



Modeling Antiretroviral Treatment to Mitigate HIV in the Brain: Impact of the Blood-Brain Barrier

Colin T. Barker¹ · Feng-Bin Wang^{2,3,4} · Naveen K. Vaidya^{5,6,7} 

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Abstract

Current research in Human Immunodeficiency Virus (HIV) focuses on eradicating virus reservoirs that prevent or dampen the effectiveness of antiretroviral treatment (ART). One such reservoir, the brain, reduces treatment efficacy via the blood-brain barrier (BBB), causing an obstacle to drug penetration into the brain. In this study, we develop a mathematical model to examine the impact of the BBB on ART effectiveness for mitigating brain HIV. A thorough analysis of the model allowed us to fully characterize the global threshold dynamics with the viral clearance and persistence in the brain for the basic reproduction number less than unity and greater than unity, respectively. Our model showed that the BBB has a significant role in inhibiting the effect of ART within the brain despite the effective viral load suppression in the plasma. The level of impact, however, depends on factors such as the CNS Penetration Effectiveness (CPE) score, the slope of the drug dose-response curves, the ART initiation timing, and the number of drugs in the ART protocol. These results suggest that reducing the plasma viral load to undetectable levels due to some drug regimen may not necessarily indicate undetectable levels of HIV in the brain. Thus, the effect of the BBB on viral suppression in the brain must be considered for developing proper treatment protocols against HIV infection.

✉ Naveen K. Vaidya
nvaidya@sdsu.edu

¹ Department of Mathematics and Computer Science, Drury University, Missouri, USA

² Department of Natural Science in the Center for General Education, Chang Gung University, Taoyuan 333, Guishan, Taiwan

³ Community Medicine Research Center, Chang Gung Memorial Hospital, Keelung 204, Keelung Branch, Taiwan

⁴ National Center for Theoretical Sciences, National Taiwan University, Taipei 106, Taiwan

⁵ Department of Mathematics and Statistics, San Diego State University, California, San Diego, USA

⁶ Computational Science Research Center, San Diego State University, California, San Diego, USA

⁷ Viral Information Institute, San Diego State University, California, San Diego, USA

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1 Introduction

Human Immunodeficiency Virus (HIV) represents one of the most serious global health issues, with approximately 36.7 million people currently living with HIV, a number that grows by roughly 1.5 million per year (United Nations Programme 2019). Despite impressive strides in antiretroviral therapy (ART), there is no known cure for HIV. Several obstacles are yet to be overcome in this ongoing search for an HIV cure. For instance, the establishment of physiological virus reservoirs, such as the brain, gut, liver, and reproductive organs (Abreu et al. 2019; Fois and Brew 2015; Gray et al. 2014; Hellmuth et al. 2015; Nath 2015), and infected cells not immediately proliferating free virions, whether they are long-lived or latently infected, all contribute significant hurdles to a cure for HIV.

The brain, in particular, may act as the viral reservoir, and viral replication within it may contribute to viral rebound within the plasma (Ash et al. 2021; Bates and Watts 1988; Beguelin et al. 2016; Kincer et al. 2023; Osborne et al. 2020) upon cessation of treatment. In addition, HIV establishment in the brain has been shown to lead to HIV-associated neurocognitive disorders (HAND), such as dementia and early-onset encephalitis (Pauza 1988). Thus, while each reservoir type deserves considerable attention, there is an urgency to develop ART protocols to mitigate HIV in the brain.

HIV can enter the brain by crossing the Blood-Brain Barrier (BBB) via infected macrophages, even during early infection (Clements et al. 2022; Fois and Brew 2015; Koppensteiner et al. 2012; Pauza 1988; Strazielle et al. 2016). Notably, the BBB affects the permeability of drugs into the brain, as measured by Letendre (2011) in terms of a CNS Penetration Effectiveness (CPE) score. We note that the other viral reservoirs may also express suboptimal drug penetration (Kepler and Perelson 1998). However, there is a lack of a numerical penetration measure, and we did not consider other reservoirs in this study. The smaller proportion of drugs in the brain may allow ongoing viral replication despite undetectable viral loads in the plasma. Moreover, the efficacy of an ART drug depends on its pharmacodynamics, and some drugs have an efficacy as low as 68% (Louie et al. 2003). Furthermore, these pharmacodynamics play a significant role in the evolution of HIV (Rosenbloom 2012). Therefore, the CPE score, as well as the efficacy of HIV drugs, must be taken into account to develop proper treatment protocols for HIV control in the brain.

Mathematical models have offered insights into the viral dynamics in the brain (Huang et al. 2017; Roda et al. 2017) and the latent reservoirs (Callaway and Perelson 2002; Stafford et al. 2000; Vaidya et al. 2010; Vaidya and Rong 2017). However, limited research exists on the effect of ART on mitigating HIV in the brain and the role of BBB on treatment effectiveness. In this study, we develop a mathematical model to analyze the role of BBB on the overall treatment effectiveness for HIV in the brain. We consider various potential ARTs by altering key drug parameters, such as the CPE score, the slope of the dose-response curve, and the treatment initiation time. We also thoroughly analyze the model to establish the local and global properties of the HIV infection dynamics in the brain. Our study identifies thresholds for the stability of

infection dynamics and highlights the critical role of the BBB on the optimal outcome of the treatment protocols.

2 Model

2.1 Model Development

In our model, we consider six mutually exclusive cell compartments: uninfected CD4+ T cells in the plasma (T), uninfected macrophages in the plasma (M), uninfected macrophages in the brain (M_B), often called microglia, infected CD4+ T cells in the plasma (T^*), infected macrophages in the plasma (M^*), and infected macrophages in the brain (M_B^*). In addition, we consider two viral compartments, V and V_B , representing the concentration of free virions in the plasma and the brain, respectively. We describe the viral dynamics using the following differential equations, and a schematic diagram of the model is presented in Fig. 1.

$$\begin{aligned}
 \frac{dT}{dt} &= \lambda - \prod_{i=1}^n (1 - \varepsilon_i) \beta VT - dT, \\
 \frac{dT^*}{dt} &= \prod_{i=1}^n (1 - \varepsilon_i) \beta VT - \delta T^*, \\
 \frac{dM}{dt} &= \lambda_M - \prod_{i=1}^n (1 - \varepsilon_i) \beta_M VM - \varphi M + \psi M_B - d_M M, \\
 \frac{dM^*}{dt} &= \prod_{i=1}^n (1 - \varepsilon_i) \beta_M VM + \psi M_B^* - \varphi M^* - \delta_M M^*, \\
 \frac{dM_B}{dt} &= \varphi M - \psi M_B - \prod_{i=1}^n (1 - \varepsilon_{\pi i}) \beta_M V_B M_B - d_M M_B, \\
 \frac{dM_B^*}{dt} &= \prod_{i=1}^n (1 - \varepsilon_{\pi i}) \beta_M V_B M_B - \psi M_B^* + \varphi M^* - \delta_M M_B^*, \\
 \frac{dV}{dt} &= \prod_{i=1}^n (1 - \varepsilon_{PIi}) p T^* + \prod_{i=1}^n (1 - \varepsilon_{PIi}) p_M M^* - cV, \\
 \frac{dV_B}{dt} &= \prod_{i=1}^n (1 - \varepsilon_{\pi PIi}) p_M M_B^* - cV_B.
 \end{aligned} \tag{1}$$

Basic Viral Dynamics in the brain and in the plasma. Uninfected T cells die at a constant rate d and are generated at a rate λ . Uninfected T cells (T) are infected (T^*) by free virions, V , within the circulation at a rate β . The infected cells then die at a rate δ . Infected cells produce viruses and release them into circulation at a rate p per infected cell per day (Vaidya et al. 2016). Similarly, HIV-1 infects uninfected macrophages (M) (Clements et al. 2022; Koppensteiner et al. 2012) at a rate β_M . The infected macrophages (M^*) produce free virions at a rate p_M per infected cell per day and die at a rate of δ_M . Uninfected macrophages die at a rate of d_M and are generated at a rate λ_M . In order for a virion to enter the cerebrospinal fluid (CSF)

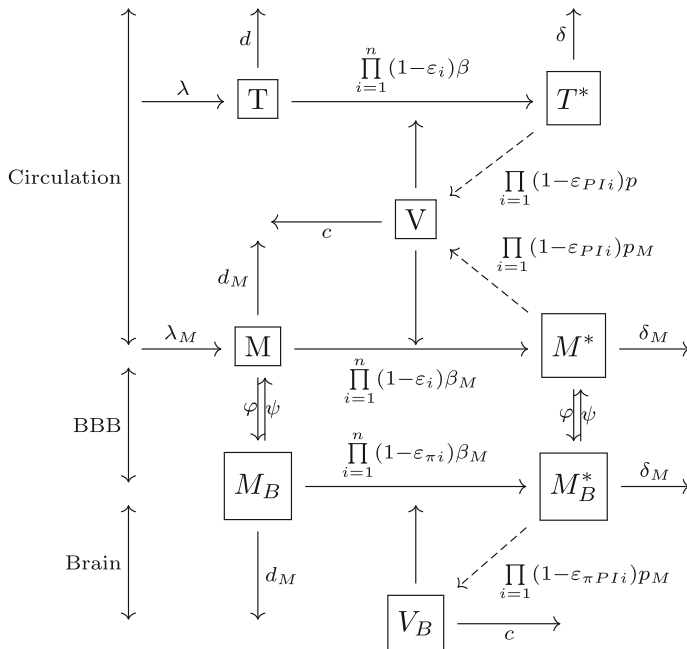


Fig. 1 Schematics of the model for HIV dynamics in the brain under antiretroviral treatment

in the brain, it must pass through the BBB. It is not fully understood what factors modulate the transit of HIV-1 RNA through the BBB into the CNS (Hellmuth et al. 2015); however, research suggests that the virus permeates the integrity of the BBB via an infected macrophage (Koppensteiner et al. 2012). We represent the per capita rate of macrophage transit through the BBB by φ . Macrophages are not known to generate independently within the brain (Prinz and Priller 2014). The uninfected brain macrophages are infected (Bednar et al. 2015; Nath 2015; Prinz and Priller 2014; Schnell et al. 2011) at the constant rate β_M , and infected macrophages produce free virions within the brain at the constant rate p_M . The free virions V and V_B die at the per capita clearance rate c . Macrophages exit the brain through the BBB into the bloodstream at a constant rate ψ . All the basic parameter values are given in Table 1.

Antiretroviral treatment. Currently, there are five classes of available ART drugs: Fusion Inhibitors (FIs), Nucleoside reverse transcriptase inhibitors (NRTIs), Non-nucleoside reverse transcriptase inhibitors (NNRTIs), Integrase inhibitors (IIs), and Protease inhibitors (PIs) (CDC 2019). The efficacy of each drug, ε , can be calculated by the formula (Vaidya and Rong 2017):

$$\varepsilon = 1 - \left(\frac{1}{1 + \left(\frac{D}{ED_{50}} \right)^m} \right),$$

Table 1 Basic model parameters. All the parameter values correspond to the per ml unit

Name	Symbol	Value	Source
<i>Initial Values</i>			
Initial uninfected T-cells	T_0	38700	Vaidya et al. (2010)
Initial infected T-cells	T_0^*	0	Kumar et al. (2004)
Initial uninfected plasma Macrophages	M_0	1463000	Haney (1981)
Initial infected plasma Macrophages	M_0^*	0	Kumar et al. (2004)
Initial uninfected CSF Macrophages	M_{B0}	20000	Haney (1981)
Initial infected CSF Macrophages	M_{B0}^*	0	Kumar et al. (2004)
Initial plasma free Virions	V_0	200 vRNA	Kumar et al. (2004)
Initial CSF free Virions	V_{B0}	0	Kumar et al. (2004)
<i>Parameter Values</i>			
Death rate for uninfected T-cells	d	0.01 (day ⁻¹)	Stafford et al. (2000)
Death rate for uninfected Macrophages	d_M	0.00185 (day ⁻¹)	Prinz and Priller (2014)
Recruitment rate for T-cells	λ	387 (day ⁻¹)	Calculated
Recruitment rate for Macrophages	λ_M	2743.55 (day ⁻¹)	Calculated
Viral production from infected T-cells	p	50000 (vRNA day ⁻¹ cell ⁻¹)	Chen (2007)
Viral production from infected macrophages	p_M	1000 (vRNA day ⁻¹ cell ⁻¹)	Schwartz et al. (2018)
Viral clearance rate	c	23 (day ⁻¹)	Ramratnam et al. (1999)
T-cell infection rate	β	3.5830E-8 (vRNA ⁻¹ day ⁻¹)	Barker and Vaidya (2020)
Death rate for infected T-cells	δ	1.4551 (day ⁻¹)	Barker and Vaidya (2020)
Macrophage infection rate	β_M	8.653E-10 (vRNA ⁻¹ day ⁻¹)	Barker and Vaidya (2020)
Death rate for infected macrophages	δ_M	0.2060 (day ⁻¹)	Barker and Vaidya (2020)
Rate of macrophage entry into the brain	φ	0.03876 (day ⁻¹)	Barker and Vaidya (2020)
Rate of macrophage exit from the brain	ψ	8.9953 (day ⁻¹)	Barker and Vaidya (2020)

where m is Hill's coefficient, D is the amount of drug concentration present, and ED_{50} represents the concentration of drugs required to obtain 50% of the maximal effect. Note that Hill's coefficient provides the slope of the dose-response curve of a given drug. The PIs reduce the viral production rates p and p_M to $(1 - \varepsilon_{PIi})p$ and $(1 - \varepsilon_{PIi})p_M$, respectively, and drugs from other classes reduce the infection rates β and β_M to $(1 - \varepsilon_i)\beta$ and $(1 - \varepsilon_i)\beta_M$, respectively. Note that integrase inhibitors (IIs) prevent viral-bearing cells from becoming productively infected due to inhibiting viral DNA integration into host DNA. This process has been modeled using a parameter governing integration by von Kleist et al. (2010). Since we have not included a detailed integration process with pre and post proviral integration, we did not require such a separate parameter in our model.

When multiple drugs are used in treatment, we assume no drug-drug interactions, a so-called 'bliss independence' approach, and the residual infection or production can be modeled by the product of residuals of drugs in combination protocol. Therefore, for FIs, IIs, and RTIs, the infection rates are reduced to $\prod_{i=1}^n (1 - \varepsilon_i)\beta$ and $\prod_{i=1}^n (1 - \varepsilon_i)\beta_M$, and for PIs the viral production rates are reduced to $\prod_{i=1}^n (1 - \varepsilon_{PIi})p$ and $\prod_{i=1}^n (1 - \varepsilon_{PIi})p_M$, where n represents the number of drugs used in the treatment protocol.

Role of blood brain barrier. The BBB reduces the effectiveness of ART drugs by limiting the amount of concentration in the CSF. A study by Letendre (2011) examined the viral loads in the CSF in the presence of ART drugs and developed a standard measure (CNS penetration effectiveness score, or CPE-score) for the effectiveness of an ART drug in entering the brain. This study utilizes several techniques to gain a qualitative measurement. We note that there are some drug-binding proteins in the blood plasma limiting the total drug effect (Boffito 2003), which are not present in the CSF. Letendre et al. have not included this potential effect (Letendre 2011). However, the study by Letendre (2011) offers a comparative measure of several drugs' effectiveness within the CSF, which we take as a proxy.

Based on the CPE score provided by Letendre (2011), we construct the parameter π to represent the reduced fraction of drugs that enter the brain as follows.

$$\pi = \frac{\text{CPE Score}}{5},$$

where the CPE score (or CNS penetration effectiveness score) ranges from one to four. In the study by Letendre (2011), drugs with a CPE score of one represent minimal CNS penetration, and a CPE score of four represents maximal CNS penetration. However, the perfect penetration is less likely due to the nature of BBB, so we take 5 to scale perfect penetration for the computation purpose. Specifically, for drugs crossing the BBB, we have the following efficacy of the drugs against HIV in the brains:

$$\varepsilon_{\pi} = 1 - \left(\frac{1}{1 + \left(\frac{\pi D}{E D_{50}} \right)^m} \right).$$

Here a lower CPE score implies a lower concentration of the ART drug in the CSF. For our purposes, we consider a score of five to mean that a drug maintains equal effectiveness in the brain as it does in the plasma. Similarly, a minimum score of zero implies that the drug cannot penetrate through the BBB at all.

3 Model Analysis

For ease of notation we now define the following variables:

$$\begin{aligned} \Phi_b &= \prod_{i=1}^n (1 - \varepsilon_i), & \Phi_p &= \prod_{i=1}^n (1 - \varepsilon_{PIi}), \text{ and} \\ \Phi_{\pi b} &= \prod_{i=1}^n (1 - \varepsilon_{\pi i}), & \Phi_{\pi p} &= \prod_{i=1}^n (1 - \varepsilon_{\pi PIi}). \end{aligned}$$

3.1 Model Feasibility

In view of (Smith 1996, Theorem 5.2.1), it follows that for any

$$(T_0, T_0^*, M_0, M_0^*, M_{B0}, M_{B0}^*, V_0, V_{B0}) \in \mathbb{R}_+^8,$$

system (1) has a unique local nonnegative solution

$$(T(t), T^*(t), M(t), M^*(t), M_B(t), M_B^*(t), V(t), V_B(t)) \in \mathbb{R}_+^8$$

through the initial value:

$$\begin{aligned} &(T(0), T^*(0), M(0), M^*(0), M_B(0), M_B^*(0), V(0), V_B(0)) \\ &= (T_0, T_0^*, M_0, M_0^*, M_{B0}, M_{B0}^*, V_0, V_{B0}). \end{aligned}$$

Substituting

$$N(t) = T(t) + T^*(t) + M(t) + M^*(t) + M_B(t) + M_B^*(t) \quad (2)$$

into system (1) leads to the following inequality

$$\frac{dN}{dt} = \lambda - (dT + \delta T^*) + \lambda_M - d_M(M + M_B) - \delta_M(M^* + M_B^*)$$

$$\begin{aligned} &\leq \lambda + \lambda_M - d_{\min}(T + T^* + M + M^* + M_B + M_B^*) \\ &= \lambda + \lambda_M - d_{\min}N, \end{aligned}$$

where $d_{\min} := \min\{d, \delta, d_M, \delta_M\}$, and hence,

$$\limsup_{t \rightarrow \infty} N(t) \leq \frac{\lambda + \lambda_M}{d_{\min}}. \quad (3)$$

This implies that $N(t)$ is ultimately bounded. Then from (2), $T(t)$, $T^*(t)$, $M(t)$, $M^*(t)$, $M_B(t)$ and $M_B^*(t)$ are ultimately bounded due to the positivity of solutions. Then there exist $t_0 > 0$ and $\Lambda > 0$ such that

$$\Phi_p p T^*(t) + \Phi_p p_M M^*(t) \leq \Lambda \text{ and } \Phi_{\pi p} p_M M_B^*(t) \leq \Lambda, \quad \forall t \geq t_0.$$

From the seventh and eighth equations of (1), we see that

$$\frac{dV}{dt} \leq \Lambda - cV, \quad \forall t \geq t_0,$$

and

$$\frac{dV_B}{dt} \leq \Lambda - cV_B, \quad \forall t \geq t_0.$$

Thus,

$$\limsup_{t \rightarrow \infty} V(t) \leq \frac{\Lambda}{c}, \text{ and } \limsup_{t \rightarrow \infty} V_B(t) \leq \frac{\Lambda}{c}, \quad (4)$$

showing that $V(t)$ and $V_B(t)$ are ultimately bounded.

From the above discussion and Theorem 3.4.8 in Hale (1990), we have the following result:

Theorem 1 $\mathbb{R}_+^8$ is positively invariant for system (1) and system (1) admits a unique and bounded solution with the initial value in $\mathbb{R}_+^8$. Further, system (1) admits a connected global attractor on $\mathbb{R}_+^8$, which attracts all positive orbits in $\mathbb{R}_+^8$.

3.2 Basic Reproduction Number

We first determine the infection-free equilibrium, E_0 , of system (1). To this end, we substitute $T^* = M^* = M_B^* = 0$ into system (1), and we have $V = V_B = 0$. Furthermore, we arrive at the following systems:

$$\frac{dT}{dt} = \lambda - dT, \quad (5)$$

and

$$\begin{cases} \frac{dM}{dt} = \lambda_M - (\varphi + d_M)M + \psi M_B, \\ \frac{dM_B}{dt} = \varphi M - (\psi + d_M)M_B. \end{cases} \quad (6)$$

It is easy to see that system (5) admits a unique positive equilibrium $\hat{T} := \frac{\lambda}{d}$, which is globally attractive in $\mathbb{R}_+$. We also see that

$$(\hat{M}, \hat{M}_B) = \left(\frac{\lambda_M a}{d_M}, \frac{\lambda_M (1-a)}{d_M} \right) \quad (7)$$

is the unique positive equilibrium of system (6), where $a = \frac{\psi + d_M}{\varphi + \psi + d_M}$. Since system (6) is cooperative (see, e.g., Smith (1996)) and it admits a unique positive equilibrium $(\hat{M}, \hat{M}_B)$, we can show the global stability of $(\hat{M}, \hat{M}_B)$ (see, e.g., Ji-Fa (1994)). The following results are concerned with the dynamics of systems (5) and (6).

Lemma 2 *The following statements are valid.*

- (i) System (5) admits a unique positive equilibrium $\hat{T} := \frac{\lambda}{d}$, which is globally attractive in $\mathbb{R}_+$;
- (ii) System (6) admits a unique positive equilibrium $(\hat{M}, \hat{M}_B)$, which is globally attractive in $\mathbb{R}_+^2$, i.e., for any $(M(0), M_B(0)) \in \mathbb{R}_+^2$, we have

$$\lim_{t \rightarrow \infty} (M(t), M_B(t)) = (\hat{M}, \hat{M}_B).$$

From the above discussions, the infection-free equilibrium of system (1) takes the form

$$E_0 = (T, T^*, M, M^*, M_B, M_B^*, V, V_B) = (\hat{T}, 0, \hat{M}, 0, \hat{M}_B, 0, 0, 0).$$

The equations for the infected cells and free virions in the plasma and the brain of the linearized system at the infection-free equilibrium, E_0 , take the form

$$\begin{cases} \frac{dT^*}{dt} = \Phi_b \beta \hat{T} V - \delta T^*, \\ \frac{dM^*}{dt} = \Phi_b \beta_M \hat{M} V + \psi M_B^* - (\varphi + \delta_M) M^*, \\ \frac{dM_B^*}{dt} = \Phi_{\pi b} \beta_M \hat{M}_B V_B + \varphi M^* - (\psi + \delta_M) M_B^*, \\ \frac{dV}{dt} = \Phi_p p T^* + \Phi_p p_M M^* - c V, \\ \frac{dV_B}{dt} = \Phi_{\pi p} p_M M_B^* - c V_B. \end{cases} \quad (8)$$

The spectral bound or the stability modulus of an $n \times n$ matrix $\mathcal{M}$, denoted by $s(\mathcal{M})$, is defined by

$$s(\mathcal{M}) := \max\{\operatorname{Re}(\lambda) : \lambda \text{ is an eigenvalue of } \mathcal{M}\}.$$

Motivated by (8), we define the following matrix:

$$J = \begin{pmatrix} -\delta & 0 & 0 & \Phi_b \beta \hat{T} & 0 \\ 0 & -(\varphi + \delta_M) & \psi & \Phi_b \beta_M \hat{M} & 0 \\ 0 & \varphi & -(\psi + \delta_M) & 0 & \Phi_{\pi b} \beta_M \hat{M}_B \\ \Phi_{pP} & \Phi_{pPM} & 0 & -c & 0 \\ 0 & 0 & \Phi_{\pi p PM} & 0 & -c \end{pmatrix}. \quad (9)$$

Clearly, J has non-negative off-diagonal elements, and J is irreducible (see a simple test on page 256 of Smith and Waltman (1995)). Then $s(J)$ is a simple eigenvalue of J with a positive eigenvector (see, e.g., (Smith and Waltman 1995, Theorem A.5)).

We now use the next generation matrix method (Van den Driessche and Watmough 2002) to compute the basic reproduction number, $\mathfrak{R}_0$. We introduce the following matrices:

$$F = \begin{pmatrix} 0 & 0 & 0 & \Phi_b \beta \hat{T} & 0 \\ 0 & 0 & 0 & \Phi_b \beta_M \hat{M} & 0 \\ 0 & 0 & 0 & 0 & \Phi_{\pi b} \beta_M \hat{M}_B \\ \Phi_{pP} & \Phi_{pPM} & 0 & 0 & 0 \\ 0 & 0 & \Phi_{\pi p PM} & 0 & 0 \end{pmatrix}, \quad (10)$$

and

$$V = \begin{pmatrix} \delta & 0 & 0 & 0 & 0 \\ 0 & \varphi + \delta_M & -\psi & 0 & 0 \\ 0 & -\varphi & \psi + \delta_M & 0 & 0 \\ 0 & 0 & 0 & c & 0 \\ 0 & 0 & 0 & 0 & c \end{pmatrix}. \quad (11)$$

Note that $J = F - V$. The basic reproduction number corresponds to the spectral radius of FV^{-1} ,

$$\mathfrak{R}_0 = \rho(FV^{-1}).$$

The following is a general result showing that the local stability of the disease-free equilibrium, E_0 , is determined by $\mathfrak{R}_0$ (see, e.g. (Van den Driessche and Watmough 2002, Theorem 2)):

Lemma 3 *The following statements hold.*

- (i) $\mathfrak{R}_0 = 1$ if and only if $s(J) = 0$;
- (ii) $\mathfrak{R}_0 > 1$ if and only if $s(J) > 0$;
- (iii) $\mathfrak{R}_0 < 1$ if and only if $s(J) < 0$.

Thus, the disease-free equilibrium E_0 is locally asymptotically stable if $\mathfrak{R}_0 < 1$, and unstable if $\mathfrak{R}_0 > 1$.

3.3 Threshold Dynamics

This subsection is devoted to studying the threshold dynamics of the system (1). Specifically, we will show that the basic reproduction number, $\mathfrak{R}_0$, is a threshold determining infection-free ($\mathfrak{R}_0 < 1$) and infection-persistent ($\mathfrak{R}_0 > 1$) dynamics. Let

$$\mathbf{X}_0 = \{(T_0, T_0^*, M_0, M_0^*, M_{B0}, M_{B0}^*, V_0, V_{B0}) \in \mathbb{R}_+^8 : T_0^* > 0, M_0^* > 0, M_{B0}^* > 0, V_0 > 0, V_{B0} > 0\},$$

and

$$\partial \mathbf{X}_0 := \mathbb{R}_+^8 \setminus \mathbf{X}_0 = \{(T_0, T_0^*, M_0, M_0^*, M_{B0}, M_{B0}^*, V_0, V_{B0}) \in \mathbb{R}_+^8 : T_0^* = 0 \text{ or } M_0^* = 0 \text{ or } M_{B0}^* = 0 \text{ or } V_0 = 0 \text{ or } V_{B0} = 0\}.$$

We first prove the following lemma.

Lemma 4 Assume that

$$(T(t), T^*(t), M(t), M^*(t), M_B(t), M_B^*(t), V(t), V_B(t))$$

is a solution of the system (1) with initial value

$$(T(0), T^*(0), M(0), M^*(0), M_B(0), M_B^*(0), V(0), V_B(0)) \in \mathbb{R}_+^8.$$

Then the following statements hold:

(i) There exists a positive constant ζ_0 such that

$$\liminf_{t \rightarrow \infty} T(t) \geq \zeta_0, \quad \liminf_{t \rightarrow \infty} M(t) \geq \zeta_0, \quad \liminf_{t \rightarrow \infty} M_B(t) \geq \zeta_0;$$

(ii) If $(T(0), T^*(0), M(0), M^*(0), M_B(0), M_B^*(0), V(0), V_B(0)) \in X_0$, then

$$T(t), T^*(t), M(t), M^*(t), M_B(t), M_B^*(t), V(t), V_B(t) \gg 0, \quad \forall t > 0.$$

Proof

Part (i): In view of equation (4) or of Theorem 1 we see that there exists a $\tilde{t}_0 > 0$ and a $\xi > 0$ such that $V(t) \leq \xi$ and $V_B(t) \leq \xi$, $\forall t \geq \tilde{t}_0$. Then it follows from the first, third, and fifth equations in system (1) that

$$\frac{dT}{dt} \geq \lambda - [\Phi_b \beta \xi + d]T, \quad \forall t \geq \tilde{t}_0,$$

and

$$\begin{cases} \frac{dM}{dt} \geq \lambda_M - [\Phi_b \beta_M \xi + \varphi + d_M]M + \psi M_B, & \forall t \geq \tilde{t}_0, \\ \frac{dM_B}{dt} \geq \varphi M - [\psi + \Phi_{\pi b} \beta_M \xi + d_M]M_B, & \forall t \geq \tilde{t}_0. \end{cases}$$

By the comparison principle, and similar arguments to those in Lemma 2, we see that

$$\liminf_{t \rightarrow \infty} T(t) \geq \frac{\lambda}{\Phi_b \beta \xi + d} \text{ and } \liminf_{t \rightarrow \infty} (M(t), M_B(t)) \geq (\underline{M}, \underline{M}_B),$$

where $(\underline{M}, \underline{M}_B)$ is the unique root of the following algebraic equation:

$$\begin{cases} \lambda_M - [\Phi_b \beta_M \xi + \varphi + d_M]M + \psi M_B = 0, \\ \varphi M - [\psi + \Phi_{\pi b} \beta_M \xi + d_M]M_B = 0. \end{cases}$$

Thus, taking $\zeta_0 = \min \left\{ \frac{\lambda}{\Phi_b \beta \xi + d}, \underline{M}, \underline{M}_B \right\}$, Part (i) is proved.

Part (ii): In view of the first equation of system (1), it follows that

$$T(t) = e^{-\int_0^t b_1(s_1) ds_1} \left[\int_0^t \lambda e^{\int_0^{s_2} b_1(s_1) ds_1} ds_2 + T(0) \right],$$

where

$$b_1(t) := d + \Phi_b \beta V(t).$$

Thus, $T(t) > 0 \forall t > 0$. From the third equation of system (1), it follows that

$$M(t) = e^{-\int_0^t b_2(s_1) ds_1} \left[\int_0^t e^{\int_0^{s_2} b_2(s_1) ds_1} a_2(s_2) ds_2 + M(0) \right],$$

where

$$a_2(t) := \lambda_M + \psi M_B(t) \geq \lambda_M,$$

and

$$b_2(t) := \Phi_b \beta_M V(t) + \varphi + d_M.$$

Thus, $M(t) > 0 \forall t > 0$. From the fifth equation of system (1), it follows that

$$M_B(t) = e^{-\int_0^t b_3(s_1) ds_1} \left[\int_0^t e^{\int_0^{s_2} b_3(s_1) ds_1} a_3(s_2) ds_2 + M_B(0) \right],$$

where

$$a_3(t) := \varphi M(t) > 0,$$

and

$$b_3(t) := \psi + \Phi_{\pi b} \beta_M V_B(t) + d_M \geq \psi + d_M.$$

Thus, $M_B(t) > 0 \forall t > 0$. Next, we regard Theorem 4.1.1 of Smith (1996) as a generalized version to nonautonomous systems, and the irreducibility of the cooperative matrix

$$\begin{pmatrix} -\delta & 0 & 0 & \Phi_b \beta T(t) & 0 \\ 0 & -(\varphi + \delta_M) & \psi & \Phi_b \beta_M M(t) & 0 \\ 0 & \varphi & -(\psi + \delta_M) & 0 & \Phi_{\pi b} \beta_M M_B(t) \\ \Phi_p p & \Phi_p p_M & 0 & -c & 0 \\ 0 & 0 & \Phi_{\pi p} p_M & 0 & -c \end{pmatrix} \quad (12)$$

implies that

$$(T^*(t), M^*(t), M_B^*(t), V(t), V_B(t)) \gg 0, \forall t > 0.$$

This completes the proof. $\square$

We now establish the following theorem for the global threshold dynamics.

Theorem 5 *The following statements hold.*

- (i) *If $\mathfrak{R}_0 < 1$, then the infection-free equilibrium E_0 is globally attractive in $\mathbb{R}_+^8$ for (1);*
- (ii) *If $\mathfrak{R}_0 > 1$, then system (1) is uniformly persistent with respect to $(\mathbf{X}_0, \partial \mathbf{X}_0)$ in the sense that there is a positive constant $\zeta > 0$ such that every solution*

$$(T(t), T^*(t), M(t), M^*(t), M_B(t), M_B^*(t), V(t), V_B(t))$$

of (1) with

$$(T(0), T^*(0), M(0), M^*(0), M_B(0), M_B^*(0), V(0), V_B(0)) \in \mathbf{X}_0$$

satisfies

$$\liminf_{t \rightarrow \infty} u(t) \geq \zeta, \text{ for each } u = T, T^*, M, M^*, M_B, M_B^*, V, V_B. \quad (13)$$

Furthermore, system (1) admits at least one (componentwise) positive equilibrium.

Proof Part (i). Assume that $\mathfrak{R}_0 < 1$. It then follows from Lemma 3 (iii) that $s(J) < 0$. Thus, there exists a sufficiently small positive number ρ_0 such that $s(J_{\rho_0}) < 0$ (see,

e.g., (Kato 2013, Section II.5.8)), where

$$J_{\rho_0} = \begin{pmatrix} -\delta & 0 & 0 & \Phi_b \beta(\hat{T} + \rho_0) & 0 \\ 0 & -(\varphi + \delta_M) & \psi & \Phi_b \beta_M(\hat{M} + \rho_0) & 0 \\ 0 & \varphi & -(\psi + \delta_M) & 0 & \Phi_{\pi b} \beta_M(\hat{M}_B + \rho_0) \\ \Phi_p p & \Phi_p p_M & 0 & -c & 0 \\ 0 & 0 & \Phi_{\pi p} p_M & 0 & -c \end{pmatrix}$$

has non-negative off-diagonal elements, and J_{ρ_0} is irreducible. From the first, third, and fifth equations of system (1), together with positivity of solutions, it follows that

$$\frac{dT}{dt} \leq \lambda - dT, \quad (14)$$

and

$$\begin{cases} \frac{dM}{dt} \leq \lambda_M - (\varphi + d_M)M + \psi M_B, \\ \frac{dM_B}{dt} \leq \varphi M - (\psi + d_M)M_B. \end{cases} \quad (15)$$

By the comparison principle and Lemma 2, we get

$$\limsup_{t \rightarrow \infty} T(t) \leq \hat{T}, \quad \limsup_{t \rightarrow \infty} (M(t), M_B(t)) \leq (\hat{M}, \hat{M}_B).$$

It follows that there is a $t_1 > 0$ such that

$$T(t) \leq \hat{T} + \rho_0, \quad M(t) \leq \hat{M} + \rho_0, \quad M_B(t) \leq \hat{M}_B + \rho_0, \quad \forall t \geq t_1. \quad (16)$$

In view of (16) and system (1), we see that

$$\begin{cases} \frac{dT^*}{dt} \leq \Phi_b \beta(\hat{T} + \rho_0)V - \delta T^*, \quad \forall t \geq t_1, \\ \frac{dM^*}{dt} \leq \Phi_b \beta_M(\hat{M} + \rho_0)V + \psi M_B^* - (\varphi + \delta_M)M^*, \quad \forall t \geq t_1, \\ \frac{dM_B^*}{dt} \leq \Phi_{\pi b} \beta_M(\hat{M}_B + \rho_0)V_B + \varphi M^* - (\psi + \delta_M)M_B^*, \quad \forall t \geq t_1, \\ \frac{dV}{dt} = \Phi_p p T^* + \Phi_p p_M M^* - cV, \quad \forall t \geq t_1, \\ \frac{dV_B}{dt} = \Phi_{\pi p} p_M M_B^* - cV_B, \quad \forall t \geq t_1. \end{cases} \quad (17)$$

Consider the following auxiliary system

$$\begin{cases} \frac{dT^*}{dt} = \Phi_b \beta(\hat{T} + \rho_0)V - \delta T^*, \quad \forall t \geq t_1, \\ \frac{dM^*}{dt} = \Phi_b \beta_M(\hat{M} + \rho_0)V + \psi M_B^* - (\varphi + \delta_M)M^*, \quad \forall t \geq t_1, \\ \frac{dM_B^*}{dt} = \Phi_{\pi b} \beta_M(\hat{M}_B + \rho_0)V_B + \varphi M^* - (\psi + \delta_M)M_B^*, \quad \forall t \geq t_1, \\ \frac{dV}{dt} = \Phi_p p T^* + \Phi_p p_M M^* - cV, \quad \forall t \geq t_1, \\ \frac{dV_B}{dt} = \Phi_{\pi p} p_M M_B^* - cV_B, \quad \forall t \geq t_1. \end{cases}$$

(18)

Since J_{ρ_0} has non-negative off-diagonal elements and J_{ρ_0} is irreducible, it follows that $s(J_{\rho_0})$ is simple and associates a strongly positive eigenvector $\tilde{v} \in \mathbb{R}^5$ (see, e.g., (Smith and Waltman 1995, Theorem A.5)). For any solution $(T(t), T^*(t), M(t), M^*(t), M_B(t), M_B^*(t), V(t), V_B(t))$ of (1) with nonnegative initial value

$$(T(0), T^*(0), M(0), M^*(0), M_B(0), M_B^*(0), V(0), V_B(0)),$$

there is a sufficiently large $b > 0$ such that

$$(T^*(t_1), M^*(t_1), M_B^*(t_1), V(t_1), V_B(t_1)) \leq b\tilde{v}$$

holds. It is easy to see that $U(t) := be^{s(J_{\rho_0})(t-t_1)}\tilde{v}$ is a solution of (18) with $U(t_1) := b\tilde{v}$. By the comparison principle (Smith and Waltman 1995, Theorem B.1), it follows that

$$(T^*(t), M^*(t), M_B^*(t), V(t), V_B(t)) \leq be^{s(J_{\rho_0})(t-t_1)}\tilde{v}, \quad \forall t \geq t_1.$$

Since $s(J_{\rho_0}) < 0$, it follows that

$$\lim_{t \rightarrow \infty} (T^*(t), M^*(t), M_B^*(t), V(t), V_B(t)) = (0, 0, 0, 0, 0).$$

It then follows that the equations for $T(t)$ and $(M(t), M_B(t))$ in (1) are asymptotic to (5) and (6), respectively. By the theory for asymptotically autonomous semiflows (see, e.g., (Thieme 1992, Corollary 4.3)) and Lemma 2, it follows that

$$\lim_{t \rightarrow \infty} T(t) = \hat{T}, \quad \lim_{t \rightarrow \infty} (M(t), M_B(t)) = (\hat{M}, \hat{M}_B).$$

Part (i) is proved.

Part (ii). Assume that $\mathfrak{R}_0 > 1$. It then follows from Lemma 3 (ii) that $s(J) > 0$. Suppose $\Pi(t)P$ is the solution maps generated by system (1) with initial value P . By Theorem 1, we see that system $\{\Pi(t)\}_{t \geq 0}$ admits a global attractor in $\mathbb{R}_+^8$. Now we prove that $\{\Pi(t)\}_{t \geq 0}$ is uniformly persistent with respect to $(\mathbf{X}_0, \partial\mathbf{X}_0)$. By Lemma 4, it follows that both $\mathbb{R}_+^8$ and $\mathbf{X}_0$ are positively invariant. Clearly, $\partial\mathbf{X}_0$ is relatively closed in $\mathbb{R}_+^8$.

Let $M_\partial := \{P \in \partial\mathbf{X}_0 : \Pi(t)P \in \partial\mathbf{X}_0, \forall t \geq 0\}$ and $\omega(P)$ be the omega limit set of the orbit $O^+(P) := \{\Pi(t)P : t \geq 0\}$. We next prove the following claims.

Claim 1: $\omega(P) = \{E_0\}$, $\forall P \in M_\partial$.

Since $P \in M_\partial$, we have $\Pi(t)P \in M_\partial$, $\forall t \geq 0$. Next, we show that

$$(T^*(t), M^*(t), M_B^*(t), V(t), V_B(t)) = (0, 0, 0, 0, 0), \quad \forall t > 0. \quad (19)$$

Assume that (19) is not true. Then there exists $\tau_0 > 0$ such that

$$(T^*(\tau_0), M^*(\tau_0), M_B^*(\tau_0), V(\tau_0), V_B(\tau_0)) \neq (0, 0, 0, 0, 0).$$

Then the irreducibility of the cooperative matrix (12) implies that

$$(T^*(t), M^*(t), M_B^*(t), V(t), V_B(t)) \gg 0, \forall t > \tau_0,$$

which contradicts the fact that $\Pi(t)P \in M_\partial$, $\forall t \geq 0$, and hence, (19) is true. By (19), it follows that the equations for $T(t)$ and $(M(t), M_B(t))$ in (1) satisfies (5) and (6), respectively. By Lemma 2, it follows that

$$\lim_{t \rightarrow \infty} T(t) = \hat{T}, \quad \lim_{t \rightarrow \infty} (M(t), M_B(t)) = (\hat{M}, \hat{M}_B).$$

Claim 1 is proved.

Since $s(J) > 0$, there exists a sufficiently small positive number σ_0 such that $s(J_{\sigma_0}) > 0$ (see, e.g., (Kato 2013, Section II.5.8)), where

$$J_{\sigma_0} = \begin{pmatrix} -\delta & 0 & 0 & \Phi_b \beta (\hat{T} - \sigma_0) & 0 \\ 0 & -(\varphi + \delta_M) & \psi & \Phi_b \beta_M (\hat{M} - \sigma_0) & 0 \\ 0 & \varphi & -(\psi + \delta_M) & 0 & \Phi_{\pi b} \beta_M (\hat{M}_B - \sigma_0) \\ \Phi_p p & \Phi_p p_M & 0 & -c & 0 \\ 0 & 0 & \Phi_{\pi p} p_M & 0 & -c \end{pmatrix}$$

has non-negative off-diagonal elements and J_{σ_0} is irreducible.

Claim 2: E_0 is a uniform weak repeller for $\Pi(t)$ in the sense that

$$\limsup_{t \rightarrow \infty} \|\Pi(t)P - E_0\| \geq \sigma_0, \quad \forall P \in \mathbf{X}_0.$$

Suppose, by contradiction, there exists $P_0 \in \mathbf{X}_0$ such that

$$\limsup_{t \rightarrow \infty} \|\Pi(t)P_0 - E_0\| < \sigma_0.$$

Thus, there exists $t_2 > 0$ such that

$$T(t) \geq \hat{T} - \sigma_0, \quad M(t) \geq \hat{M} - \sigma_0, \quad M_B(t) \geq \hat{M}_B - \sigma_0, \quad \forall t \geq t_2. \quad (20)$$

In view of (20) and system (1), we see that

$$\begin{cases} \frac{dT^*}{dt} \geq \Phi_b \beta (\hat{T} - \sigma_0) V - \delta T^*, \quad \forall t \geq t_2, \\ \frac{dM^*}{dt} \geq \Phi_b \beta_M (\hat{M} - \sigma_0) V + \psi M_B^* - (\varphi + \delta_M) M^*, \quad \forall t \geq t_2, \\ \frac{dM_B^*}{dt} \geq \Phi_{\pi b} \beta_M (\hat{M}_B - \sigma_0) V_B + \varphi M^* - (\psi + \delta_M) M_B^*, \quad \forall t \geq t_2, \\ \frac{dV}{dt} = \Phi_p p T^* + \Phi_p p_M M^* - c V, \quad \forall t \geq t_2, \\ \frac{dV_B}{dt} = \Phi_{\pi p} p_M M_B^* - c V_B, \quad \forall t \geq t_2. \end{cases} \quad (21)$$

Consider the following auxiliary system

$$\begin{cases} \frac{dT^*}{dt} = \Phi_b \beta (\hat{T} - \sigma_0) V - \delta T^*, \quad \forall t \geq t_2, \\ \frac{dM^*}{dt} = \Phi_b \beta_M (\hat{M} - \sigma_0) V + \psi M_B^* - (\varphi + \delta_M) M^*, \quad \forall t \geq t_2, \\ \frac{dM_B^*}{dt} = \Phi_{\pi b} \beta_M (\hat{M}_B - \sigma_0) V_B + \varphi M^* - (\psi + \delta_M) M_B^*, \quad \forall t \geq t_2, \\ \frac{dV}{dt} = \Phi_p p T^* + \Phi_p p_M M^* - c V, \quad \forall t \geq t_2, \\ \frac{dV_B}{dt} = \Phi_{\pi p} p_M M_B^* - c V_B, \quad \forall t \geq t_2. \end{cases} \quad (22)$$

Since J_{σ_0} is irreducible and has non-negative off-diagonal elements, it follows that $s(J_{\sigma_0})$ is simple and associates a strongly positive eigenvector $\tilde{u} \in \mathbb{R}^5$ (see, e.g., (Smith and Waltman 1995, Theorem A.5)). By Lemma 4, it follows that

$$(T^*(t_2), M^*(t_2), M_B^*(t_2), V(t_2), V_B(t_2)) \gg 0.$$

Thus, there is a positive number $\varsigma > 0$ such that

$$(T^*(t_2), M^*(t_2), M_B^*(t_2), V(t_2), V_B(t_2)) \geq \varsigma \tilde{u}$$

holds. It is easy to see that $W(t) := \varsigma e^{s(J_{\sigma_0})(t-t_2)} \tilde{u}$ is a solution of (22) with $W(t_2) := \varsigma \tilde{u}$. By the comparison principle (Smith and Waltman 1995, Theorem B.1), it follows that

$$(T^*(t), M^*(t), M_B^*(t), V(t), V_B(t)) \geq \varsigma e^{s(J_{\sigma_0})(t-t_2)} \tilde{u}, \quad \forall t \geq t_2.$$

Since $s(J_{\sigma_0}) > 0$, it follows that

$$\lim_{t \rightarrow \infty} T^*(t) = \lim_{t \rightarrow \infty} M^*(t) = \lim_{t \rightarrow \infty} M_B^*(t) = \lim_{t \rightarrow \infty} V(t) = \lim_{t \rightarrow \infty} V_B(t) = \infty.$$

This contradiction proves the claim 2.

From the above claims, it follows that any forward orbit of $\Pi(t)$ in M_∂ converges to E_0 which is isolated in $\mathbb{R}_+^8$ and $W^s(E_0) \cap \mathbf{X}_0 = \emptyset$, where $W^s(E_0)$ is the stable set of E_0 (see Smith and Zhao (2001)). It is obvious that there is no cycle in M_∂ from E_0 to E_0 . By (Thieme 1993, Theorem 4.6) (see also (Zhao et al. 2003, Theorem 1.3.1) and (Hirsch et al. 2001, Theorem 4.3 and Remark 4.3)), we conclude that system (1) is uniformly persistent with respect to $(\mathbf{X}_0, \partial \mathbf{X}_0)$ in the sense that there is a positive constant $\zeta_1 > 0$ such that

$$\liminf_{t \rightarrow \infty} u(t) \geq \zeta_1, \quad \forall u = T^*, M^*, M_B^*, V, V_B.$$

From Lemma 4 (i), we let $\zeta := \min\{\zeta_0, \zeta_1\} > 0$. Then it is easy to see that (13) holds.

By (Zhao 1995, Theorem 2.4) (see also (Zhao et al. 2003, Theorem 1.3.7)), system (1) has at least one equilibrium

$$(\check{T}, \check{T}^*, \check{M}, \check{M}^*, \check{M}_B, \check{M}_B^*, \check{V}, \check{V}_B) \in \mathbf{X}_0,$$

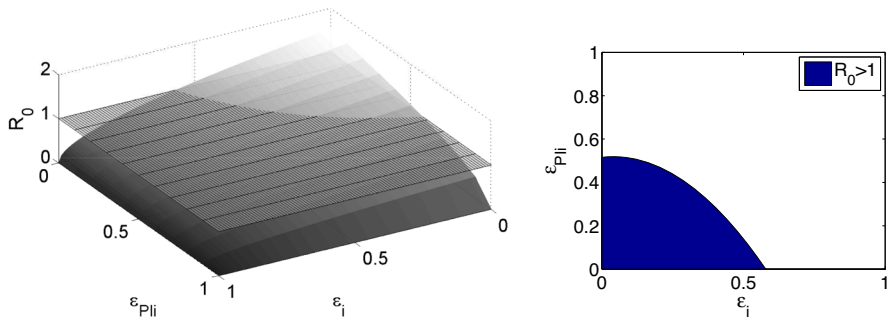


Fig. 2 (Left) The reproduction number $\mathfrak{R}_0$ depending on the effectiveness of PIs (x -axis) and RTIs (y -axis). The horizontal plane represents when $\mathfrak{R}_0 = 1$. (Right) The region in $\varepsilon_i \varepsilon_{PIi}$ -space for $\mathfrak{R}_0 < 1$ and $\mathfrak{R}_0 > 1$

and hence, $\check{T}^* > 0$, $\check{M}^* > 0$, $\check{M}_B^* > 0$, $\check{V} > 0$, and $\check{V}_B > 0$. Furthermore, we see that

$$\check{T} = \frac{\lambda}{\Phi_b \beta \check{V} + d},$$

and $(\check{M}, \check{M}_B)$ satisfies

$$\begin{cases} \lambda_M - \Phi_b \beta_M \check{V} M - \varphi M + \psi M_B - d_M M = 0, \\ \varphi M - \psi M_B - \Phi_{\pi b} \beta_M \check{V}_B M_B - d_M M_B = 0, \end{cases} \quad (23)$$

From (23), it is not hard to see that $\check{M} > 0$ and $\check{M}_B > 0$. Thus,

$$(\check{T}, \check{T}^*, \check{M}, \check{M}^*, \check{M}_B, \check{M}_B^*, \check{V}, \check{V}_B)$$

is a (componentwise) positive equilibrium of system (1). This completes the proof of Part (ii). $\square$

Theorem 5 indicates that the basic reproduction number, $\mathfrak{R}_0$, is a critical threshold, which allows us to determine whether the infection is avoided ($\mathfrak{R}_0 < 1$) or persists ($\mathfrak{R}_0 > 1$) in the brain. As the threshold, $\mathfrak{R}_0$, is the function of control parameters, such as pre-exposure prophylaxis, the established threshold condition allows us to identify the strength of such treatment required to avoid the infection. In Fig. 2, we present how the value of $\mathfrak{R}_0$ changes based on the drug efficacies ε_i and ε_{PIi} . Moreover, we also identified the region in $\varepsilon_i \varepsilon_{PIi}$ -space, in which $\mathfrak{R}_0 < 1$, asserting the infection control threshold.

4 Numerical Simulations

In this section, we present the numerical simulations of the plasma viral load (PVL) and the brain viral load (BVL) under different treatment protocols. Consistent with the

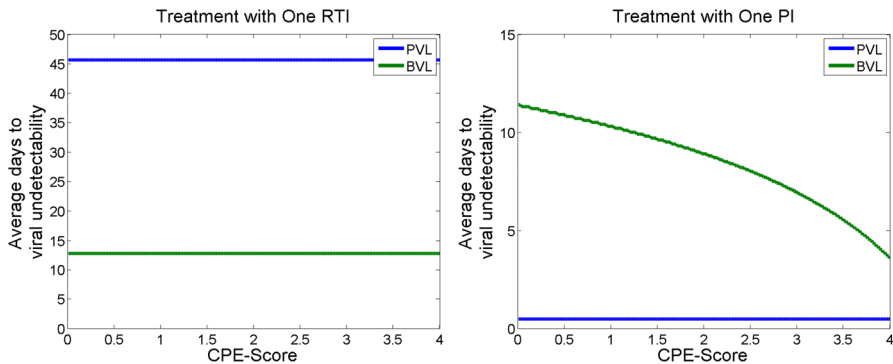


Fig. 3 The average time the viral loads in the plasma (blue) and the brain (green) become undetectable depending on the mean CPE score of the ART regimen with either a single RTI (left) or PI (right) (Color figure online)

analytical result established in Theorem 5, we observed that our numerical simulations of viral loads dynamics converge to the infection-free steady state or infected steady state depending upon the choice of drug efficacies from the white ($\mathfrak{R}_0 < 1$) or blue ($\mathfrak{R}_0 > 1$) regions, respectively, shown in Fig. 2 (right). Since there is no known cure for HIV rather than viral elimination, an undetectable viral load is a marked success for current treatment protocols. Therefore, we take the time for the viral load to be undetectable as the index for the treatment evaluation. For all simulations, we consider a detectable viral load to be 50 copies of viral RNA per mL of blood plasma, the standard lower limit to measure HIV according to current assays (aidsinfo 2018).

We consider how the different protocols affect the time the viral loads take to reach undetectable levels. We first examine whether the CPE score alters the treatment time for the viral load to become undetectable in the plasma and the brain. Next, we explore how the slope of the dose-response curve affects the time for viral undetectability. Then, we analyze the effect of the number of drugs in a given ART regimen. Finally, we examine if the treatment initiation time affects the average time for the PVL and BVL to fall below the detectable level.

4.1 Effect of the CPE Score

To better understand the effect of the CPE score on the overall treatment of HIV, we considered its effect on the time that the PVL and the BVL reduce to undetectable levels in the presence of constant drug levels. In Fig. 3, we show the average time the viral loads in the brain and the plasma become undetectable depending on the CPE score of an ART regimen with a single drug. Treatment was initiated after a steady state viral load was achieved (~ 250 dpi), and we considered a single RTI (Fig. 3, left) and a single PI (Fig. 3, right).

We observe that the CPE score has a negligible effect on the plasma viral load, as the average number of days for the PVL to become undetectable remains constant despite the CPE score or the drug type (RTI or PI). However, even with one drug present, we observe that the CPE score affects the number of days to viral undetectability for a PI

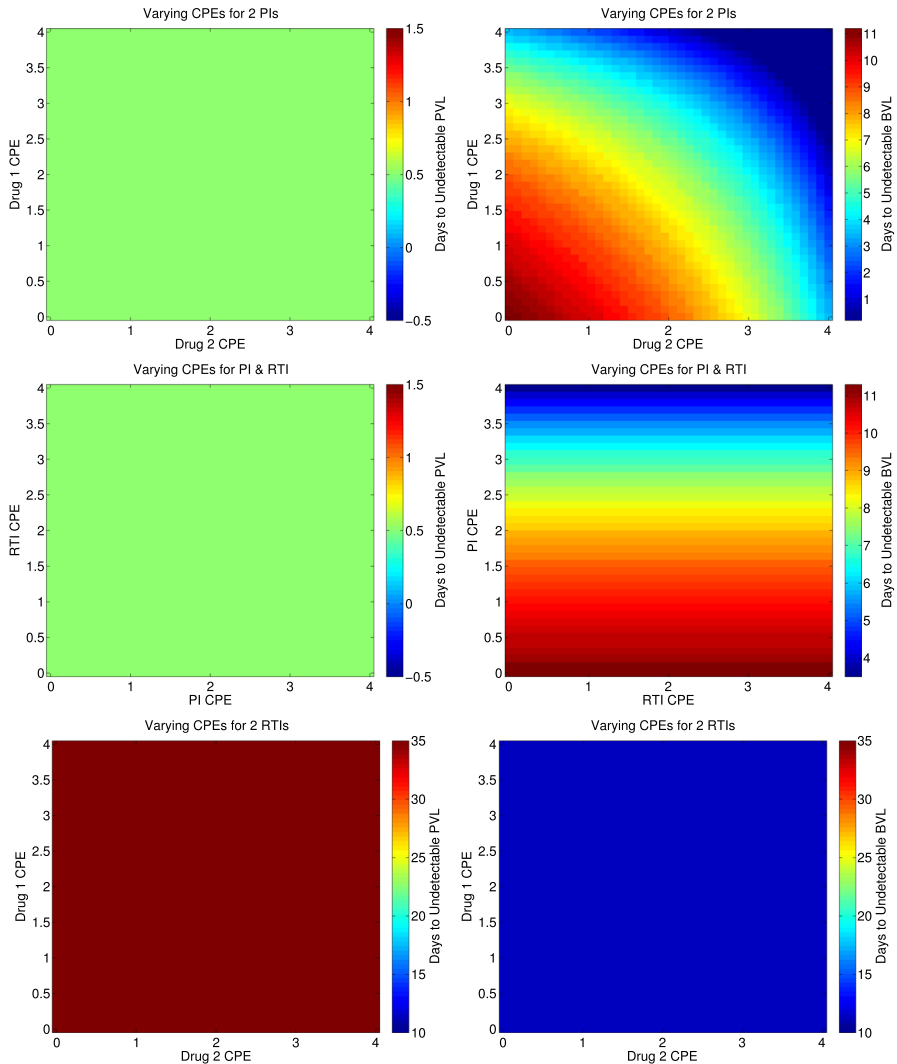


Fig. 4 Average days to viral undetectability in the PVL (left column) and BVL (right column) depending on the CPE scores for two PIs (top row), two RTIs (bottom row) and a combination of one RTI and one PI (middle row). We used different color scales for different figures as appropriate for visibility purposes

differently than it does for an RTI. In particular, as the CPE score increases for a PI, the number of days for the BVL to reach undetectable levels decreases (~ 10 days vs. ~ 3 days). There is no observed effect of the CPE score and the BVL if an ART protocol includes only a single RTI. Hence, the BBB affects single-drug protocols with PIs more than RTIs.

We next analyzed the effect of the CPE score under the ART regimen with two drugs. We considered two PIs, two RTIs, or a combination of one PI and one RTI. We present the simulated number of days to viral undetectability in the PVL (Fig. 4,

left column) and BVL (Fig. 4, right column). Similar to the treatments with a single drug, we observe no discernible effect of the CPE score on the PVL with two drugs. However, we observe a strong effect of the CPE score on the days for which the BVL becomes undetectable in the presence of two drugs. For ART with two PIs, we see that as the CPE increases for either drug, the days to viral clearance decrease (~ 9 days vs. ~ 1 day). Furthermore, if ART includes an RTI and a PI, we note that as the CPE score increases for the PI, the time to undetectable BVL decreases; however, the CPE score for the RTI shows a negligible effect on the time to the undetectability of BVL. In fact, if treatment includes only two RTIs, we do not observe any noticeable effect of the CPE score on time to viral undetectability. These results combined suggest that PIs with higher CPE scores should be considered more than RTIs to control HIV in the brain better.

4.2 Effect of the Slope of the dose-response Curve

We used our model (1) to explore the influence of the slope of the dose-response curve on the time viral RNA becomes undetectable. We first considered treatment with one drug. Based on experimental evidence (Shen 2008), we considered any drug whose slope, m , is greater than 1.9 to be a PI, while a drug with $m \leq 1.9$ is considered to be an RTI (Table 2). We present the results on time to viral undetectability with a single drug of a low CPE score (CPE = 1; Fig. 5, left) and a high CPE score (CPE = 4; Fig. 5, right) for the slope of the dose-response curve from 0 to 5. As mentioned before, the treatment was initiated after a steady-state viral load was achieved in the brain and the plasma (~ 250 dpi).

We observe that if $m \leq 1.9$ (RTI), then the PVL becomes undetectable after about only 40 days, whereas if $m > 1.9$ (PI), then the PVL reaches the undetectable level within a single day. The number of days the BVL takes to reach the undetectable level also decreases as the slope of the dose-response curve increases; however, this reduction is significantly less than that observed in the PVL (~ 40 days less in PVL compared to ~ 6 days less in BVL). Interestingly, for low slopes that correspond to an RTI, we note that the PVL becomes undetectable several weeks after the BVL becomes undetectable and that this behavior switches for the slope corresponding to a PI (Fig. 5). This switch occurs regardless of the drug's CPE score, reinforcing the previous section's observation that RTIs are less effective for the PVL.

To examine the effect of the slope of the dose-response curve further, we considered the ART regimen of two drugs, including both RTI and PI. We considered combinations of RTIs and PIs of both high and low CPE scores and computed the time to undetectability of PVL. Our simulations show that in all regimens considered, neither the BVL nor the PVL has any noticeable difference in the time to undetectability, suggesting that once multiple drugs are present in the ART regimen, the slope of the dose-response curve has less effect on the time to viral undetectability (See Supplemental Information). For ART with two drugs, even if the slopes of the dose-response curves are low, the average number of days to viral undetectability is much less than the regimen with one drug (~ 10 days in two drugs compared to ~ 40 days in one

Table 2 Parameters related to drug pharmacodynamics and CPE scores. Note that Φ_j represents the residual viral infection (production) rate for FIs, IIs, and RTIs (PIs) and $\varepsilon_j = 1 - \Phi_j$ represents the drug's efficacy

Drug Type	Drug Name	Drug Abbreviation	Drug CPE Score (according to Letendre, 2011[31])	Inhibitory Quotient (Davg/IC50)	Hill's coefficient m_i	Φ_j	ε_j
NRTI	Abacavir	ABC	3	50.9	0.95	0.023353685	0.976646315
	Didanosine	ddl	2	2.4	1.07	0.281556981	0.718443019
	Emtricitabine	FTC	3	226.9	1.18	0.001657276	0.998342724
	Lamivudine	3TC	2	101.4	1.15	0.004908169	0.995091831
	Stavudine	d4T	2	0.85	1.13	0.545782997	0.454217003
	Tenofovir	TDF	1	2.7	0.97	0.276187136	0.723812864
	Zalcitabine	ddC	1	Not included	Not included	Not calculated	not calculated
	Zidovudine	AZT	4	2.4	0.85	0.322097664	0.677902336
	Delavirdine	DLV	3	101.2	1.56	0.000744038	0.999255962
	Efavirenz	EFV	3	1042.5	1.69	7.93319E-6	0.999992067
NNRTI	Etravirine	TMC125	2	203.4	1.81	6.63523E-5	0.999933648
	Nevirapine	NVP	4	195.6	1.55	0.000280709	0.99719291
	Atazanavir	ATV	2	199.8	2.69	6.47736E-7	0.999999352
	Darunavir/r	DRV	3	410.6	3.61	3.67754E-10	1
PI	Fosamprenavir	APV	2	39.7	2.09	0.000455334	0.999544666
	Indinavir	IDV	3	60	4.53	8.80998E-9	0.9999999991
	Lopinavir/r	LPV	3	343.2	2.05	6.34053E-6	0.999993659
	Nelfinavir	NFV	1	21.5	1.81	0.003860172	0.996139828
	Saquinavir	SQV	1	120	3.65	2.57625E-8	0.999999974
	Tipranavir/r	TPV	1	244.5	2.51	1.01256E-6	0.999998987
	Enfuvirtide	T20	1	25.1	1.65	0.004879933	0.995120067
	Raltegravir	RAL	3	89.8	1.1	0.007052165	0.992947835

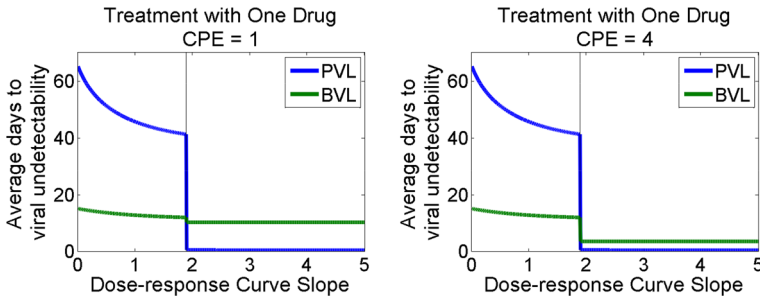


Fig. 5 Simulated number of days for the viral load in the plasma (blue) and in the brain (green) to become undetectable depending on the slope of the dose-response curve for ART regimen with a single drug of a CPE score of one (left) and four (right). Here, a dose-response slope greater than 1.9 (represented by the vertical line) corresponds to a PI, while a dose-response slope less than 1.9 corresponds to an RTI. The vertical lines separate the type of drugs based on this slope value

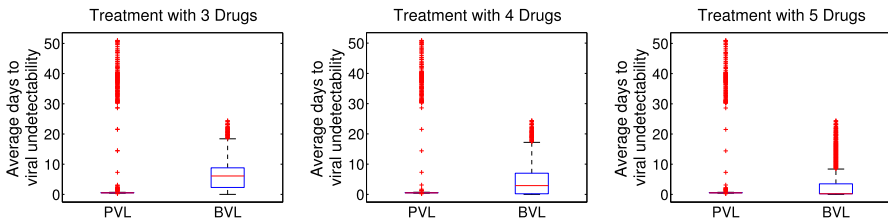


Fig. 6 Box plots showing the time for the virus to become undetectable (in days) depending on the number of drugs in an ART regimen. For each case, 15000 samples of drug were randomly generated by choosing the drug-response slope between zero and five and the CPE score between zero and five

drug). In particular, we observe that if both an RTI and a PI are present in ART, the BVL reaches undetected levels at least three days after the PVL becomes undetectable.

4.3 Effect of Multiple Drugs

In the previous section, our model predictions showed that more than one drug in ART regimens led to less time for the virus to become undetectable. Here we sought to examine whether this correlation remains the same for ART regimens with three or more drugs. For our computations, we randomly selected the sample of 15000 combinations of drugs in each of 3-, 4-, and 5-drug regimens by choosing the uniformly distributed drug-response slope between zero and five and the uniformly distributed CPE score between zero and five. Drug types were categorized by the slope of the dose-response curve selected as follows: RTI if $m \leq 1.9$ and PI if $m > 1.9$. Again, the drug concentration was assumed to be constant, and the treatment was initiated after the viral load reached a steady-state (~ 250 dpi).

In many cases (Fig. 6), we observed that ART regimens with multiple drugs reduce the PVL to the undetectable level before the BVL. However, many outliers appeared in our samples among the PVL, implying more uncertainty in PVL outcomes. This is likely because we chose uniformly distributed random slopes between 0 and 5, which

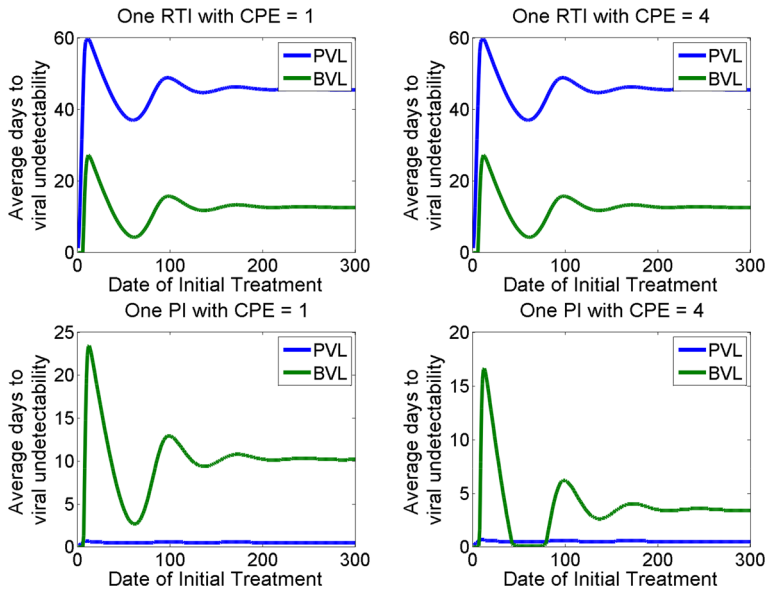


Fig. 7 The time (in days) for the viral load to become undetectable in the plasma (blue) and the brain (green) depending on the treatment initiation time of one RTI (top row) and one PI (bottom row) with a low CPE score (left column) and a high CPE score (right column)

increases the likelihood of selecting slopes corresponding to PIs ($1.9 < m < 5$) than RTIs ($0 < m \leq 1.9$).

Note that the number of drugs in a treatment regimen highly affects the time for the BVL to become undetectable. Specifically, the median days for the BVL to become undetectable decreases from ~ 7 days for three drugs to ~ 0.5 days for five drugs. We also observed that viral suppression in the plasma might not imply viral suppression in the brain for drug regimens with a higher number of drugs. This result highlights the role of the BBB, impacting the permeability of many drugs in regimens with multiple drugs.

4.4 Effect of Treatment Initiation Time

In Fig. 7, we present the predicted time in days post-infection that the plasma and brain viral load achieve undetectable levels depending on the treatment initiation time. We performed computations using a single RTI or PI with a corresponding CPE score of either one or four. The time of treatment initiation was varied between one day and 300 days post-infection (dpi).

We observed that the earliest initiated treatment (< 3 dpi) is more effective as it can prevent infection from reaching detectable viral levels in the brain. The effectiveness of early treatment revealed in our results is consistent with previous studies (Chun and Engel 1998; Vaidya and Rong 2017). Furthermore, our simulations suggest that, in general, the time for the PVL and BVL to reach undetectable levels varies significantly

within the first 100 days post-infection. For instance, if treatment begins during the second-week post-infection, the virus is detectable in both the plasma and the brain for longer (15 – 20 dpi) than for any other treatment initiation time. If the treatment is initiated between eight and ten weeks post-infection, the time to viral undetectability (<5 dpi in the brain, ~ 8 dpi in the plasma) is significantly less than other treatment initiation times. Once the steady state is reached, the treatment initiation time does not affect the time for the virus to fall below undetectable levels.

We also compared the outcome of PIs and RTIs for varying treatment initiation times. We found that treatment with a PI is highly effective at reducing the PVL but less effective at reducing the BVL. In contrast, treatment with an RTI reduces the BVL consistently more efficiently than the PVL. In some cases with high CPE scores, the treatment initiation time may result in the BVL becoming undetectable faster than the PVL. However, in treatment with a low CPE score, we did not observe such a case in which the BVL becomes undetectable before the PVL.

5 Discussion

Despite the success of ART in controlling HIV, a cure remains beyond the scope of current treatment, mainly due to the formation of viral reservoirs, such as the brain. In particular, the effect of the BBB, which blocks the drugs from entering the brain, remains a challenge for developing proper treatment protocols. A comprehensive look at the infection of HIV in the brain and the effect the BBB poses on ART has not been explored in previous studies.

The main objective of this study was to develop a mathematical model to investigate the impact of BBB on treatment-mediated viral suppression in the brain. Our model provides new insights that may help mitigate HIV from the brain. A critical finding from the model simulations is that the CPE score plays a significant role in the viral suppression in the brain for drugs with high slopes ($m > 1.9$), compared to drugs with low slopes ($m < 1.9$). A more significant suppression with a high-slope drug indicates that the protease inhibitors are more effective because, generally, ART drugs with larger slopes ($m > 1.89$) tend to be protease inhibitors (aidsinfo 2018) (see Table 2). As expected, our predictions suggest that changing the CPE score does not affect the time for the PVL to become undetectable for either drug type; however, the CPE score significantly impacts the time for the BVL to reach undetectable levels. Particularly for PIs, a higher CPE score corresponds to a shorter time for the BVL to become undetectable. For the drugs with low slopes, the CPE score has a negligible impact on the time to viral undetectability in the brain. A similar phenomenon was observed when we considered ART with two drugs. PIs, which often have a higher CPE score, generally manage to enter the brain with a higher percentage of drugs, resulting in a lower time to the BVL undetectability. Our simulations are also supported by the results of Letendre (2011), which illustrate the lower impact of the BBB on PI treatments to control HIV in the brain.

We further considered the effect the BBB has on drug regimens with higher dose-response curve slopes than those with lower slopes. In this case, we found that the PVL reached undetectable levels in significantly less time (≈ 50 days vs. ≈ 1 day) if the

slope of the dose-response curve of a drug is over 1.9, independent of the CPE score. This drastic difference in reduction time for PIs was not observed in the case of BVL. However, the BVL becomes undetectable roughly three weeks before the PVL for ART with lower slopes, unlike the results from ART with higher slopes. Furthermore, our simulations suggest that the BBB reduces the effect of ART on controlling HIV in the brain, especially for drugs with higher slopes. Therefore, depending on the slope of the dose-response curves, control of the PVL may not necessarily indicate control of the BVL.

The time for the viral load to reach undetectable levels depends on the treatment initiation time. While an early treatment may prevent the establishment of a viral reservoir, as demonstrated in previous studies (Archin et al. 2012), our model suggests that for the treatment initiated after three dpi, early ART may not always result in a shorter time for viral undetectability. For example, the treatment initiated during the second-week post-infection (10–14 dpi) may take longer for the viral load to become undetectable than the treatment begun at 60 dpi (Fig. 7). We used our model to formulate the basic reproduction number, $\mathcal{R}_0$, which we prove (Theorem 5) to provide a threshold condition for the global stability of the infection-free equilibrium ($\mathcal{R}_0 < 1$) or persistence of infection ($\mathcal{R}_0 > 1$) in the brain. Based on this formulation, we can compute the combination of ART drugs that asserts $\mathcal{R}_0 < 1$ to avoid infection.

We acknowledge several limitations of this study. We are unable to present the model fitting to the realistic viral dynamics data because of its unavailability. However, we would like to note that our model is based on experimental evidence on realistic HIV dynamics. Without treatment, this model has been carefully developed based on solid biological evidence and validated using experimental data from SIV/SHIV-infected macaques in a previous study (Barker and Vaidya 2020). We only studied constant treatment, often leading to viral eradication. In reality, maintaining a constant drug concentration is less likely, and so far, no evidence of consistent viral eradication has occurred. Time-varying drug concentration may be necessary, as done previously (Duwal et al. 2019; Vaidya and Rong 2017), to model a more-likely scenario.

The study by Vaidya and Rong (2017) suggests that the pharmacodynamics of each drug play a critical role in the control of infection. They also found that the basic reproduction number may not be the most reasonable indicator of infection persistence. They suggested the infection invasion threshold incorporating time-dependent drug concentration for more accurate criteria for infection control. We did not take into account the drug resistance nor the potential for viral mutation, which could result in viral rebound even amid treatment. A previous study (Strazielle et al. 2016) suggests that astrocytes and T-cells may harbor viral RNA in the brain, neither of which was considered in our model. Explaining drug concentration in the CSF entirely based on CPE score may also have some limitations; experiments analyzing more detailed drug concentrations may provide a better drug profile in the CSF. While these theoretical results offer insight into potential ART treatment improvements, they must be tested by *in vitro* and *in vivo* experiments before any recommendations can be offered in practice.

A similarly structured model may be utilized for each viral reservoir, contributing to viral rebound. This study did not include the presence of latently-infected cells and reservoirs, which are known to contribute to viral rebound (Ho and Shan 2013)

significantly. While our study provides a great insight into the brain virus contributing to the HIV reservoir, more complex models with all potential reservoirs in combination can provide a complete picture of potential HIV eradication through early treatments. However, such models need data with all the reservoirs collected simultaneously.

In summary, the model developed in this study underscores the role of BBB in the altered effectiveness of ART on viral control in the brain. The BBB-impacted CPE scores, the dose-response slope, the number of drugs in an ART regimen, and the treatment initiation time are the essential factors that must be considered to design the ideal treatment protocol for mitigating HIV in the brain. All these results combined indicate that the choice of drugs in the treatment regimens is vital for successfully controlling the virus in the brain.

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Data Availability All data generated or analyzed during this study are included in this published article.

Declarations

Conflicts of interest Authors declare NO conflict of interest.

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