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Impact of macrophages in the spread of HIV

Two mathematical models

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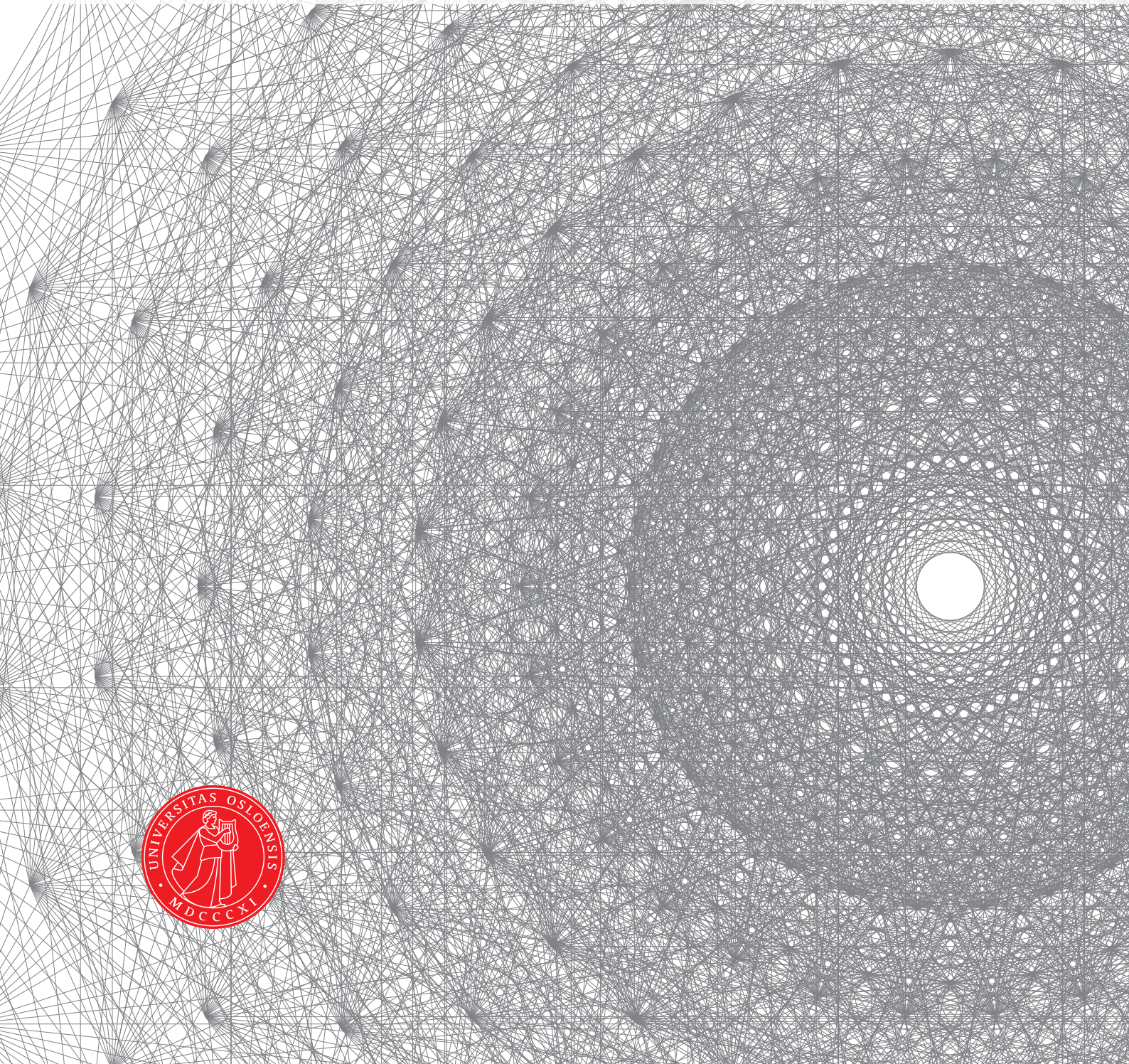


Abstract

Current treatment regimens have been effective in suppressing the progression of HIV. They prevent transmission and support people living with HIV to lead healthy lives. However, there are numerous clinical, social, and structural reasons that make people stop their treatment. HIV can re-surge after the treatment is stopped, which can also contribute to drug resistance and prevent further treatment. This is one reason why the search for an HIV cure is still essential for global public health. One major obstacle to developing a cure for HIV is the presence of what is called latent HIV reservoirs in the body. While CD4+ T-cells (one type of immune cell) are the most widely recognized reservoir, macrophages (another type of immune cell) have also been shown to contribute to the HIV reservoir. This thesis provides two novel mathematical models to understand the role macrophages play in the development of HIV pathogenesis. Both models start out with a reservoir of infected macrophages and the absence of infected CD4+ T-cells, reflecting the scenario where an individual with HIV stops treatment and that treatment has been fully effective in eliminating infected CD4+ T-cells. The two models differ in how the virus spreads, also called a transmission route. To focus solely on the role of macrophages, the first model only considers infections caused by macrophages. On the other hand, the second model also takes into account the transmission route between CD4+ T-cells. We study the stability of both systems around equilibrium points. This helps us know whether the disease would die out or establish itself and propagate further in the body. In both models, we have shown that a stable productive equilibrium point is attained under certain conditions. This proves that macrophages can indeed be a source of HIV persistence, which in turn undermines the importance of further study on macrophages for the ultimate goal of finding an HIV cure.

Acknowledgements

Dedicated to a close one whose fear of having contracted HIV was almost like a death sentence for them.

Contents

Chapter 1

Introduction - Defining the biological context

In this chapter, we will provide an overview of key biological concepts that are essential for understanding the derivation of the mathematical models. Each concept is given its own section. Subsequently, we present a brief summary of two relevant studies that were conducted earlier on this topic. In this summary, we describe the methodology and results of these studies and compare them with the current work. We define all field-specific terms, particularly those originating from biology, in text when they first appear. When they reappear throughout this text, we refer to the glossary defined at the end of this work.

1.1 What is HIV?

Human immunodeficiency virus (HIV) is a virus that targets the body's immune system, in particular the white blood cells known as CD4+ T-cells. HIV is the virus that can lead to Acquired Immune Deficiency Syndrome (AIDS). However, not everyone with HIV has AIDS. AIDS can be viewed as the most advanced stage of HIV, and a common diagnosis criterion for AIDS is having a CD4+ T-cell count of less than 200 cells per mm^3 [24]. According to [25], more than 38 million people around the world have been living with HIV by the end of 2021.

There is currently no cure for HIV. One of the biggest challenges for developing an HIV cure is HIV's ability to remain persistent in dormant immune cells [11] creating the so-called HIV reservoir. An HIV reservoir is a group of immune cells that are infected by HIV but are not actively reproducing the virus. The reservoir is heterogeneous and persistent, consisting of different types of immune cells [17]. While treatment for HIV has been successful in suppressing the virus, it does not eliminate those reservoirs [28].

1.2 Antiretroviral therapy

Antiretroviral therapy is a treatment regimen for HIV. It consists of at least two different drugs and targets the viral load in the body during its various stages. This therapy is effective in reducing HIV in the body to undetectable levels. At this point, the virus cannot be transmitted to another individual [4].

The treatment involves taking a pill, which contains multiple drugs, daily. It usually takes about six months before the treatment gets the virus under control. However, viral rebound—the state when the virus repopulates in the body after it has been suppressed—can be observed when treatment is stopped [23]. In most cases, this requires treatment for the duration of one's life.

This rebound has been attributed to the presence of HIV reservoirs in the body. These reservoirs often go undetected by the body's own immune system and can escape ART [29]. HIV reservoirs are one of the main challenges to finding a cure for HIV.

However, if the treatment effectively suppresses the virus and stops transmission, is there still a need to develop an HIV cure?

1.3 The current need for an HIV cure

Structural factors are social determinants of health that are beyond an individual's control and exert external pressure on patients with HIV. Poverty and lack of access to healthcare are two major structural factors that stand as barriers between HIV patients and treatment [8].

Even in the absence of such structural factors, there are social and clinical reasons that may also influence a patient to stop their treatment. Stigma and discrimination can lead to feelings of shame and guilt, which may be soothed by distancing oneself from treatment. Mental health issues such as depression and anxiety can also make it difficult for people living with HIV to adhere to their treatment regimen, which can be rigid and continuous [22].

Some clinical factors that cause people to stop their treatment include toxicity caused by the drug [26], oral barriers to taking drugs such as gastroenteritis and pancreatitis, and surgical procedures [21]. Patients may also discontinue their therapy for a host of clinical reasons, such as complex regimens, and low health literacy [20].

These factors lead to a high treatment drop-out rate and make it relevant to further study HIV to find a cure [20]. We claim that understanding the role of macrophages as an HIV reservoir is a prerequisite for developing a cure for HIV.

1.4 Macrophages

Macrophages are a type of white blood cells in the immune system. They occur in almost all tissues of the body [6], and they develop in the bone marrow from cells known as monocytes [6]. After the monocytes leave the bone marrow and

circulate in the blood, they enter body tissues where they evolve to become macrophages [6].

Macrophages possess numerous characteristics that make them good candidates for an HIV reservoir. They have a long lifespan [19], which allows the virus to persist in the body for a long period of time. Moreover, they can also resist the virus-induced cytopathic effects [14]. This allows them to survive after being infected with the virus.

In addition to that, macrophages are tissue-dependent and terminally differentiated; they reach the end of their development potential and can no longer divide. Depending on which tissue in the body they reside in, macrophages take different forms and adapt to the local environment. Some examples of macrophages in different tissues are alveolar macrophages in the lungs, Kupffer cells in the liver, and microglial macrophages in the central nervous system and the brain [6]. The latter is considered to be an immune-privileged compartment.

Immune-privileged compartments are anatomical regions that are naturally less subject to immune responses than most other areas of the body [3]. The creation of immune-privileged compartments is partly done through the blood-brain barrier. This barrier is a highly selective border that prevents elements from the circulating blood from entering the extracellular fluid of the central nervous system, where neurons reside [30]. The process of differentiation from macrophage to microglial gives macrophages access to an immune-privileged compartment through the blood-brain barrier. This allows macrophages to be carriers of HIV and go undetected by the immune system.

The persistence of this HIV reservoir in the brain has also been shown to cause comorbidities. Comorbidities are the simultaneous presence of two or more diseases that are not necessarily caused by one another but might have the same risk factors. HIV-infected microglia cause inflammation, which in turn leads to symptoms such as confusion and forgetfulness, an inability to concentrate, and mood disorders such as anxiety and depression [15].

In summary,

long life-span	cytopathic resistance	presence in immune-privileged areas

are some characteristics that macrophages have which makes them contributors to HIV pathogenesis. In what ways can a singular macrophage interact with other immune cells in the body to spread HIV?

1.5 Mode of transmission

A mode of transmission is a mechanism that describes how new infections are formed. To study the different modes of transmissions, the following population groups are considered:

1. Macrophages
    - Susceptible (healthy)

- Infected

2. CD4+ T-cells (abbreviated as T-cells)
   - Susceptible (healthy)
   - Infected
3. Virus particles

Among these population groups, there are two main modes of transmission. One mode is when a free virus particle − virion − particle infects a susceptible cell. This is referred to as cell-free transmission. On the other hand, cell-to-cell transmission happens when an infected cell infects a susceptible cell.

Cell-cell transmission has been shown to be the most prominent transmission mode for HIV [7]. It has a higher transmission rate in comparison. Moreover, it takes multiple virion particles to infect a single cell [27], rendering it less efficient than cell-to-cell transmission. Finally, this mode also allows viral infections to spread in a more subtle manner, making them less likely to be detected by the immune system than cell-free transmission [31]. With that in mind, this study only considers cell-to-cell transmission modes.

There are several routes within cell-to-cell transmission mode. The following table describes how the two target cells (macrophages and T-cells) interact with each other and with one another in the context of HIV pathogenesis.

Table 1.1: Transmission routes

	Macrophage	T-cell
Macrophage	Virological synapse	Virological synapse
T-cell	Phagocytosis	Virological synapse

The above table can be read as follows:

An infected macrophage can spread the virus to a susceptible macrophage through virological synapses [31]. A virological synapse is an organized cellular junction, and HIV has been shown to instigate the formation of these junctions between the infected (donor) and uninfected (target) cells to allow cell-to-cell transmission. [13] The formation of virological synapses is also a mechanism of HIV spread between T-cells, and from macrophages to T-cells [13] [10]. On the other hand, an infected T-cell can transmit HIV to a susceptible macrophage through the process of phagocytosis. Phagocytosis is a mechanism performed by macrophages where they engulf an infected cell—in this case, an infected T-cell. However, when phagocytosis is unsuccessful, this process can lead to the infection of macrophages.

To simplify the model, the production of infected cells through the process of phagocytosis is assumed to be negligible. This is a reasonable assumption, as the number of macrophages is relatively small compared to that of T-cells, and inefficient phagocytosis is a relatively ineffective transmission route compared to the formation of virological synapses.

1.6 Previous work

In their work on modelling the effects of latency reversing agents on macrophages [12], the authors use a nonlinear dynamical system to model the dynamics of infected macrophages in the brain. They make a distinction between latently infected macrophages and productively infected macrophages. Latently infected macrophages are those which carry the virus but are not currently producing it, whereas productively infected macrophages are active producers of the virus. Their paper focuses on the brain as this is an immune-privileged compartment, as we have seen in section 1.4. The model produces the overarching observation that effective drug treatment can suppress productively infected brain macrophages but leaves a residual latent viral reservoir in brain macrophages. This conclusion supports the hypothesis that macrophages play a key role in maintaining an HIV infection, and that an HIV cure is contingent on understanding HIV reservoirs further. Our study and the aforementioned one differ in two key areas:

1. We will not consider latently infected macrophages as a different infection state. We propose only two states: susceptible and infected. This is a simplification as the work done by [12] also shows how the dynamics of the model differ between latently and productively infected macrophages.

2. We will consider two population cell groups: macrophages and T-cells. Since our study aims to primarily highlight the role macrophages have in the pathogenesis of HIV, we are interested in studying how this cell group interacts with the dominant HIV cell target, which are T-cells.

Another major influence was the study done by [18]. The authors develop an HIV model that includes the infection of T-cells and macrophages via cell-free virus infection and cell-to-cell viral transmission. The modeling study shows that the infection of macrophages can contribute to the low viral load persistence during drug therapy. It supports the claim that improving drug responsiveness in mixed target cells (T-cells and macrophages) might be crucial for the elimination of HIV from infected individuals. While we both carry out a study of a nonlinear dynamical system with two-target cells groups, the models differ by the following elements:

1. We do not consider cell-free transmission. The reason for this simplification is elaborated on in section 1.5, while the cited model includes virus particles as an additional variable to the model.

2. We include the birth routes arising from macrophages (an infected macrophage can infect a susceptible macrophage and a susceptible T-cell), while the referenced paper focuses primarily on birth routes from infected T-cells and virus particles.

Both of the works mentioned in this section have been strong inspirations to us. While each model has a different approach, they key outtake is that

macrophages play an important role in helping HIV persist in the body, and thus stand in the way of obtaining an HIV cure. With this review on previous work concluded, we are now ready to introduce our first model.

Chapter 2

Model I

The first proposed mathematical model considers two target population cells: macrophages and T-cells, each of which has two states: susceptible and infected. To undermine the role of macrophages in the spread of HIV pathogenesis, this model only considers transmission routes caused by those cells. The highlighted transmission routes are considered in this model:

Table 2.1: Transmission routes for Model I

	Macrophage	T-cell
Macrophage	Virological synapse	Virological synapse
T-cell	Phagocytosis	Virological synapse

In this chapter, we will introduce the first mathematical model. To do so, we define the variables, parameters and formulate the model as a system of nonlinear differential equations. Then we derive the reproduction number of this system. We compute the equilibrium points and study their stability. Finally, we wrap the chapter by a section summarizing the findings and coming up with a conclusion.

2.1 Derivation of Model I

One of the most fundamental models in the field of epidemiology is the Kermack-McKendrick SIR model [16]. It compartmentalizes people into one of three categories: those who are **S**usceptible to the disease, those who are currently **I**nfectious, and those who have **R**ecovered, hence the name. Our proposed model is a variation of this foundational model. We also propose a compartmental model. However, instead of considering HIV infection on a population level, we consider it on a micro scale. Our population groups are immune cells, and the interactions are not between two individual people, but between two individual cells.

The model we will derive describes the time evolution of four dependent variables given in Table 2.2. We define initial conditions in Table 2.3. The initial number of infected T-cells is set to zero to eliminate the contribution of T-cells to HIV pathogenesis. This condition allows us to focus primarily on the contribution macrophages can make to the evolution of the virus. A schematic drawing of the system is given in Figure 2.1.

Table 2.2: Variables of Model I

Variable	Description
$x = x(t)$	number of susceptible macrophages
$y = y(t)$	number of infected macrophages
$u = u(t)$	number of susceptible T-cells
$v = v(t)$	number of infected T-cells

Table 2.3: Initial Conditions for Model I

Symbol	Description
x_0	initial number of susceptible macrophages
y_0	initial number of infected macrophages
u_0	initial number of susceptible T-cells
$v_0 = 0$	number of infected T-cells

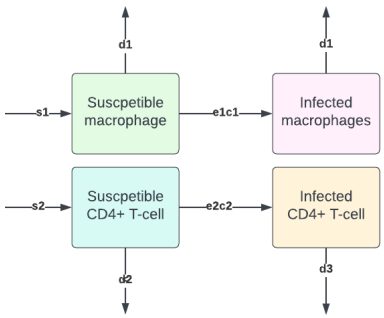


Figure 2.1: Illustration of Model I

The parameters that govern this system can be qualitatively split into three categories: *birth* parameters, *death* parameters, and *interaction* parameters. Birth parameters describe epidemiological birth—how cells are populated in the system. Death parameters describe epidemiological death—how cells are eliminated from the system; and finally, interaction parameters describe how cells interact with each other and with one another.

There are two birth parameters. The first one, s_1, represents the production rate of susceptible macrophages. This is the body's known natural rate of producing new macrophages in the bone marrow. The second birth parameter, s_2, is the equivalent of s_1 but for T-cells. In other words, s_2 is the production rate of susceptible T-cells in the body.

The death parameters d_1, d_2 and d_3 represent the death rates of susceptible and infected macrophages, susceptible T-cells, and infected T-cells, respectively. Since macrophages resist the cytopathic effects of the virus, and can reside in an immune-privileged compartment, the death rate of susceptible and infected macrophages is assumed to be the same, d_1. However, the death rate of infected T-cells d_3 is assumed to be greater than or equal that of healthy T-cells d_2 since infected T-cells are more likely to be detected and thus eliminated by other immune cells than their healthy counterparts.

Interaction parameters are categorized into contact rates and efficiency rates. The contact rate is the rate at which a given cell encounters another. The efficiency rate describes how epidemiologically successful this contact is in transmitting the virus to the encountered cell. This model considers encounters among two macrophages, governed by the contact rate c_1 and the efficiency rate e_1, and between one macrophage and one T-cell, governed by the contact rate c_2 and the efficiency rate e_2. Biologically, these interaction parameters model the process of forming virological synapses between the cell populations. Table 2.4 summarizes the parameters in the model. The conditions on the parameters are derived from what is biologically plausible. Later in this paper when we perform some numerical investigations in Section 3.6, the sources and claims supporting those conditions are specified.

Table 2.4: Parameters of Model I

Parameter	Description	Conditions
s_1	production rate of susceptible macrophages / ml / day	> 0
s_2	production rate of susceptible T-cells / ml / day	> 0
d_1	natural death rate of macrophages / ml / day	$\in [0.1\%, 5\%]$
d_2	natural death rate of T-cells / ml / day	$\in [0.1\%, 5\%]$
d_3	death rate of infected T-cells	$\geq d_2$
e_1	transmission efficiency rate between two macrophages	$\in [0.001\%, 0.01\%]$
e_2	transmission efficiency rate between one macrophage and one T-cell	$\in [0.001\%, 0.01\%]$
c_1	contact rate between two macrophages	$\in [0.1\%, 50\%]$
c_2	contact rate between one macrophage and one T-cell	$\in [0.1\%, 50\%]$

After having defined the mathematical context around this model, we now formulate it as a dynamical system.

2.2 Formulation

The model can be described as a system of nonlinear differential equations. The "dot" symbol represents the time derivative of the four dependent variables.

$$\begin{aligned} \dot{x} &= s_1 - e_1 c_1 xy - d_1 x \\ \dot{y} &= e_1 c_1 xy - d_1 y \\ \dot{u} &= s_2 - e_2 c_2 uy - d_2 u \\ \dot{v} &= e_2 c_2 uy - d_3 v \end{aligned} \tag{2.1}$$

We rewrite (2.1) in matrix form using the following matrices. First we define our vector of unknowns X, and then we define a function F which depends on X.

$$X := \begin{pmatrix} x \\ y \\ u \\ v \end{pmatrix}, \quad F(X) := \begin{pmatrix} s_1 - e_1 c_1 xy - d_1 x \\ e_1 c_1 xy - d_1 y \\ s_2 - e_2 c_2 uy - d_2 u \\ e_2 c_2 uy - d_3 v \end{pmatrix}.$$

We obtain the following system:

$$\dot{X} = F(X). \tag{2.2}$$

After having derived the system and written it in matrix form, we carry out a qualitative study. First, we compute the disease-free equilibrium and use the next-generation matrix method to derive the reproduction number. We find all equilibrium points in the system and define their admissibility criteria. Admissibility criteria refer to a set of biological constraints to distinguish between physically plausible scenarios and those that are pure mathematical artifacts. We study the asymptotic local and global stability of the equilibrium points and correlate the stability conditions with the reproduction number.

Before proceeding with the qualitative study of the above system, we make and prove an observation based on the decoupled nature of the first two equations in (2.1).

Lemma 1. *The asymptotic behavior of solutions to the system can be restricted to the following region:*

$$\Gamma = \left\{ X \in \mathbb{R}^4_+ : X(1) + X(2) = \frac{s_1}{d_1} \right\}.$$

Proof. Observe that the first two equations of the system are decoupled from the two other variables:

$$\begin{aligned} \dot{x} &= s_1 - e_1 c_1 xy - d_1 x \\ \dot{y} &= e_1 c_1 xy - d_1 y. \end{aligned}$$

Adding those two equations gives us:

$$\dot{x} + \dot{y} = s_1 - d_1(x + y) \iff$$
$$\frac{d}{dt}(x + y) = s_1 - d_1(x + y).$$

Let $z := x + y$, then the above can be rewritten as:

$$\dot{z} = s_1 - d_1 z.$$

Let $\tilde{z} := z - \frac{s_1}{d_1}$, then $\dot{\tilde{z}} = \dot{z}$ and the equation can be further reduced to

$$\dot{\tilde{z}} = s_1 - d_1\left(\tilde{z} + \frac{s_1}{d_1}\right) \iff$$
$$\dot{\tilde{z}} = -d_1\tilde{z}.$$

Using the characteristic polynomial to solve this differential equation, we get that:

$$\tilde{z} = Ce^{-d_1 t}$$

where C is a constant. By back substitution, we get:

$$x + y = \frac{s_1}{d_1} + Ce^{-d_1 t}.$$

As $t \to \infty, x + y \to \frac{s_1}{d_1}$. This completes the proof. □

With that in mind, we will later only consider initial conditions that are in Γ.

2.3 Reproduction number

The reproduction number, usually denoted by R_0, is a key epidemiological parameter that describes how contagious the infection is. It is defined as the average number of secondary infections that result from one infected agent in an otherwise completely susceptible population. The basic reproduction number is one of the conceptual cornerstones of mathematical epidemiology [2]. As such, the derivation of this reproduction number is a major part of this study. We will derive the reproduction number using the next generation matrix technique described in [5].

A pre-requisite to computing the reproduction number of this system is to get the disease-free equilibrium point. This point is characterized by having the infection state to be zero. The infected state X_I is given by

$$X_I = \begin{pmatrix} y \\ v \end{pmatrix}.$$

Note that the components of X_I correspond to the number of infected macrophages and infected T-cells. Setting the left-hand side of the system (2.2) to zero and using that X_I is equal to zero, we obtain the following equilibrium point:

$$E_1 = \begin{pmatrix} \frac{s_1}{d_1} \\ 0 \\ \frac{s_2}{d_2} \\ 0 \end{pmatrix}.$$

After calculating the disease-free equilibrium point, we proceed to calculate the reproduction number of this system.

The first step is to consider the infected subsystem, which models the production of new infections, and linearize it around the disease-free equilibrium. The linearized infected subsystem can be written as:

$$\dot{X_I} = L_I X_I \tag{2.3}$$

where

$$L_I := \begin{pmatrix} \frac{e_1 c_1 s_1}{d_1} - d_1 & 0 \\ \frac{e_2 c_2 s_2}{d_2} & -d_3 \end{pmatrix}.$$

We obtain L_I by considering the differential equations for y and v in (2.1), and substituting the values of x and u by their corresponding values in E_1. This step linearizes the original system as the nonlinear terms xy and uv have now become functions of only y and v, respectively. From an epidemiological perspective, this subsystem describes the potential for the initial spread of infected macrophages and infected T-cells when they are introduced into a fully susceptible population of healthy cells. There is an implicit assumption that the change in the susceptible population is negligible during the initial spread [5].

After getting the matrix of coefficients L_I, we decompose it as $T + \Sigma$ where T represents the transmission matrix, and Σ the transition matrix to obtain:

$$T := \begin{pmatrix} \frac{c_1 e_1 s_1}{d_1} & 0 \\ \frac{c_2 e_2 s_2}{d_2} & 0 \end{pmatrix} \quad \Sigma := \begin{pmatrix} -d_1 & 0 \\ 0 & -d_3 \end{pmatrix}.$$

Using this decomposition, we can proceed as follows.

$$\begin{aligned} L_I &= T + \Sigma \\ &= (T\Sigma^{-1} + I)\Sigma \\ &= (I - K)\Sigma \end{aligned}$$

where

$$K = -T\Sigma^{-1} = \begin{pmatrix} \frac{c_1\, e_1\, s_1}{{d_1}^2} & 0 \\ \frac{c_2\, e_2\, s_2}{d_1\, d_2} & 0 \end{pmatrix}.$$

The matrix K is called the next-generation matrix as defined in [5]. This name derives from the entries of K representing the expected number of infected cells produced by a single infected cell. These infected cells represent the second (or next) generation of infections. Table 2.5 gives the epidemiological interpretation of the matrices used to construct K.

Table 2.5: Interpretation of matrices

Value	Description
T_{ij}	rate of infected cell type j produced by one infected cell type i [5]
$-\Sigma_{ij}^{-1}$	expected time that an infected cell type j will spend being infected cell type i [5]

With that interpretation in mind, it is apparent that $-\Sigma_{ij}^{-1}$ is zero whenever i differs from j since an infected macrophage (respectively, T-cell) would never become an infected T-cell (respectively, macrophage). Moreover, since individual cells do not "recover", death is the only mechanism to escape an infected state. Hence, the only non-zero entries in $-\Sigma^{-1}$ are the death rates of respective cell types. The two non-zero entries in T correspond to the two viable modes of transmission:

1. An infected macrophage can infect a susceptible macrophage.
2. An infected macrophage can infect a susceptible T-cell.

The second column of T being zero indicates that there are no infections generated by T-cells. This will be the main difference between the two models proposed, where in the second model, T-cells can infect each other. With the epidemiological construction of T and $-\Sigma^{-1}$ in mind, K_{ij} is thus the expected number of infected "offspring" with state i at infection produced by an infected cell of type j. Therefore, the *reproduction number* R_0 is defined to be the largest eigenvalue of K. Since K is a diagonal matrix, its eigenvalues are 0 and $\frac{c_1 e_1 s_1}{{d_1}^2} > 0$. Hence,

$$R_0 = \frac{c_1 e_1 s_1}{d_1^2}. \tag{2.4}$$

We have now computed the reproduction number of (2.2). Taking a closer look at the parameters involved in R_0 (and given by Table 2.4), we substitute the minimal and maximal values of c_1 and e_1 to bound our reproduction number in the following interval:

$$10^{-8}\frac{s_1}{d_1^2} \leq R_0 \leq (5 \times 10^{-7})\frac{s_1}{d_1^2}. \tag{2.5}$$

Written this way, we can see that a key value in determining the HIV spread potential of this model is $\frac{s_1}{d_1^2}$. This value represents the relative presence of macrophages in the body, where they get created through the source s_1 and cleared out at a rate of d_1.

We now proceed to find other equilibrium points of this model.

2.4 Equilibrium points

In addition to the disease-free equilibrium E_1, the system admits another equilibrium point:

$$E_2 = \begin{pmatrix} \frac{d_1}{c_1\, e_1} \\ \frac{s_1}{d_1} - \frac{d_1}{c_1\, e_1} \\ -\frac{c_1\, d_1\, e_1\, s_2}{c_2\, e_2\, (d_1{}^2 - c_1\, e_1\, s_1) - c_1\, d_1\, d_2\, e_1} \\ -\frac{c_2\, e_2\, s_2\, \left(d_1{}^2 - c_1\, e_1\, s_1\right)}{d_3\, (-c_2\, d_1{}^2\, e_2 + c_1\, d_1\, d_2\, e_1 + c_1\, c_2\, e_1\, e_2\, s_1)} \end{pmatrix}.$$

We call E_2 the productive equilibrium point, since both infected values (y and v) are non-zero. Thus, this equilibrium point describes a state where the infection is maintained by both cell types. The admissibility criteria for the equilibrium points are simply that each component is non-negative, i.e. $E_i \geq 0$. (Note that $E_i \geq 0$ for $i \in \{1, 2\}$ means that $E_i(j) \geq 0$ for $j \in \{1, 2, 3, 4\}$.)

E_1 satisfies the admissibility criteria without the need to impose any additional constraints on the parameters. However, for E_2 the following constraint needs to be imposed:

$$d_1^2 - c_1 e_1 s_1 \overset{!}{\leq} 0$$

Reformulating this constraint in terms of the reproduction number R_0, the following admissibility condition for E_2 is obtained:

$$d_1^2(1 - R_0) \leq 0 \iff R_0 \geq 1.$$

This is significant as it implies that when $R_0 < 1$, the only equilibrium point the system has is the disease-free equilibrium. So in that case if we show that E_1 is stable, then the system will always tend to the disease-free equilibrium regardless of where we start out. In the next section, we will formalize the previous claim and prove stability results for both E_1 and E_2.

2.5 Stability analysis

To study the local asymptotic stability of those two equilibrium points, consider the Jacobian matrix of the system (2.2) given by:

$$J_X := \nabla F(X) = \begin{pmatrix} -d_1 - c_1\, e_1\, y & -c_1\, e_1\, x & 0 & 0 \\ c_1\, e_1\, y & -d_1 + c_1\, e_1\, x & 0 & 0 \\ 0 & -c_2\, e_2\, u & -d_2 - c_2\, e_2\, y & 0 \\ 0 & c_2\, e_2\, u & c_2\, e_2\, y & -d_3 \end{pmatrix}.$$

Lemma 2. *The disease-free equilibrium point E_1 is locally asymptotically stable if and only if $R_0 < 1$.*

Proof. The eigenvalues of J_X evaluated at E_1, written as J_{E_1}, are given by the following vector:

$$\text{eig}(J_{E_1}) = \begin{pmatrix} -d_1 \\ -d_2 \\ -d_3 \\ -d_1(1-R_0) \end{pmatrix}$$

The local asymptotic stability criterion is that all eigenvalues need to have negative real parts. Hence, E_1 is locally asymptotically if and only if $R_0 < 1$. □

Lemma 3. *The productive equilibrium E_2 is locally asymptotically stable if and only if $R_0 > 1$.*

Proof. Similarly to the previous proof, we compute the eigenvalues of J_{E_2} and define the vector $\text{eig}(J_{E_2})$ as:

$$\text{eig}(J_{E_2}) = \begin{pmatrix} -d_1 \\ -d_3 \\ d_1(1-R_0) \\ \frac{c_2 e_2 d_1(1-R_0)}{c_1 e_1} - d_2 \end{pmatrix}$$

The third eigenvalue is negative if and only if $R_0 > 1$. With $R_0 > 1$, the fourth eigenvalue is also guaranteed to be negative. Hence, E_2 is locally asymptotically stable when $R_0 > 1$. If R_0 is equal to 1, the third eigenvalue is zero, rendering the point not locally asymptotically stable. We do not consider the case when $R_0 < 1$ as the point is not admissible in that case. □

2.6 Conclusion

The model (2.2) we have considered in this chapter primarily tries to answer the following question:

> Does there exist a scenario where an infected set of macrophages can by themselves corroborate an HIV infection and maintain the disease over time?

The key phrase in the above question is "by themselves". In an actual situation, there are many more contributing factors. Other contributing factors can be virus particles, T-cells and other types of immune cells that can propagate the infection. However, if we theoretically assume that those contributions are negligible, we were still able to derive conditions for a locally stable productive equilibrium point. Another key phrase is "exist a scenario". We have shown that when $R_0 > 1$, the productive equilibrium is locally asymptotically stable. However, is there a biological plausibility that R_0 can in fact attain values greater than 1?

To answer this question, we use the inequality for R_0 given by (2.5), and observe that the upper bound attains its minimum when s_1 is minimized and d_1 maximized. We vary the death parameter d_1 along the sample values: 0.001,

0.006, 0.011, ..., 0.046, and consider different values of s_1. The values of s_1 are estimates based on the parameter value given in [18], where $s_1 \approx 10$. We plot the values of the lower and upper bound with respect to d_1. The plots are given in Figure 2.2. The lower bound is less than 1 in all of the cases. However, the upper bound attains values of greater than 1 in all of those cases except when $s_1 = 1$. Therefore, it is reasonable to assume that $R_0 > 1$ can be biologically attainable. In other words, it is biologically plausible for this system to have a locally stable productive equilibrium point, indicating that an infection can incur and be sustained over time.

These results complement those found in the previous work discussed in section 1.6 where macrophages have been shown to be able to maintain and propagate HIV infection. What we have argued here is that they are also able to do so even in the absence of other agents. While this isolation is purely theoretical, it helps emphasize the role macrophages by removing the contributions of other factors to the infection. In the next chapter, we will add one of those contributing factors, namely T-cells, and study how the dynamics of the system change.

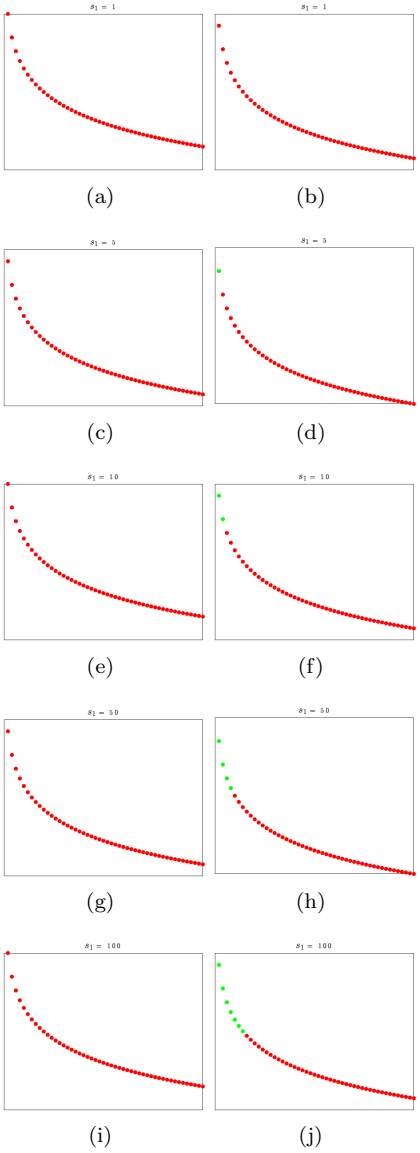


Figure 2.2: Plotting the lower and upper bounds (semilogy) of R_0 over several values of s_1 and d_1. The death rate d_1 increases within its range along the x−axis. On the right are the lower bounds of R_0, while on the left are its upper bounds. Red points indicate values less than 1, while green dots indicate values greater than 1.

Chapter 3

Model II

This model builds on the first one by considering an additional infection route. The new infection route is between infected and susceptible T-cells. As this is one of the primary ways HIV spreads in the body, we are interested in including it in this model. The table below highlights the three different cell-to-cell transmissions taken into account.

Table 3.1: Transmission routes for Model II

	Macrophage	T-cell
Macrophage	Virological synapse	Virological synapse
T-cell	Phagocytosis	Virological synapse

To bring the focus back to the role of macrophages in HIV pathogenesis, the initial number of infected T-cells is assumed to be zero, while that of infected macrophages is assumed to be greater than zero. We have seen in the conclusion of the previous chapter that macrophages alone can be sufficient to induce and maintain an HIV pathogenesis. What we are trying to dig deeper into in this chapter is understanding how potent macrophages can be as HIV reservoirs, and in their role in triggering something like a chain reaction by infecting T-cells, and letting the infected T-cells become the primary propagator of the virus. By deriving a mathematical model to describe those dynamics, we aim to gain further understanding on the role of macrophages by considering a more realistic biological context.

To achieve that, we will formulate and derive a system of nonlinear differential equations to model the dynamics highlighted in Table 3.1. As we are considering another transmission route compared to (2.2), we will non-dimensionalize the system for the purpose of simplification. We will then identify one key parameter and re-write the system in a way that highlights the significance of this parameter. This will be the final version of the system. As in the previous chapter, we will compute the reproduction number and equilibrium points. We will study the admissibility of those points, and stability of the derived system

around them. We will perform some numerical investigations to complement the qualitative study. Finally, we will answer the questions posed in the previous paragraph in reference to the results obtained.

3.1 Formulation

We start this section by a sketch to illustrate the birth, death and transition of our two cell populations. The sketch is given in Figure 3.1.

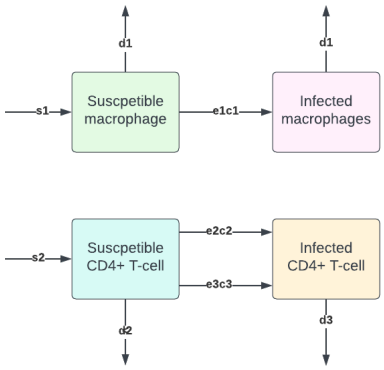


Figure 3.1: Illustration of Model II

The epidemiological birth and death of the target cells follows from the previous model with one additional birth route. The constants e_3 and c_3 are two new parameters that, respectively, represent the efficiency and contact rates between T-cells. The model can be described by a system of nonlinear differential equations as follows:

$$\begin{aligned} \dot{x} &= s_1 - e_1 c_1 xy - d_1 x \\ \dot{y} &= e_1 c_1 xy - d_1 y \\ \dot{u} &= s_2 - e_2 c_2 uy - e_3 c_3 uv - d_2 u \\ \dot{v} &= e_2 c_2 uy + e_3 c_3 uv - d_3 v. \end{aligned} \tag{3.1}$$

This system includes three non-linear terms, $e_1 c_1 xy$, $e_2 c_2 uy$ and $e_3 c_3 uv$, in comparison with the first model, which only includes the first two non-linear terms.

To highlight the biological significance of the death parameters d_2 and d_3, we rewrite d_3 as:

$$d_3 = d_2 + \varepsilon d_2$$

where $\varepsilon \in [0, 1]$. Recall that d_2 and d_3 represent the respective death rates of susceptible and infected T-cells. This models the cytopathic on infected T-cells

(which reduces their lifespan) and also the fact that an infected T-cell is more likely to be recognized and eliminated by other immune cells.

We re-write the system in matrix form, using the vector of unknowns X as defined in (2.2). We define the function G as follows:

$$G(X) := \begin{pmatrix} s_1 - e_1c_1xy - d_1x \\ e_1c_1xy - d_1y \\ s_2 - e_2c_2uy - e_3c_3uv - d_2u \\ e_2c_2uy + e_3c_3uv - (d_2 + \varepsilon d_2)v \end{pmatrix}.$$

We obtain the following system:

$$\dot{X} = G(X). \tag{3.2}$$

Now that we have formulated our model, we proceed with the non-dimensionalization process.

3.2 Non-dimensionalized formulation

We non-dimensionalize the system to reduce the number of parameters and obtain the following system. Note that we use the same symbols for the non-dimensionalized variables as their dimensionalized counterparts in the interest of not introducing too many variables. The detailed step-by-step process is described in Appendix .1.

$$\begin{aligned} \dot{x} &= 1 - xy - \alpha_1 x \\ \dot{y} &= xy - \alpha_1 y \\ \dot{u} &= 1 - \alpha_2 uy - uv - u \\ \dot{v} &= \alpha_2\alpha_3 uy + \alpha_3 uv - (1+\varepsilon)v. \end{aligned} \tag{3.3}$$

In matrix form, we have

$$\dot{X} = G(X), \text{where } G(X) = \begin{pmatrix} 1 - xy - \alpha_1 x \\ xy - \alpha_1 y \\ 1 - \alpha_2 uy - uv - u \\ \alpha_2\alpha_3 uy + \alpha_3 uv - (1+\varepsilon)v \end{pmatrix}. \tag{3.4}$$

This system gives rise to three non-dimensionalization parameters α_1, α_2 and α_3, in addition to the parameter ε. The system has been reduced from having 10 parameters to four. Table 3.2 below defines those parameters in terms of the dimensionalized ones.

Table 3.2: Parameters for Model II

Parameter	Value	Meaning
α_1	$\frac{d_1}{d_2} > 0$	relative death rate of macrophages and T-cells
α_2	$\frac{e_2 c_2 s_1}{d_2^2} > 0$	macrophage contribution to the relative birth and death of T-cells
α_3	$\frac{e_3 c_3 s_2}{d_2^2} > 0$	T-cell contribution to the relative birth and death of T-cells
ε	$\in [0, 1]$	relative death rate of infected T-cells to their susceptible counterparts

As a final step in deriving our model, we re-write the non-dimensionalization parameters as functions of one another to highlight the significance of the parameter α_1.

$$\alpha_2 = b\alpha_1^2, \text{ where } b = \frac{e_2 c_2 s_1}{d_1^2} > 0$$
$$\alpha_3 = a\alpha_1^2, \text{ where } a = \frac{e_3 c_3 s_2}{d_1^2} > 0.$$

The system becomes:

$$\dot{X} = G(X), \text{where } G(X) = \begin{pmatrix} 1 - xy - \alpha_1 x \\ xy - \alpha_1 y \\ 1 - b\alpha_1^2 uy - uv - u \\ ab\alpha_1^4 uy + a\alpha_1^2 uv - (1+\varepsilon)v \end{pmatrix}. \tag{3.5}$$

Written this way, the term α_1 appears to be of major significance to the study of this model. Biologically, α_1 represents the relative death rate of susceptible macrophages to that of T-cells. The below table translates threshold values of α_1 to their biological interpretation.

Table 3.3: Threshold values of α_1

α_1	Interpretation
$= 1$	healthy macrophages and T-cells have the same lifespan
> 1	healthy T-cells live longer than healthy macrophages
< 1	healthy T-cells live shorter than healthy macrophages

We observe one more property of our parameters, particularly a and b, which we will make use of later on.

We relate the parameters a and b in the following way using biologically observed phenomena:

$$a \geq \mathcal{O}(10^4) \cdot b. \tag{3.6}$$

We provide the following evidence to back up this observation. Note that

$$\frac{a}{b} = \frac{e_3 c_3 s_2}{e_2 c_2 s_1}.$$

According to [18], $\frac{s_2}{s_1} = \mathcal{O}(10^3)$. This means that T-cells are generated in the body at a much higher rate than macrophages. Since the number of T-cells is in the order of 10^3 as high as that of macrophages, the contact rate between two T-cells $-c_3-$ will be higher than the contact rate between one T-cell and one macrophage $-c_2-$ by at least an order of 10^2. Since $e_2, e_3 \in [0.001\%, 0.01\%]$, we get $\frac{e_3}{e_2}$ is at most of order 10^{-1}, and hence we get the required result.

Now that we have gained some more understanding about all the parameters of the system (3.5), we carry out a qualitative study of the model, where we compute the reproduction number, find equilibrium points, and study their stability.

3.3 Reproduction number

We follow the same steps as in the derivation of the reproduction number for the previous model, given in Section 2.3. Namely, we use the next generation method described in [5]. The first step is finding the disease-free equilibrium, which is given by:

$$E_1 = \begin{pmatrix} \frac{1}{\alpha_1} \\ 0 \\ 1 \\ 0 \end{pmatrix}.$$

We then derive the infected subsystem by considering the equations for y and v and substituting the values of x and u by their corresponding values in E_1. We obtain the following:

$$\dot{X}_I = G_I X_I \tag{3.7}$$

where

$$G_I = \begin{pmatrix} \frac{1}{\alpha_1} - \alpha_1 & 0 \\ a\,{\alpha_1}^4\, b & -1 - \varepsilon + a\,{\alpha_1}^2 \end{pmatrix}.$$

Note that this is a linearized version of the original system. We decompose the matrix of coefficients as $G_I = T + \Sigma$ where the so-called transmission and transition matrices T and Σ are given by:

$$T := \begin{pmatrix} \frac{1}{\alpha_1} & 0 \\ a\,{\alpha_1}^4\, b & a\,{\alpha_1}^2 \end{pmatrix} \quad \Sigma := \begin{pmatrix} -\alpha_1 & 0 \\ 0 & -1-\varepsilon \end{pmatrix}$$

The next-generation matrix K is defined as $K = -T\Sigma^{-1}$ and is given by:

$$K = \begin{pmatrix} \frac{1}{{\alpha_1}^2} & 0 \\ a\,{\alpha_1}^3\, b & \frac{a\,{\alpha_1}^2}{1+\varepsilon} \end{pmatrix}.$$

Since K is a diagonal matrix, its eigenvalues are its diagonal entries. Thus, K has two positive eigenvalues:

$$R_{01} = \frac{1}{{\alpha_1}^2},$$
$$R_{02} = \frac{a\,{\alpha_1}^2}{1+\varepsilon}.$$

The reproduction number R_0 is given by:

$$R_0 = \max\{R_{01}, R_{02}\}.$$

R_{01} is the reproduction number from macrophage infection, while R_{02} is that due to T-cell infection. The epidemiological interpretation of those values clarify the reasoning behind those definitions. The numerator of R_{02} represents the birth rate of infected T-cells, while the denominator represents the death rate. Hence if $R_{02} > 1$, infected T-cells are being produced at a faster rate than they are being cleared out, causing the infection to spread. Similarly for when $R_{01} > 1$, infected macrophages are epidemiologically birthed at a higher pace than they are cleared out. Unlike the first model, both eigenvalues in this case are positive. From an epidemiological point of view, this reflects that the infection can now be caused by two different agents, macrophages and T-cells. While in the first model, the agent of propagation was only one cell type: macrophages.

In the next section, we will derive the equilibrium points of this system and define their admissibility criteria in relation to the reproduction numbers.

3.4 Equilibrium points

We have already seen that there exists a disease-free equilibrium E_1. In addition to that, the system admits three equilibrium points. The first one is given by:

$$E_2 = \begin{pmatrix} \frac{1}{\alpha_1} \\ 0 \\ \frac{1+\varepsilon}{a\,{\alpha_1}^2} \\ R_{02} - 1 \end{pmatrix}.$$

Since the number of infected macrophages is zero while that of infected T-cells is greater than zero when R_{02} is greater than 1, this equilibrium point represents a state where the infection is only carried out by T-cells. The two other equilibrium points are given by:

$$E_3 = \begin{pmatrix} x^* \\ y^* \\ u^* \\ v^* \end{pmatrix}, \quad E_4 = \begin{pmatrix} x^* \\ y^* \\ \hat{u} \\ \hat{v} \end{pmatrix}$$

where

$$
\begin{aligned}
x^* &= \alpha_1 > 0 \\
y^* &= R_{02} - 1 \\
u^* &= \frac{-\alpha_1\, b + a}{2\, a} + \frac{b}{2\, a\, \alpha_1} + \frac{\sqrt{P_\varepsilon} + 1}{2\, a\, {\alpha_1}^2} \\
v^* &= \frac{a\, {\alpha_1}^2}{2} - \frac{\sqrt{P_\varepsilon}}{2} - \frac{\alpha_1\, b}{2} + \frac{{\alpha_1}^3\, b}{2} - \frac{1}{2} \\
\hat{u} &= u^* - \frac{\sqrt{P_\varepsilon}}{(1+\varepsilon) R_{02}} \\
\hat{v} &= v^* + \frac{\sqrt{P_\varepsilon}}{1+\varepsilon}.
\end{aligned}
$$

Here P_ε is a polynomial of the variables a, b and α_1, having ε as a parameter. It is given by this rather complex formula.

$$
\begin{aligned}
P_\varepsilon = {} & 1 + 2\,\varepsilon + \varepsilon^2 + 2\,\alpha_1\, b + 4\,\alpha_1\, b\,\varepsilon + 2\,\alpha_1\, b\,\varepsilon^2 + {\alpha_1}^2\, b^2 + 2\,{\alpha_1}^2\, b^2\,\varepsilon \\
& + {\alpha_1}^2\, b^2\,\varepsilon^2 - 2\,{\alpha_1}^3\, b - 4\,{\alpha_1}^3\, b\,\varepsilon - 2\,{\alpha_1}^3\, b\,\varepsilon^2 - 2\,{\alpha_1}^4\, b^2 \\
& - 4\,{\alpha_1}^4\, b^2\,\varepsilon - 2\,{\alpha_1}^4\, b^2\,\varepsilon^2 + {\alpha_1}^6\, b^2 + 2\,{\alpha_1}^6\, b^2\,\varepsilon \\
& + {\alpha_1}^6\, b^2\,\varepsilon^2 - 2\,a\,{\alpha_1}^2 - 2\,a\,{\alpha_1}^2\,\varepsilon \\
& + 2\,a\,{\alpha_1}^3\, b + 2\,a\,{\alpha_1}^3\, b\,\varepsilon - 2\,a\,{\alpha_1}^5\, b - 2\,a\,{\alpha_1}^5\, b\,\varepsilon + a^2\,{\alpha_1}^4.
\end{aligned}
$$

For the most of the following study, we will only be interested in the value P_0 (i.e. P_ε evaluated when ε is equal to zero). Both of the equilibrium points E_3 and E_4 have non-zero values for infected T-cells and infected macrophages. Hence, they both represent states of productive equilibrium, where the disease is propagated by both types of cells. We summarize all four equilibrium points in the following table:

Table 3.4: Equilibrium points of Model II

Equilibrium point	Interpretation
E_1	disease-free equilibrium
E_2	T-cell only productive equilibrium
E_3	T-cell and macrophage productive equilibrium
E_4	T-cell and macrophage productive equilibrium

Upon initial inspection, E_3 and E_4 seem to be having the same role in the system. However, as we will see in the upcoming section, they have different stability properties. We also note the absence of a macrophage-only productive equilibrium. That point would have been characterized by not having infected T-cells while having infected macrophages. The absence of such equilibrium is not surprising. Even in the previous model, where macrophages had a higher role

in spreading the infection than T-cells did (by not considering the transmission route between T-cells), the productive equilibrium was maintained by both cells, and not just by macrophages. These findings complement the biological claim that it is T-cells that are the primary propagators of HIV in the body, and thus a sustainable infection is one that presupposes the presence of infected T-cells.

Before we proceed in defining the admissibility criteria for the equilibrium points E_3 and E_4, we make the following observation. The proof is given in Appendix .2.

Lemma 4. *P_0 is non-negative.*

The following lemmas define regions of admissibility for the equilibrium points. As in the previous chapter, admissibility refers to each component being non-negative. Doing that allows us to focus on only biologically plausible scenarios.

Lemma 5. *The admissibility region of the equilibrium point E_3 falls in the region $\{R_{01} \leq 1 \leq R_{02}\}$.*

Proof. For E_3 to be of biological significance, all its components need to be non-negative. Note that $y^* \geq 0$ if and only if $R_{02} \geq 1$. The aim is to show that v^* is always negative if and only if R_{01} is greater than 1. To proceed, we simplify P_ε by substituting it with P_0. We make the following argument to show that considering this particular value of ε does not take away from the generality of the result:

> Recall that v^* represents the number of infected T-cells. Since the death rate of infected T-cells is given by $1+\varepsilon$ (in the non-dimensionalized system (3.5)), as ε increases, infected T-cells are being cleared out at a faster rate. Hence, v^* decreases. This means that v^* is maximized when the death rate of infected T-cells is minimized, which corresponds to $\varepsilon = 0$. If even in that scenario, where v^* is maximal, $v^* < 0$ then v^* is guaranteed to remain negative when ε varies between 0 and 1.

With this simplification in place, we have:

$$v^* = \frac{1}{2}\left(Q - \sqrt{P_0}\right)$$

where

$$Q := a\alpha_1^2 - 1 - \alpha_1 b + \alpha_1^3 b.$$

If $Q < 0$, then $v^* < 0$ follows readily without needing to impose further conditions. Note that we are implicitly using that $P_0 \geq 0$ given by Lemma 4 to guarantee that $\sqrt{P_0}$ is a real positive number.

If $Q \geq 0$, then:

$$
\begin{aligned}
Q - \sqrt{P_0} < 0 \quad &\iff \\
Q < \sqrt{P_0} \quad &\iff \\
Q^2 < P_0 \quad &\iff \\
Q^2 - P_0 < 0 \quad &\iff \\
4a\alpha_1^3 b(-1+\alpha_1^2) < 0 \quad &\iff \\
\alpha_1 < 1 \quad &\iff \\
R_{01} > 1. &
\end{aligned}
$$

This proves that $v^* < 0$ if and only if $R_{01} > 1$, rendering E_3 inadmissible. Hence, the region of admissibility of E_3 is within the domain $\{R_{01} \leq 1 \leq R_{02}\}$. □

Lemma 6. *The admissibility region of the equilibrium point E_4 falls in the domain $\{\min(R_{01}, R_{02}) \geq 1\}$.*

Proof. The three conditions to check are:

1. $y^* \geq 0$
2. $\hat{u} \geq 0$
3. $\hat{v} \geq 0$

The first condition is straightforward from the fact that R_{02} is greater than 1. For the third condition, using the same argument for ε that was made in the previous lemma, i.e. we consider $\varepsilon = 0$. Assume that $Q \leq 0$. Then:

$$
\begin{aligned}
\hat{v} \geq 0 \quad &\iff \\
v^* + \sigma \geq 0 \quad &\iff \\
\frac{1}{2}Q + \frac{1}{2}\sqrt{P_0} \geq 0 \quad &\iff \\
Q^2 - P_0 \leq 0 \quad &\iff \\
4a\alpha_1^3(-1+\alpha_1^2) \leq 0 \quad &\iff \\
\alpha_1 \leq 1 \quad &\iff \\
R_{01} \geq 1. &
\end{aligned}
$$

If $Q > 0$, then

$$\hat{v} = \frac{1}{2}\left(Q + \sqrt{P_0}\right) \geq 0.$$

For the second condition, consider $\varepsilon = 0$ based on the following argument:

> Recall that $\hat{u}$ represents the number of susceptible T-cells. Susceptible T-cells decrease as infected T-cells increase. That is because the interaction between those two cells convert the susceptible cell into an infected one. Hence, when the number of infected T-cells is maximized, the number of

susceptible T-cells is minimized. The number of infected T-cells is maximized when their death rate is minimized, which corresponds to ε being zero. Hence, when ε is zero, the number of susceptible T-cells is minimized. So if we manage to prove that u^* is non-negative when $\varepsilon = 0$, we are guaranteed that u^* will remain non-negative as ε increases in its domain of definition.

Assume that $R_{01} < 1$, then:

$$\begin{aligned}
\alpha_1 > 1 \quad &\implies \\
Q > 0 \quad &\implies \\
-Q < \sqrt{P_0} \quad &\implies \\
-\alpha_1^3 b + a\alpha_1^2 + \alpha_1 b + 1 < \sqrt{P_0} \quad &\implies \\
(-\alpha_1 b + a)\alpha_1^2 + \alpha_1 b + \sqrt{P_0} + 1 < 2\sqrt{P_0} \quad &\implies \\
\frac{-\alpha_1 b + a}{2a} + \frac{b}{2a\alpha_1} + \frac{\sqrt{P_0}+1}{2a\alpha_1^2} < \frac{\sqrt{P_0}}{R_{02}} \quad &\implies \\
u^* < \frac{\sqrt{P_0}}{R_{02}} \quad &\implies \\
\hat{u} < 0 &
\end{aligned}$$

The second implication follows from observing that Q can be rewritten as in the equation below, and that $R_{02} > 1$ is a necessary condition for admissibility.

$$Q = (R_{02} - 1) + b(\alpha_1^3 - \alpha_1).$$

Hence we have that shown $\hat{u} \geq 0 \implies R_{01} \geq 1$. □

We rewrite the admissibility regions in terms of the singular reproduction number R_0 and display the results in the Table 3.5. This shows that all productive equilibrium are admissible only when the reproduction number is greater than or equal to 1. However, in the study of stability, using the reproduction numbers R_{01} and R_{02}, instead of their maximum R_0, will prove useful. Therefore, we also provide a visual illustration of the admissibility regions of the equilibrium points in terms of R_{01} and R_{02}, given in Figure 3.2. Inspecting the figure further, we can see that at most the system can have three equilibrium points simultaneously. That is because the regions of admissibility of E_3 and E_4 are not overlapping.

Table 3.5: Admissibility regions in terms of R_0

Equilibrium point	Reproduction number
E_1	admissible everywhere
E_2	$R_0 \geq 1$
E_3	$R_0 = R_{02} \geq 1$
E_4	$R_0 \geq 1$

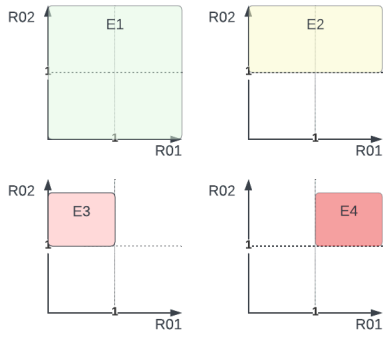


Figure 3.2: Admissibility regions in terms of R_{01} and R_{02}

3.5 Stability analysis

We begin this section by computing the Jacobian associated with the system (3.5).

$$J_X := \nabla G(X) = \begin{pmatrix} -\alpha_1 - y & -x & 0 & 0 \\ y & -\alpha_1 + x & 0 & 0 \\ 0 & -{\alpha_1}^2\, b\, u & -1 - v - {\alpha_1}^2\, b\, y & -u \\ 0 & a\,{\alpha_1}^4\, b\, u & a\,{\alpha_1}^2\, v + a\,{\alpha_1}^4\, b\, y & -1 - \varepsilon + a\,{\alpha_1}^2\, u \end{pmatrix}.$$

Having this matrix in place, we will proceed to prove several local asymptotic stability properties for the four equilibrium points.

Lemma 7. *The disease-free equilibrium E_1 is locally asymptotically stable if and only if $R_0 < 1$.*

Proof. The eigenvalues of J_{E_1} are given by the following vector:

$$\mathrm{eig}(J_{E_1}) = \begin{pmatrix} -1 \\ -\alpha_1 \\ -\frac{-1+{\alpha_1}^2}{\alpha_1} \\ (1+\varepsilon)(R_{02}-1) \end{pmatrix}$$

The first two eigenvalues are always negative. The third eigenvalue is negative if and only if $\alpha_1 > 1$, which is a sufficient and necessary condition for R_{01} to be less than one. Moreover, the fourth eigenvalue is negative if and only if R_{02} is less than 1. □

Lemma 8. *When $R_{01} < 1 < R_{02}$, the T-cell induced infection state at E_2 is locally asymptotically stable.*

Proof. The eigenvalues of J_{E_2} are given by the following vector:

$$\mathrm{eig}(J_{E_2}) = \begin{pmatrix} -\alpha_1 \\ \frac{1}{\alpha_1} - \alpha_1 \\ -\frac{\sigma + a\,{\alpha_1}^2}{2\,(1+\varepsilon)} \\ \frac{\sigma - a\,{\alpha_1}^2}{2\,(1+\varepsilon)} \end{pmatrix}$$

where

$$\sigma = \sqrt{4 + 12\,\varepsilon + 12\,\varepsilon^2 + 4\,\varepsilon^3 - 4\,a\,{\alpha_1}^2 - 8\,a\,{\alpha_1}^2\,\varepsilon - 4\,a\,{\alpha_1}^2\,\varepsilon^2 + a^2\,{\alpha_1}^4}$$

The second eigenvalue $\frac{1}{\alpha_1} - \alpha_1$ is negative if and only if $R_{01} < 1$. If we assume that σ is non-negative, the third eigenvalue is always negative. Thus the local asymptotic stability of E_2 depends on the fourth eigenvalue being negative; that is:

$$\begin{aligned} \sigma < a\alpha_1^2 \qquad & \iff \\ \sigma^2 < a^2\alpha_1^4 \qquad & \iff \\ \sigma^2 - a^2\alpha_1^4 < 0 \qquad & \iff \\ 4(1+\varepsilon)^3(1 - R_{02}) < 0 & \end{aligned}$$

The last inequality is true if and only if $R_{02} > 1$.

Now, we consider the case when σ is an imaginary number. This corresponds to the polynomial under the square root being negative. In that case, σ is a pure imaginary number, and the real part of the third and fourth eigenvalues is given by $-\frac{a\alpha_1^2}{2(1+\varepsilon)}$ which is negative. Hence, E_2 is locally asymptotically stable. □

Lemma 9. *E_3 is not locally asymptotically stable.*

Proof. Since $R_{01} < 1$ is a necessary condition for the validity of E_3, we have that α_1 is greater than 1. One of the eigenvalues of J_{E_3} is $\alpha_1 - \frac{1}{\alpha_1} > 0$, rendering this point locally unstable. □

Conjecture 1. *When $R_{01} > 1$ and $R_{02} > 1$, the productive equilibrium E_4 is locally asymptotically stable.*

Sketch of Proof. We compute the eigenvalues of J_{E_4} and give them in the following vector:

$$\mathrm{eig}(\mathrm{J_{E_4}}) = \begin{pmatrix} \frac{-1+{\alpha_1}^2}{\alpha_1} \\ -\alpha_1 \\ \_\frac{3\,\varepsilon-\sigma_5+\varepsilon\,\sigma_6+2\,\sigma_6+\varepsilon^2+\sigma_1-\alpha_1\,b\,\varepsilon-\sigma_4-\sigma_3+\sigma_2+2}{4\,(1+\varepsilon)} \\ \_\frac{3\,\varepsilon+\sigma_5+\varepsilon\,\sigma_6+2\,\sigma_6+\varepsilon^2+\sigma_1-\alpha_1\,b\,\varepsilon-\sigma_4-\sigma_3+\sigma_2+2}{4\,(1+\varepsilon)} \end{pmatrix}$$

The first eigenvalue is negative if and only if $R_{01} > 1$. The second eigenvalue is always negative. For the third and fourth eigenvalues, we consider sample values of the variables a, b, α_1 and ε ensuring that all those values fall within the admissibility domain defined in Lemma 6. We also make use of (3.6) to inform us about biologically plausible values for a and b. The following sample values are considered:

$$\begin{aligned} \varepsilon &= 0, 0.25, 0.5, 1 \\ \alpha_1 &= 0.1, 0.11, 0.12, \ldots, 0.99 \\ a &= 20001, 30001, 40001, \ldots, 990001 \\ b &= a/10^4 \end{aligned}$$

We have chosen $\alpha_1 < 1$ to meet the necessary stability requirement that $R_{01} > 1$. We have chosen the minimum value of a to be 20000 to meet the necessary admissibility requirement that $R_{02} > 1$.

The below plots show the maximum value attained by the third and fourth eigenvalues as ε and α_1 vary. The maximum is over all possible values of a and b as α_1 and ε are fixed.

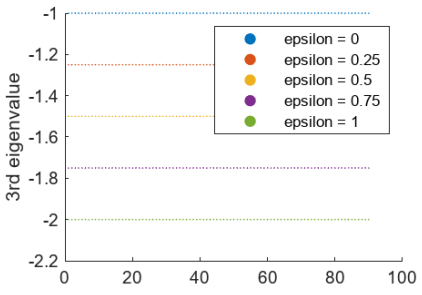


Figure 3.3: Maximum value of the third eigenvalue as α_1 varies

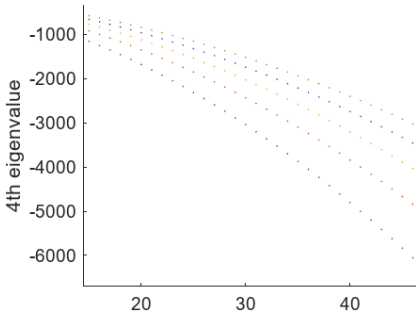


Figure 3.4: Maximum value of the third eigenvalue as α_1 varies

Since the values of both eigenvalues never exceed a negative number, we can conclude that this equilibrium point is locally asymptotically stable in its region of admissibility (within those considered values of the parameters). □

We give one more result to show that the disease-free equilibrium is in fact globally stable.

Lemma 10. *There exists a region within the local asymptotic stability region of E_1 where the disease-free equilibrium is globally stable. Recall that the local asymptotic stability region of E_1 is given by $\{R_0 < 1\}$.*

Proof. We will first prove that E_1 is Lyapunov stable. To do so, we will construct a functional $V(X)$ and prove that it is a Lyapunov function. This will give us Lyapunov stability. To go from Lyapunov stability to global stability, we will show that the functional is radially unbounded.

Define a functional V as:

$$V(X) := A\left(x - \frac{1}{\alpha_1} - \frac{1}{\alpha_1}\ln(\alpha_1 x)\right) + Ay + B\left(u - 1 - ln(u)\right) + Bv, \tag{3.8}$$

where A and B are two positive constants to be defined. This construction has been inspired by what is called the Volterra-type Lyapunov functions, which have been shown to be good candidates for Lyapunov functions for the disease-free equilibrium [9]. The aim is to show that V is a Lyapunov function. For that to be the case, V needs to satisfy three conditions:

1. $V(E_1) = 0$, and
2. $V(X) > 0$ for all $X \neq E_1$, and
3. $\dot{V} := \frac{d}{dt}V(X(t)) < 0$.

The first condition comes readily when we substitute X with E_1. The second condition is satisfied and the proof is given in Appendix .3. Before we check for the third condition, we define the constants A and B to be:

$$A = \frac{\alpha_1^3 b}{(\alpha_1 + 1)(1 - R_{02})},$$
$$B = \frac{\alpha_1 - 1}{(1 + \varepsilon)(1 - R_{02})}.$$

The assumption that R_0 is less than 1 is necessary to guarantee that A and B are indeed positive. Using the chain rule, we get the following equation for $\dot{V}$:

$$\begin{aligned}\dot{V} = &- \frac{\alpha_1 - 1}{u(1+\varepsilon)(1-R_{02})} \\ &- \frac{u(-1+\alpha_1)(1+v(1-(1+\varepsilon)R_{02}) + \alpha_1^2 by(1-(1+\varepsilon)R_{02})}{(1+\varepsilon)(1-R_{02})} \\ &- \frac{\varepsilon vx(\alpha_1^2-1) + \varepsilon xy\alpha_1^2 b(\alpha_1^2-1)}{x(1+\alpha_1)(1+\varepsilon)(1-R_{02})} \\ &- \frac{M_{\varepsilon,\alpha_1,b}(x)}{x(1+\alpha_1)(1+\varepsilon)(1-R_{02})}\end{aligned}$$

where

$$M_{\varepsilon,\alpha_1,b}(x) = \alpha_1^4 b(1+\varepsilon)x^2 - 2(\alpha_1^2 + \alpha_1^3 b + \alpha_1^3 b\varepsilon - 1)x + \alpha_1^2 b(1+\varepsilon),$$

Written this way, we can examine the sign of each expression for $\dot{V}$ to prove that $\dot{V}$ is strictly negative. The first and third expressions being strictly negative follow readily from the assumptions that $R_{01} < 1$ and $R_{02} < 1$. The second expression is non-negative when $R_{02} \leq \frac{1}{1+\varepsilon}$. To examine the sign of the fourth expression, we consider M as a quadratic polynomial in x. Using the quadratic formula, M admits two roots r_1 and r_2 given below:

$$r_1 = \frac{1}{\alpha} - \frac{\sqrt{(-1+\alpha)\,(1+\alpha)\,(-1+\alpha^2+2\,\alpha^3\,b+2\,\alpha^3\,b\,\varepsilon)} - \alpha^2 + 1}{\alpha^4\,b\,(1+\varepsilon)},$$
$$r_2 = \frac{1}{\alpha} + \frac{\alpha^2 + \sqrt{(-1+\alpha)\,(1+\alpha)\,(-1+\alpha^2+2\,\alpha^3\,b+2\,\alpha^3\,b\,\varepsilon)} - 1}{\alpha^4\,b\,(1+\varepsilon)}.$$

Examining the sign of M, we get that $M_{\varepsilon,\alpha_1,b}(x) > 0$ when $x \in [0, r_1]$. Therefore, in that region, the fourth component of $\dot{V}$ is negative. Note that the second root r_2 is rejected since it is greater than $\frac{1}{\alpha_1}$, using Lemma 1. This means that our condition that $x \in [0, r_1]$ only eliminates values of x that fall between the two roots.

Let $\Omega := \{X \in \mathbb{R}^4_+ : R_{01} < 1, R_{02} \leq \frac{1}{1+\varepsilon}, x \in [0, r_1]\}$. Then V is a Lyapunov function in Ω. Moreover, since V is radially unbounded (i.e. $V(\|X\|) \to \infty$ as $\|X\| \to \infty$). Since x and y are bounded by Lemma 1, $\|X\| \to \infty$ if and only if $\|u\| \to \infty$ or $\|v\| \to \infty$. Hence, V is radially unbounded.

Putting everything together, we have shown that there exists a subdomain Ω of the local asymptotic stability domain for E_1 where the disease-free equilibrium is globally stable. This means that as long as the initial condition lies within Ω, we are guaranteed that the system will approach a disease-free state. This is a useful result especially since Ω only depends on x (and not on y, u or v) meaning that a certain bound on the initial number of susceptible macrophages is sufficient to guarantee the disease-free state of the model presupposing that the reproduction numbers are less than 1. □

To wrap up this section, we summarize the regions of local stability of the four equilibrium points in relation to the two reproduction numbers R_{01} and R_{02} in the diagram given in Figure 3.5. The equilibrium point E_3 is not visualized below since it's not locally asymptotically stable anywhere. Unsurprisingly, those local stability regions for the other three points are not overlapping.

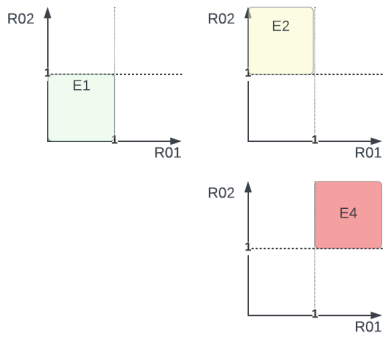


Figure 3.5: Local stability regions

3.6 Numerical investigation

In this section we will perform some numerical simulations for the solution. The aim of this section is to complement the stability analysis and to illustrate how the solution behave as the key parameters, alongside the reproduction numbers R_{01} and R_{02}, vary.

First we will estimate the parameters based on existing literature, and then we will define our initial point. In the following subsection, we will vary the two variables ε and α_1 and plot the solution across the different considered values. We will describe the plots and relate them to the stability analysis.

3.6.1 Parameter estimates

We begin this section by noting down that estimating parameters for this kind of study is not a straightforward exercise. Most parameter estimates for HIV study come from SIV data. SIV (Simian Immunodeficiency Virus) is a virus that infects monkeys and apes and is closely related to HIV. Because of the similarities of the two viruses, SIV is often used as a model for studying HIV [12] [18].

As we have seen in Section 1.4, macrophages are specialized cells that reside in specific tissues and adapt to the local environment. This means that a macrophage residing in the liver might be more susceptible to one residing in the brain when it comes to transmission efficiency. In addition to that, since the brain is an immune-privileged compartment, it is likely the case that there are less T-cells residing in the brain which would in turn affect the values of the contact rates between macrophages and T-cells. Hence, it is important to highlight that the estimates given below are a generalization and might not apply to individual cases. With that said, we believe that there is value to be gained from performing this simulation to deepen our understanding on the significance of some key parameters in the model.

Table 3.6: Parameters Estimates

Parameter	Value	Source
s_1	10	[18]
s_2	10^4	[18]
d_1	10^{-2}	[18]
d_2	$\frac{d_1}{\alpha_1}$	definition
d_3	$d_2 + \varepsilon d_2$	definition
e_1	3×10^{-5}	definition
e_2	2×10^{-5}	$e_2 < e_1$
e_3	10^{-5}	$e_3 < e_2$
c_1	10^{-5}	[12]
c_2	10^{-4}	$c_2 > c_1$
c_3	10^{-2}	$c_3 > c_2$

Table 3.6 gives the parameter estimates we have considered. The values for d_2 and d_3 are given in terms of α_1 and ε which are the two parameters that we will vary. According to [1], the efficiency rate of transmission between macrophages is likely to be higher than that between T-cells. We define e_1 to be 3×10^{-5} and choose the values for e_2 and e_3 such that $e_1 > e_2 > e_3$. For the contact rate parameters, since the number of macrophages is less than that of T-cells, the contact rate between T-cells needs to be higher than that between macrophages, or between one T-cell and one macrophage. In other words, we have the following relationship: $c_3 > c_2 > c_1$. We have chosen c_1 to be equal to 10^{-5} guided by the estimate given in [12], and then chosen the values of c_2 and c_3 to be increasingly greater than that of c_1.

Now that we have estimates our parameters, we define the initial point:

$$X_0 = \begin{pmatrix} x_0 \\ y_0 \\ u_0 \\ v_0 \end{pmatrix}.$$

Recall that in Lemma 1, we have shown that the solution needs to lie in Γ as time goes to infinity. Hence, we have the following constraint:

$$x_0 + y_0 = \frac{s_1}{d_1}.$$

Using the parameter estimates, we get that:

$$x_0 + y_0 = 10^3.$$

To emphasize the role of infected macrophages, we choose $y_0 = 750$ and $u_0 = 250$. We also start out with an initial value of 0 for infected T-cells so that the propagation of the virus is only carried out by macrophages. Finally, we choose

u_0 to be 200. Recall that in Section 1.1, this value is the detection limit for AIDS. Hence, we have:

$$X_0 = \begin{pmatrix} 250 \\ 750 \\ 200 \\ 0 \end{pmatrix}.$$

In the next section, we will use the parameter estimates and the initial point to simulate the solution over time.

3.6.2 Solution modeling

We consider the following values for ε and α_1:

$$\varepsilon = 0, 0.5, 1$$
$$\alpha_1 = 0.5, 1, 1.5.$$

The tables below summarize the values of the reproduction numbers based on the values of α_1 and ε. The reproduction numbers are rounded to the nearest tenth.

Table 3.7: $\varepsilon = 0$.

α_1	0.5	1	1.5
R_{01}	4	1	0.4
R_{02}	0.3	1	2.3
R_0	4	1	2.3

Table 3.8: $\varepsilon = 0.5$.

α_1	0.5	1	1.5
R_{01}	4	1	0.4
R_{02}	0.2	0.6	1.5
R_0	4	1	1.5

Table 3.9: $\varepsilon = 1$.

α_1	0.5	1	1.5
R_{01}	4	1	0.4
R_{02}	0.1	0.5	1.1
R_0	4	1	1.1

We highlight the combinations of values which give us local asymptotic stability in the tables below. The highlighted values correspond to the local stability region for E_2.

Table 3.10: $\varepsilon = 0$.

α_1	0.5	1	1.5
R_{01}	4	1	0.4
R_{02}	0.3	1	2.3
R_0	4	1	2.3

Table 3.11: $\varepsilon = 0.5$.

α_1	0.5	1	1.5
R_{01}	4	1	0.4
R_{02}	0.2	0.6	1.5
R_0	4	1	1.5

Table 3.12: $\varepsilon = 1$.

α_1	0.5	1	1.5
R_{01}	4	1	0.4
R_{02}	0.1	0.5	1.1
R_0	4	1	1.1

We will see in the solution plots that for those combinations of ε and α_1, where E_2 is locally asymptotically stable, will approach the dimensionalized value of E_2. Recall from the non-dimensionalization process described in Appendix .1,

$$E_2 = \begin{pmatrix} \frac{s_1}{d_2}\tilde{x} \\ \frac{s_1}{d_2}\tilde{y} \\ \frac{s_2}{d_2}\tilde{u} \\ \frac{d_2}{e_3 c_3}\tilde{v} \end{pmatrix},$$

where the tilde denotes the non-dimensionalized variable, and E_2 is now written in its dimensionalized form.

We plot the solution over the next 20 years. The plots are given in Figure 3.6, Figure 3.7 and Figure 3.8. In all three figures, where $\alpha_1 = 1.5$, the solution approached the equilibrium point E_2. We can also see that in all the cases, the number of both susceptible and infected macrophages are similar. Susceptible macrophages eventually increase to their asymptotic value of 1000, while that of infected macrophages goes to zero. These findings complement the assumption that an HIV pathogenesis – if it occurs – needs to be maintained by T-cells. While macrophages themselves cannot carry out an HIV infection over a long period of time, they are capable of inducing it by infecting T-cells and then allowing the infected T-cells to propagate the infection. With these observations, we conclude this section.

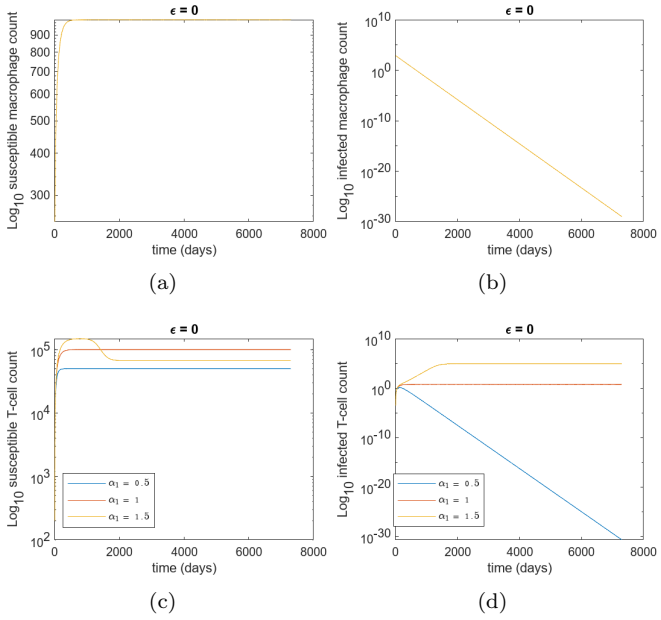


Figure 3.6: Plots of cell populations over time where $\varepsilon = 0$.

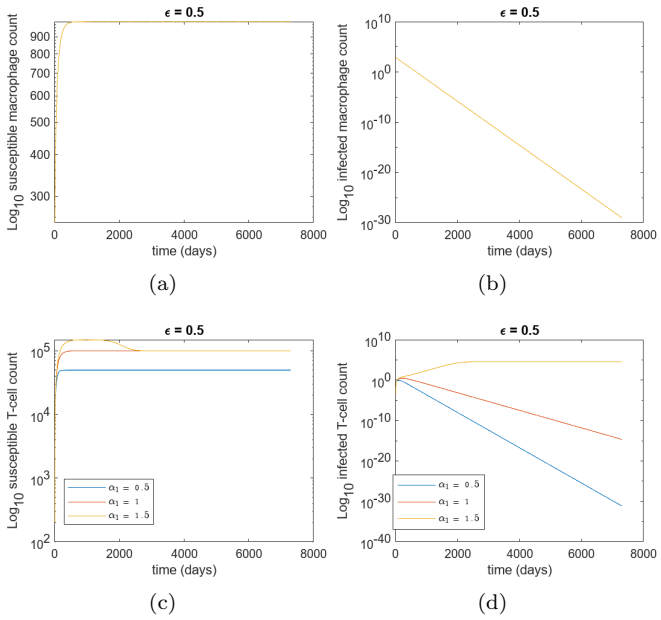


Figure 3.7: Plots of cell populations over time where $\varepsilon = 0.5$.

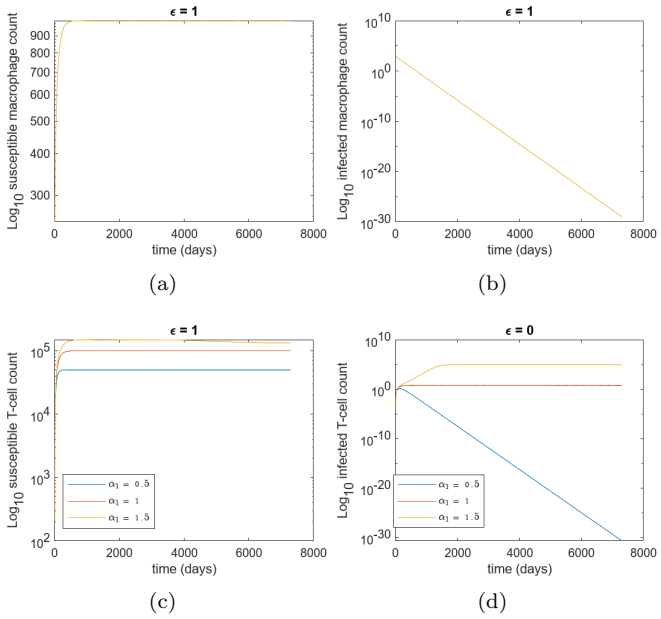


Figure 3.8: Plots of cell populations over time where $\varepsilon = 1$.

3.7 Conclusion

In this chapter, we considered a non-linear model (3.5) to supplement that studied in the first chapter (2.2) by taking into account a more realistic scenario. While the first model informed us that macrophages can by themselves lead to a plausible infection steady state, this model tries to shed light on the following question:

> How important of a role do macrophages have in creating and maintaining an infection state?

By considering the additional transmission route between T-cells, we underlined that the role of macrophages does not just revolve around how they *directly* propagate the virus, but also in how they *indirectly* do so. A direct propagation of the virus means that the infection is maintained by a high number of infected macrophages; on the other hand, an indirect propagation of the virus is concerned with the existence of an infection state independent on the cell type. As we have noted in Section 3.4, there does not exist an equilibrium point where the virus is only propagated by macrophages. However, there does exist one where the virus is only propagated by T-cells, namely E_2. Using the terminology of the preceding sentence, macrophages are indirect propagators of the virus. This particular equilibrium point was also shown to be locally asymptotically stable, and in the numerical investigations given in Section 3.6 we saw that there exist biologically plausible values of the parameters where the local asymptotic stability of this point is attained.

Going back to the question at hand, we have shown that macrophages have a major role in creating and maintaining an infection state. The significance of this role is dependent on how capable macrophages are in infecting the initially purely susceptible population of T-cells. Efficiency and contact parameters, especially those between macrophages and T-cells, govern this process. Those parameters are dependent on where in the body the infection lies, as that will influence how successful macrophages are in establishing virological synapses for T-cells, and also how much those two cell types are in contact with each other. Unsurprisingly, those parameters appear in the reproduction number R_{02}, and as they increase so does the reproduction number. Finally, we have also defined conditions where an infection can be maintained. In other words, when the productive equilibrium E_4 is locally stable, an infection state can be maintained over time as long as our starting point is sufficiently close to the productive equilibrium.

Chapter 4

Discussion

Although HIV treatment has been successful in suppressing the disease, a cure has yet to be found. Consequently, HIV infection is currently a chronic disease. The presence of HIV reservoirs impedes the development of a cure. These reservoirs can cause the infection to re-surge if treatment is paused. Macrophages have been shown to be constituents of these HIV reservoirs. Therefore, understanding the role of macrophages is crucial for understanding the HIV reservoir.

In this study, we employed two mathematical models to gain insight into the understanding of HIV reservoirs established by macrophages. The first model poses the question of whether an infected set of macrophages can maintain an HIV infection over time without the help of other cells, while the second model is concerned with how important of a role macrophages have in creating and maintaining an HIV infection state. The latter model supplements the first one by considering additional infection route: T-cells can spread the infected among each other. Both models have two cell population groups, namely macrophages and T-cells. The interpretation of the results of both models are given in sections 2.6 and 3.7. The common conclusion is that macrophages are an important factor in HIV pathogenesis. Even by themselves, they can potentially induce and maintain an infection state. However, that role becomes more significant when we consider a more realistic biological context. This result is consistent with previous studies such as [12], [18]. What can we take out of this conclusion?

With our conclusion, we aim to further emphasize the need to expand our knowledge of macrophages and the HIV reservoirs in general. Previous HIV research has been skewed towards T-cells leaving a big knowledge gap in our understanding of other contributors. While our models have also shown that T-cells are the primary propagators of HIV, that does not invalidate the role of macrophages. By considering an initial starting point with zero infected T-cells, we have shown that an infection state can still be achieved due to an initial population of infected macrophages.

We have made two simplifications. The first one is that we have not made a distinction between latently infected macrophages and productively infected macrophages. The behavior of macrophages in those states can be different, and

thus influence the dynamics of the model. The second simplification is that we have not considered a specific body tissue. Macrophages are highly specialized cells and they adapt to the local environment they permanently reside in. We suggest future research to focus on one body tissue, such as the brain. This would improve parameter estimation, and thus open up the room for further numerical investigation. Numerical investigation for those models might prove very useful. As both models contain several nonlinear terms that are the result of considering a heterogeneous cell population group, an analytical approach is challenging.

To conclude this work, we provide an overarching summary:

> Macrophages are an essential piece of the puzzle when it comes to finding a cure for HIV. While CD4+ T-cells have been the main focus of research in the past, recent studies and ours have demonstrated that macrophages also play a crucial role in the development of HIV pathogenesis. By understanding the role macrophages play in HIV pathogenesis, we can develop more effective treatments and ultimately find a cure for this disease. Every step we take towards understanding this complex disease brings us one step closer to finding a cure and changing the lives of millions of people around the world.

Appendices

.1 Non-dimensionalization of Model II

The non-dimensionalization of the system 3.1 is carried out as follows:

Let x^0, y^0, t^0, u^0 and v^0 be positive constants such that:

$$\begin{aligned} x^0 &= \frac{s_1}{d_2} \\ y^0 &= \frac{s_1}{d_2} \\ t^0 &= \frac{1}{d_2} \\ u^0 &= \frac{s_2}{d_2} \\ v^0 &= \frac{d_2}{e_3 c_3} \end{aligned}$$

Then letting $\tilde{x} = \frac{x}{x_0}$, $\tilde{y} = \frac{y}{y^0}$, $\tilde{t} = \frac{t}{t^0}$, $\tilde{u} = \frac{u}{u^0}$ and $\tilde{v} = \frac{v}{v^0}$, the system can be re-written in terms of the new variables as:

$$\begin{aligned} \dot{\tilde{x}} &= 1 - \tilde{x}\tilde{y} - \frac{d_1}{d_2}\tilde{x} \\ \dot{\tilde{y}} &= \tilde{x}\tilde{y} - \frac{d_1}{d_2}\tilde{y} \\ \dot{\tilde{u}} &= 1 - \frac{e_2 c_2 s_1}{d_2^2}\tilde{u}\tilde{y} - \tilde{u}\tilde{v} - \tilde{u} \\ \dot{\tilde{v}} &= \frac{e_2 c_2 s_1}{d_2^2}\frac{e_3 c_3 s_2}{d_2^2}\tilde{u}\tilde{y} + \frac{e_3 c_3 s_2}{d_2^2}\tilde{u}\tilde{v} - (1+\varepsilon)\tilde{v} \end{aligned}$$

Choose the non-dimensionalization parameters as follows:

$$\begin{aligned} \alpha_1 &= \frac{d_1}{d_2} \\ \alpha_2 &= \frac{e_2 c_2 s_1}{d_2^2} \\ \alpha_3 &= \frac{e_3 c_3 s_2}{d_2^2}. \end{aligned}$$

Finally, we get the following non-dimensionalized system:

$$\begin{aligned} \dot{\tilde{x}} &= 1 - \tilde{x}\tilde{y} - \alpha_1\tilde{x} \\ \dot{\tilde{y}} &= \tilde{x}\tilde{y} - \alpha_1\tilde{y} \\ \dot{\tilde{u}} &= 1 - \alpha_2\tilde{u}\tilde{y} - \tilde{u}\tilde{v} - \tilde{u} \\ \dot{\tilde{v}} &= \alpha_2\alpha_3\tilde{u}\tilde{y} + \alpha_3\tilde{u}\tilde{v} - (1+\varepsilon)\tilde{v} \end{aligned}$$

This system now has four parameters instead of ten.

.2 Proof that P_0 is non-negative

Lemma 11. *P_0 is non-negative.*

Proof. First, we consider P_0 as a quadratic polynomial in b, with a and α_1 as parameters.

$$\begin{aligned} P_0(b) = 1 &+ 2\alpha_1 b + {\alpha_1}^2 b^2 \\ &- 2{\alpha_1}^3 b - 2{\alpha_1}^4 b^2 + {\alpha_1}^6 b^2 - 2a{\alpha_1}^2 \\ &+ 2a{\alpha_1}^3 b - 2a{\alpha_1}^5 b + a^2 {\alpha_1}^4 \end{aligned}$$

Viewed this way, P_0 admits two roots:

$$b_1^* = -\frac{\left(\sqrt{a}\,\alpha_1 - 1\right)^2}{\alpha_1 - {\alpha_1}^3}$$

$$b_2^* = -\frac{\left(\sqrt{a}\,\alpha_1 + 1\right)^2}{\alpha_1 - {\alpha_1}^3}$$

The following is the sign table for P_0:

		b_1^0		b_2^0	
$P_0(b)$	$+$	$\bullet$	$-$	$\bullet$	$+$

The first claim we will prove is that when $R_{01} > 1$, $P_0(b)$ is always positive.

$$\begin{aligned} R_{01} > 1 &\implies \\ \alpha_1 < 1 &\implies \\ \max(b_1^*, b_2^*) < 0 &\implies \\ b > \max(b_1^*, b_2^*) &\implies \\ P_0(b) > 0. & \end{aligned}$$

In what follows, we will assume that $R_{01} \leq 1$. In that case, $b_2^0 > b_1^0$.
We define g as a function of a, and compute its derivative.

$$\begin{aligned} g(a) &:= a - b_1^* \\ g'(a) &= 1 - \frac{\sqrt{a}\alpha_1 - 1}{\sqrt{a}(-1 + \alpha_1^2)} \end{aligned}$$

We solve for $g'(a) = 0$ to get

$$a^* := \frac{1}{(1 + \alpha_1 - \alpha_1^2)^2}$$

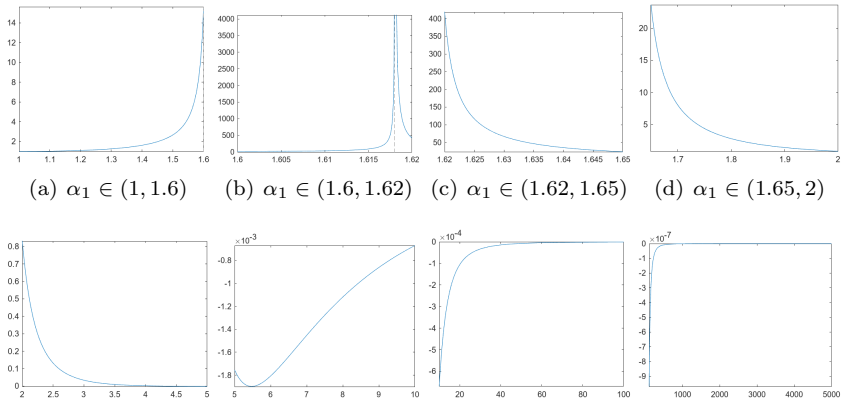
The following is the table of variation for the function g:

	a^*		
$g'(a)$	$+$	0	$-$
$g(a)$	$\nearrow$		$\searrow$

Hence, g attains its maximum at a^*. Now we consider $g(a^*)$ as a function of α_1:

$$g(a^*)(\alpha_1) = \frac{3\,{\alpha_1}^3 - {\alpha_1}^4 + \alpha_1\left(2\left|1+\alpha_1-{\alpha_1}^2\right| - 3\right) - 1}{\alpha_1\left(-1+{\alpha_1}^2\right)\left(1+\alpha_1-{\alpha_1}^2\right)^2}$$

We plot this function over various intervals of α_1 as described in the figure below:



(a) $\alpha_1 \in (1, 1.6)$ (b) $\alpha_1 \in (1.6, 1.62)$ (c) $\alpha_1 \in (1.62, 1.65)$ (d) $\alpha_1 \in (1.65, 2)$

(e) $\alpha_1 \in (2, 5)$ (f) $\alpha_1 \in (5, 10)$ (g) $\alpha_1 \in (10, 1e^2)$ (h) $\alpha_1 \in (1e^2, 5e^3)$

Figure 1: Plotting $g(a^*)$ over several intervals of α_1

The function attains a local maximum value in the second chosen interval where $\alpha_1 \in (1.6, 1.62)$. In fact, this value is reached when $\alpha_1 \approx 1.6180$, and its value is ≈ 8133. As the value of α_1 increases, we can see that $g(a^*)$ is negative and approaches zero. The negative sign of $-\alpha_1^4$ in the numerator eventually dominates.

By 3.6 since $a \geq \mathcal{O}(10^4)b$ and $\max_{\alpha_1} g(a^*)(\alpha_1) < 10^4$, we conclude that $b \overset{!}{<} b_1^*$. Hence, P_0 is always positive in this case.

□

.3 Proof that $V(X)$ is positive when $X \neq E_1$

Lemma 12. *$V(X)$, defined in 3.8, is positive positive when $X \neq E_1$.*

Proof. First we will consider a real-valued function f, with parameter x_0, defined as:

$$f(x) = x - x_0 - x_0 \ln \frac{x}{x_0},$$

where x_0 is a fixed given point. We will show that this function admits a local minimum at $x = x_0$. The derivative of f is given by:

$$\frac{df}{dx} = 1 - \frac{x_0}{x}.$$

Solving $\frac{df}{dx} = 0$, we get that $x = x_0$. The table of variable of f as a function of x is given below:

	x_0	
$f'(x)$	$-$	$+$
$f(x)$	$\searrow$	$\nearrow$

Hence, f attains its minimum at $x = x_0$, and $f(x_0) = 0$. This proves our first claim. Observe that $V(X) = Af_{E_1(1)}(x) + Ay + Bf_{E_1(3)}(u) + Bv$. Since A and B are positive constants, the functions $Af_{E_1(1)}$ and $Bf_{E_1(3)}$ have the same table of variation as that of f. Moreover, since y and v are both non-negative, their minimum is attained when they are zero; i.e. when $y = E_1(2)$ and $v = E_1(3)$. This proves that V is positive for all (admissible) X as long as $X \neq E_1$. $\square$

Glossary

admissibility criteria A set of biological constraints to distinguish between physically plausible scenarios and those that are pure mathematical artifacts. 12, 16, 25

alveolar The name of macrophages residing in the lungs. 5

Antiretroviral therapy A drug-based treatment regimen for HIV. 4

blood-brain barrier A highly selective border that prevents elements from the circulating blood from entering the extracellular fluid of the central nervous system. 5

cell-free A transmission mode between one cell and one virion. 6, 7

cell-to-cell A transmission mode between two cells. 6, 7, 20

comorbidities The simultaneous presence of two or more diseases that are not necessarily caused by one another but might have the same risk factors. 5

cytopathic Cytopathic effects are structural changes that happen to the cell after having been infected by a virus; those effects can shorten the lifespan on some infected cells. 5, 11, 21

HIV A virus that targets the body's immune system, and can cause the disease known as AIDS. 3, 35

HIV reservoirs A group of immune cells that are infected by HIV but are not actively reproducing the virus. 1, 4, 7, 20, 41

immune-privileged compartment An anatomical region that is naturally less subject to immune responses than most other areas of the body. 5, 7, 11, 35

Kupffer The name of macrophages residing in the liver. 5

latency reversing agents Drugs that can reactivate latent HIV reservoirs from their dormant state with the aim of making infected cells visible to the immune system. [7]

microglial The name of macrophages residing in the brain and central nervous system. [5]

mode of transmission A mechanism that describes how new infections are formed. [5]

monocytes Monocytes are the state macrophages have before they mature and specialize. Macrophages are derived from monocytes. [4]

next-generation matrix A matrix whose entries represent the expected number of infected cells produced by a single infected cell. These infected cells represent the next generation of infections. [15, 24]

pathogenesis Development of disease. [1, 10, 20, 38, 41]

phagocytosis A mechanism performed by macrophages where they engulf an infected cell. [6]

reproduction number The average number of secondary infections that result from one infected agent in an otherwise completely susceptible population. [13, 15, 16, 24, 40]

terminally differentiated Once macrophages mature into specialized cells, they achieve their final (or terminal) state remain in that state for the duration of their lifespan. [5]

transmission route Mechanism of how the disease spreads. [1, 20, 40]

viral rebound The state when the virus repopulates in the body after it has been suppressed by treatment. [4]

virion A free virus particle. [6]

virological synapses Organized cellular junctions. HIV has been shown to instigate the formation of these junctions between the infected (donor) and uninfected (target) cells to allow cell-to-cell transmission. [6, 11, 40]

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