, \mu_{42} = 0.21, \mu_V = 0.22, \mu_2 = 0.6, k_1 = 0.02, k_2 = 0.03$. By calculation, we have $\mathcal{R} = 2.05$. It is verified that all the assumptions of Theorem 8 hold. The equilibrium $E^4 = (24, 24, 7, 0)$ is locally asymptotically stable, which means the Theorem 8 is true.

According to Remark 6, the model (4) may have more than one stable equilibrium, and we choose a set of parameters to validate it by numerical simulation.

The values of parameters in Fig. 5, Fig. 6($a$) are taken as $\Lambda = 30, \alpha_1 = 0.635, \alpha_2 = 0.365, \beta = 0.03, N = 0.3, \mu_{41} = 0.205, \mu_{42} = 0.21, \mu_V = 0.22, \mu_2 = 0.23, k_1 = 0.02, k_2 = 0.03$. By calculation, we have $\mathcal{R} = 5.99$. It is verified that the equilibria $E^2, E^4$ are both locally asymptotically stable.

From Fig. 5($a$), we can find that there is a bi-stability phenomenon in model (4), according to Fig. 5($b$), 6($a$) we can find that the two equilibria of model (4) are $E^{21} = (0, 0, 0, 130), E^{41} = (24, 119, 34, 0)$. This means that two types of equilibria could stably coexist under certain conditions after HSCT.

## 5.2 | Numerical simulation of bifurcation

Chimerism is an important threshold that could affect the dynamics of stability of equilibrium, in this subsection we focus on model (4) with the change of $\alpha_2$. First we give the values and sources of the parameters.

**TABLE 2** Parameter values and sources.

| Variables/parameters | value | Source | Variables/parameters | value | Source |
|---|---|---|---|---|---|
| $\Lambda$ | 30 | [36] | $\alpha_1(\alpha_2)$ | varied | - |
| $\mu_{41}$ | 0.1 | [25] | $\mu_{42}$ | 0.5 | [25] |
| $\mu_V$ | 0.5 | [25] | $\mu_2$ | 0.6 | Assumed |
| $\beta$ | 0.03 | Assumed | $k_1$ | 0.00002 | [38] |
| $k_2$ | 0.003 | Assumed | $N$ | 0.36 | Assumed |

We fix the initial values $(T_{41}, T_{42}, V, T_2) = (60, 20, 40, 10)$. First, we analyse the effect of value change with $\alpha_1, \alpha_2$ on the dynamical of model (4). From Fig. 6($b$) it is clear that with $\alpha_2 = 0.8$, the number of infected cells eventually tends to a positive equilibrium. When $\alpha_2$ increases to 0.817, there is a periodic solution of infected cells. When $\alpha_2$ increases further, the number of infected cells tends to 0. According to Fig. 7($a$), it can be seen that the value of $\alpha_2$ has a great influence on the number of infected cells.

As shown in Fig. 7($b$), we obtain the forward branching graph at $E^1$ with $\beta$ as the branching parameter.

As shown in Fig. 8, we choose $\alpha_2$ as the bifurcation parameter, which is verified that all the assumptions of Theorem 12 are satisfied. According to Fig. 8($a$) and 8($b$), we can see that the Hopf bifurcation occurs at the equilibrium $E^0$. From Fig. 8, we can see that the stability of the equilibrium changes around $\alpha_2 = 0.813$. Then we take $\alpha_1 = 0.187, \alpha_2 = 0.813$, and then a limit loop would appear as shown in Fig. 9.

As known in Fig. 9, we find that when the degree of chimerism reaches about 81.3%, there would be a Hopf bifurcation. It is easy to see that when the degree of chimerism exceeds 81.3%, the HIV can be well controlled even to disappear, which is much consistent to the results in the literature [28].

As shown in Fig. 10, we change the values of $\Lambda$, $\mu_{42}$ to 20, 0.8, respectively, then we find that bifurcation diagrams display the phenomenon of endemic bubble.

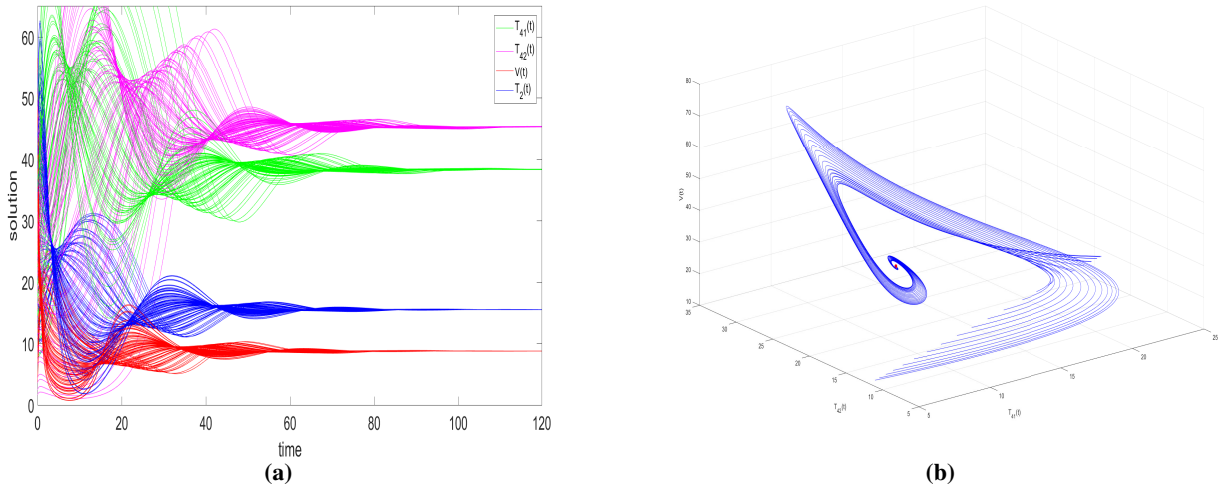
# 6 | CONCLUSION

Involving the degree of chimerism with the donor CD4+T cells in body, we propose a class of HSCT model with HIV virus-to-cell infection, with saturation recruitment rates functions of donor and host CD4+T cells and immune exclusion.

Considering the real background of HIV infection, we assume that the basic reproduction number $\mathcal{R} \geq 1$ in model (4). We find that there are five types of equilibrium in model (4). The existence and stability of all kinds of feasible equilibria are much associated with the values of $\alpha_1, \alpha_2$, which is much consistent with the fact that chimerism is an important threshold value to determine the success rate of transplantation of HSCT.

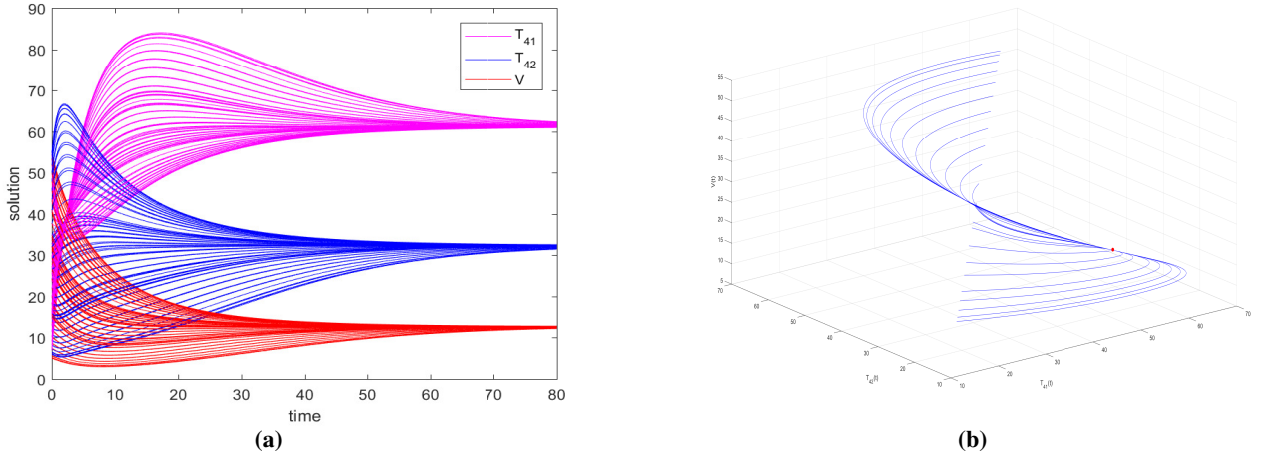
For the mixed chimerism infection equilibrium $E^0$, we find that there would be more assumptions for the existence and stability. According to Theorem 12, model (4) has Hopf bifurcation at $E^0$, which is confirmed by numerical simulation as well. The presence of Hopf bifurcation implies that there would exist some complex dynamical behaviour of model (4). When the value of $\alpha_2$ changes and crosses a certain critical value, the stability of the system suddenly changes. We find that model (4) also has two bi-stable equilibria under some certain conditions.

Currently, there is no complete cure for HIV infection with various treatment methods except few of AIDS patients with HSCT. We find that in model (4) with HSCT, the HIV would tend to extinction under the same set of parameters even $\mathcal{R} > 1$. Therefore, HSCT is an essentially method for curing AIDS. In addition, the most important factor that could greatly affect the stability of model (4) is the degree of chimerism rate $\alpha_2$ of donor CD4+T cells. When $\alpha_2$ changes, the stability of equilibria of model (4) changes as well. When the chimerism is not low enough to reach the stable condition of the complete donor chimerism infection-free equilibrium, timely re-infusion of hematopoietic stem cells should be carried out to ensure the effectiveness of transplantation. Our results also provide a theoretical guideline for the size of chimerism, which would be a core issue in curing AIDS by HSCT in the future.



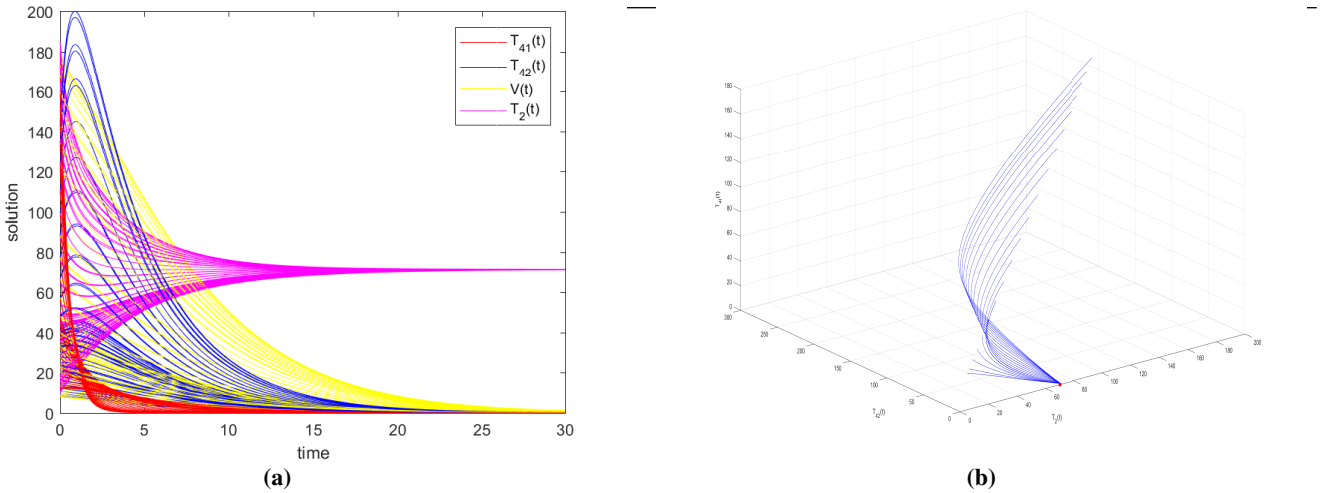

(a) (b)

**FIGURE 1** Locally asymptotical stability of mixed chimerism infection equilibrium $E^0$ of model (4).



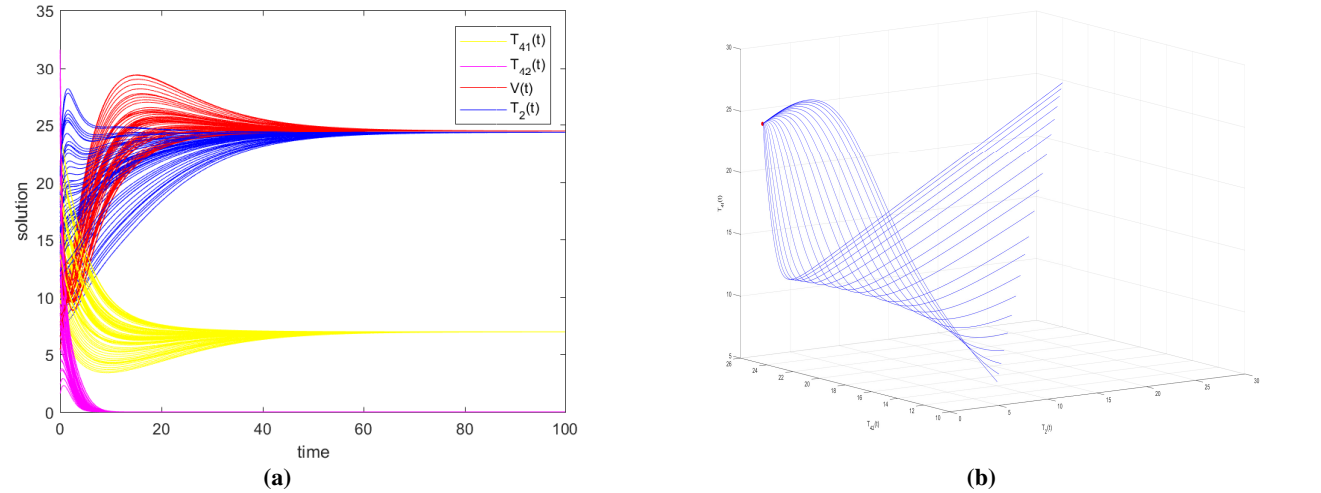

(a) (b)

**FIGURE 2** Globally asymptotical stability of endemic equilibrium $E_*$ of models (1).



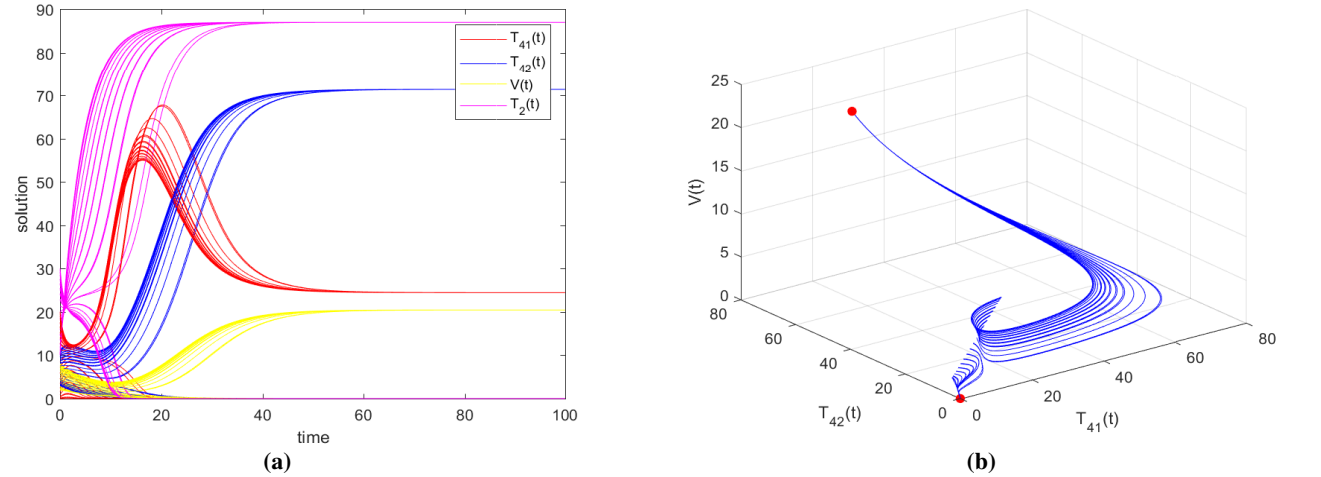

(a) (b)

**FIGURE 3** Globally asymptotical stability of complete donor chimerism infection-free equilibrium $E^2$ of model (4).



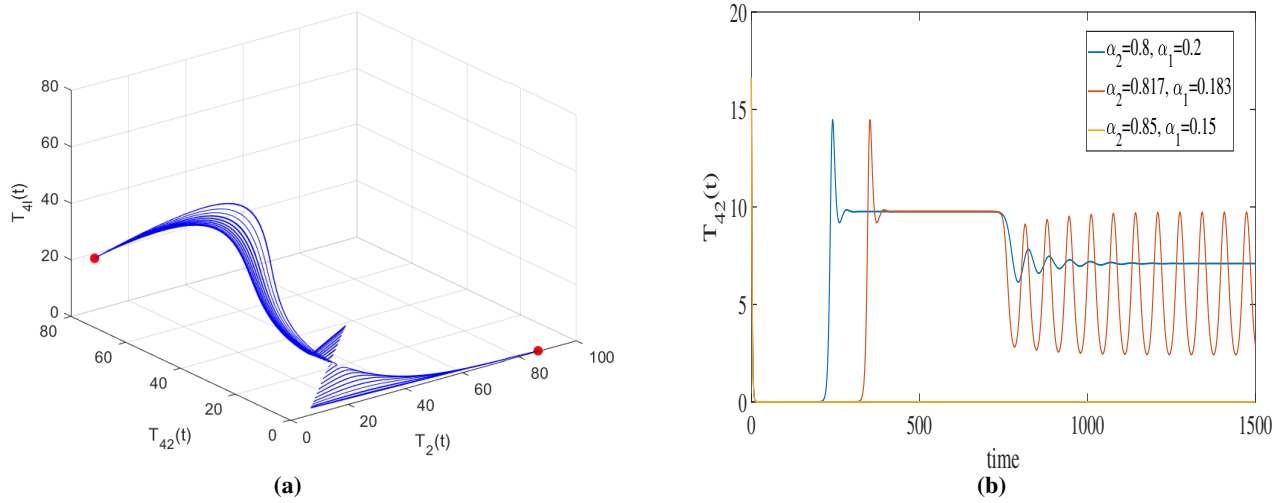

(a) (b)

**FIGURE 4** Locally asymptotical stability of transplantation failure infection equilibrium $E^4$ of model (4).



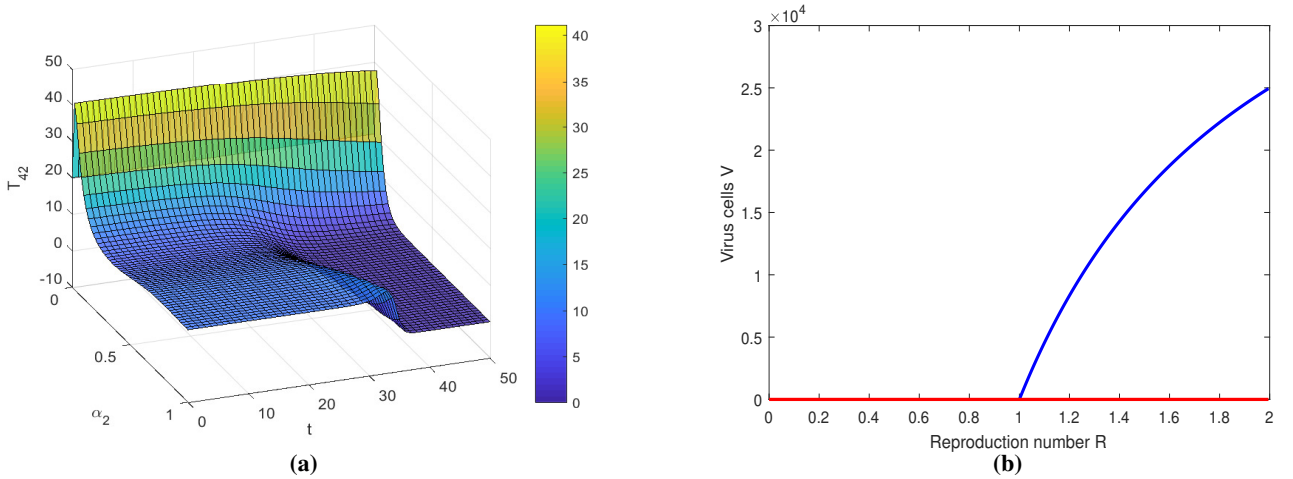

(a) (b)

**FIGURE 5** (c) Time series diagram of the solution of model (4). (d) The 3D phase of bi-stability behavior of $T_{41}$, $T_{42}$, $V$ of model (4).



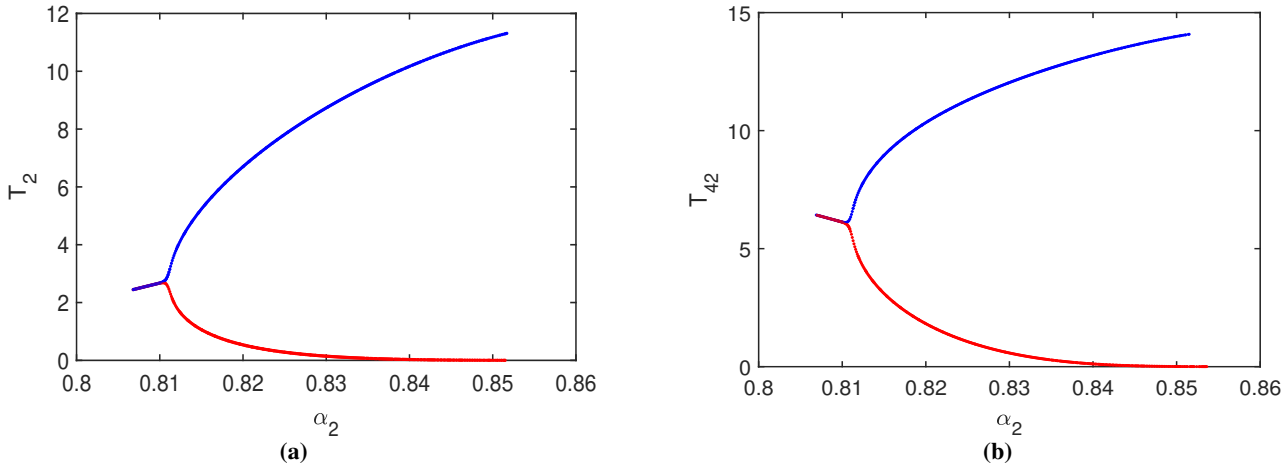

(a) (b)

**FIGURE 6** (a) The 3D phase of bi-stability behavior of $T_2, T_{42}, T_{41}$ of model (4). (b) Time series diagram of infected cells at different value of $\alpha_1, \alpha_2$ of model (4).



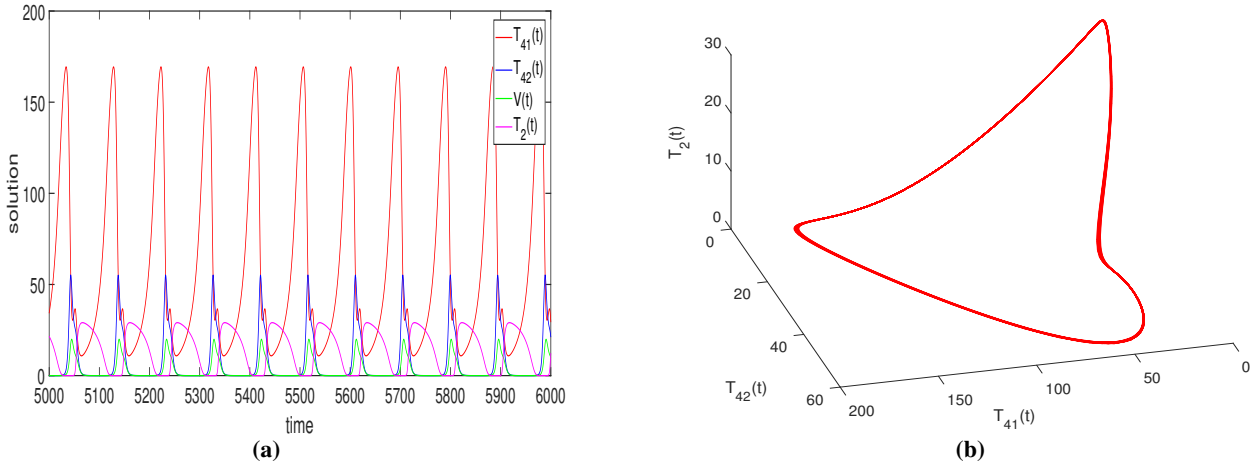

(a) (b)

**FIGURE 7** (a) Three-dimensional phase diagram of the number of infected cells over time with $\alpha_2$ change of model (4). (b) Forward bifurcation of model (4) with respect to $\mathcal{R}$.



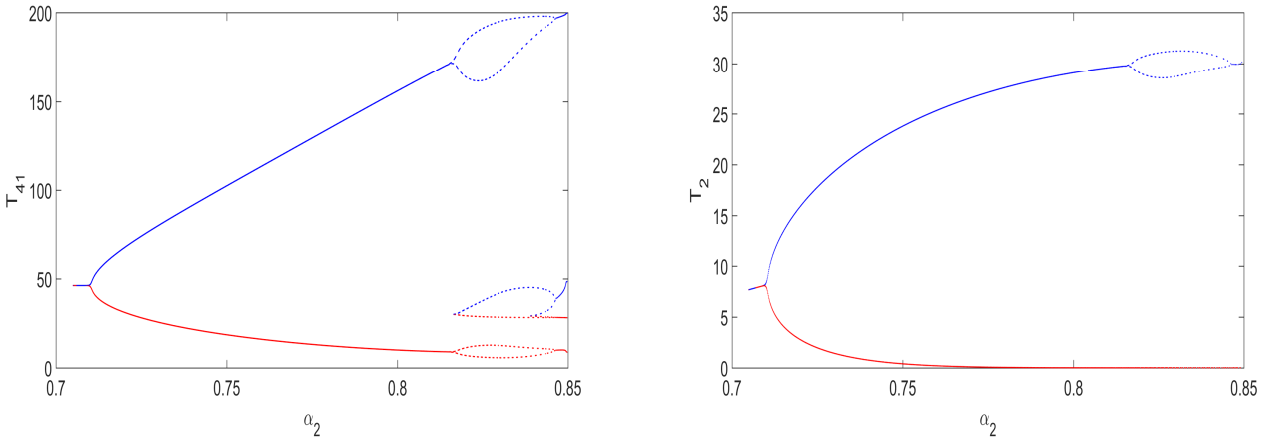

(a) (b)

**FIGURE 8** (a) Hopf bifurcation of $T_2$ with $\alpha_2$ at $E^0$ of model (4). (b) Hopf bifurcation of $T_{42}$ with $\alpha_2$ at $E^0$ of model (4).




(a) (b)

**FIGURE 9** (a) The equilibrium $E^0$ of model (4) is unstable. (b) Three-dimensional phase diagrams of periodic solution of model (4).




(a) (b)

**FIGURE 10** Bifurcation diagrams of model (4) at $E^1$ with $\alpha_2$.

## AUTHOR CONTRIBUTIONS

Wencong Wang: Conceptualization, Writing-original draft, Writing-review & editing, Software. Long Zhang: Supervision, Funding acquisition, Project administration, Writing-review & editing. Hong-Li Li: Supervision, Resources. Zhidong Teng: Methodology, Formal analysis.

## ACKNOWLEDGMENTS

This work was supported by the National Natural Science Foundation of China (12261087, 12262035, 12371504, 12201540), the Natural Science Foundation of Xinjiang Province, People's Republic of China (2022D01E41), the Leading Talents of Tianshan Project in Xinjiang Autonomous Region, China (2023TSYCLJ0054).

## FINANCIAL DISCLOSURE

None reported.

## CONFLICT OF INTEREST

The authors declare no potential conflict of interests.

## REFERENCES

1. Faria NR, Rambaut A, Suchard MA, et al. The early spread and epidemic ignition of HIV-1 in human populations. *science.* 2014;346(6205):56–61.

2. World Health Organization. https://www.afro.who.int/health-topics/hivaids; 2024.
3. Wilen CB, Tilton JC, Doms RW. HIV: cell binding and entry. *Cold Spring Harbor perspectives in medicine.* 2012;2(8):a006866.
4. Phillips AN, Cambiano V, Nakagawa F, et al. Cost-effectiveness of public-health policy options in the presence of pretreatment NNRTI drug resistance in sub-Saharan Africa: a modelling study. *The lancet HIV.* 2018;5(3):e146–e154.
5. Siliciano JD, Siliciano RF. HIV cure: The daunting scale of the problem. *Science.* 2024;383(6684):703–705.
6. Lin YL, Mettling C, Portales P, Reynes J, Clot J, Corbeau P. Cell surface CCR5 density determines the postentry efficiency of R5 HIV-1 infection. *Proceedings of the National Academy of Sciences.* 2002;99(24):15590–15595.
7. Choe H, Farzan M, Sun Y, et al. The $\beta$-chemokine receptors CCR3 and CCR5 facilitate infection by primary HIV-1 isolates. *Cell.* 1996;85(7):1135–1148.
8. Doranz BJ, Rucker J, Yi Y, et al. A dual-tropic primary HIV-1 isolate that uses fusin and the $\beta$-chemokine receptors CKR-5, CKR-3, and CKR-2b as fusion cofactors. *Cell.* 1996;85(7):1149–1158.
9. Deng HongKui DH, Liu R, Ellmeier W, et al. Identification of a major co-receptor for primary isolates of HIV-1.. 1996.
10. Alkhatib G, Combadiere C, Broder CC, et al. CC CKR5: a RANTES, MIP-1$\alpha$, MIP-1$\beta$ receptor as a fusion cofactor for macrophage-tropic HIV-1. *Science.* 1996;272(5270):1955–1958.
11. Liu R, Paxton WA, Choe S, et al. Homozygous defect in HIV-1 coreceptor accounts for resistance of some multiply-exposed individuals to HIV-1 infection. *Cell.* 1996;86(3):367–377.
12. Mummidi S, Ahuja SS, Gonalez E, et al. Genealogy of the CCR5 locus and chemokine system gene variants associated with altered rates of HIV-1 disease progression. *Nature medicine.* 1998;4(7):786–793.
13. Hütter G, Nowak D, Mossner M, et al. Long-term control of HIV by CCR5 Delta32/Delta32 stem-cell transplantation. *New England Journal of Medicine.* 2009;360(7):692–698.
14. Gupta RK, Peppa D, Hill AL, et al. Evidence for HIV-1 cure after CCR5$\Delta$32/$\Delta$32 allogeneic haemopoietic stem-cell transplantation 30 months post analytical treatment interruption: a case report. *The Lancet HIV.* 2020;7(5):e340–e347.
15. Hsu J, Van Besien K, Glesby MJ, et al. HIV-1 remission and possible cure in a woman after haplo-cord blood transplant. *Cell.* 2023;186(6):1115–1126.
16. Jensen BEO, Knops E, Cords L, et al. In-depth virological and immunological characterization of HIV-1 cure after CCR5$\Delta$32/$\Delta$32 allogeneic hematopoietic stem cell transplantation. *Nature medicine.* 2023;29(3):583–587.
17. Eberhard JM, Angin M, Passaes C, et al. Vulnerability to reservoir reseeding due to high immune activation after allogeneic hematopoietic stem cell transplantation in individuals with HIV-1. *Science translational medicine.* 2020;12(542):eaay9355.
18. Dickter JK, Aribi A, Cardoso AA. HIV-1 remission after allogeneic hematopoietic-cell transplantation. *The New England journal of medicine.* 2024;390(7):669.
19. Xu L, Wang J, Liu Y, et al. CRISPR-edited stem cells in a patient with HIV and acute lymphocytic leukemia. *New England Journal of Medicine.* 2019;381(13):1240–1247.
20. OBrien SJ. Legacy of a magic gene—CCR5- 32: From discovery to clinical benefit in a generation. *Proceedings of the National Academy of Sciences.* 2024;121(12):e2321907121.
21. Copelan EA. Hematopoietic stem-cell transplantation. *New England Journal of Medicine.* 2006;354(17):1813–1826.
22. Merzoni J, Ewald GM, Paz AA, Daudt LE, Jobim LFJ. Quantification of mixed chimerism allows early therapeutic interventions. *Revista Brasileira de Hematologia e Hemoterapia.* 2014;36(5):369–372.
23. Locatelli F, Lucarelli B, Merli P. Current and future approaches to treat graft failure after allogeneic hematopoietic stem cell transplantation. *Expert opinion on pharmacotherapy.* 2014;15(1):23–36.
24. Ozdemir ZN, Bozdağ SC. Graft failure after allogeneic hematopoietic stem cell transplantation. *Transfusion and apheresis science.* 2018;57(2):163–167.
25. Bonhoeffer S, May RM, Shaw GM, Nowak MA. Virus dynamics and drug therapy. *Proceedings of the National Academy of Sciences.* 1997;94(13):6971–6976.
26. Nakaoka S, Aihara K. Mathematical study on kinetics of hematopoietic stem cells–theoretical conditions for successful transplantation. *Journal of Biological Dynamics.* 2012;6(2):836–854.
27. Precup R, Erban MA, Trif D. Asymptotic stability for cell dynamics after bone marrow transplantation. 2013.
28. Hill AL, Rosenbloom DI, Fu F, Nowak MA, Siliciano RF. Corrections: Predicting the outcomes of treatment to eradicate the latent reservoir for HIV-1 (Proc Natl Acad Sci USA (2014) 111,(13475-13480. *Proceedings of the National Academy of Sciences of the United States of America.* 2014;111(43):15598.
29. Kallel-Jallouli S, Alaziz SN. A compressive mathematical model including an eclipse stage of infected cells to study the impact of stem cells transplantation on one HIV1 patient. *Network Modeling Analysis in Health Informatics and Bioinformatics.* 2021;10(1):9.
30. Alqudah MA, Aljahdaly NH. Global stability and numerical simulation of a mathematical model of stem cells therapy of HIV-1 infection. *Journal of Computational Science.* 2020;45:101176.
31. Short S, Lewik G, Issa F. An immune atlas of T cells in transplant rejection: pathways and therapeutic opportunities. *Transplantation.* 2023;107(11):2341–2352.
32. Hale J, Lunel SV. *An Introduction to Functional Differential Equations*. An Introduction to Functional Differential Equations, 1993.
33. Driessche V. dP, Watmough J. Reproduction numbers and sub-threshold endemic equilibria for compartmental models of disease transmission. *Mathematical biosciences.* 2002;180(1-2):29–48.
34. DeJesus EX, Kaufman C. Routh-Hurwitz criterion in the examination of eigenvalues of a system of nonlinear ordinary differential equations. *Physical Review A.* 1987;35(12):5288.
35. Castillo-Chavez C, Feng Z, Huang W. On the Computation of R(o) and Its Role on Global Stability. In: 2001.
36. Castillo-Chavez C, Song B. Dynamical models of tuberculosis and their applications. *Mathematical Biosciences & Engineering.* 2004;1(2):361–404.
37. Liu WM. Criterion of Hopf bifurcations without using eigenvalues. *Journal of Mathematical Analysis and Applications.* 1994;182(1):250–256.
38. Lou J, Ruggeri T, Ma Z. Cycles and chaotic behavior in an AIDS-related cancer dynamic model in vivo. *Journal of Biological Systems.* 2007;15(02):149–168.

## SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.