ISSN: 3033-3652

Journal of Physical Mathematics & its Applications

Research Article

Open Access

Mathematical Modeling of the Dynamics between CD4+ T Cell Depletion and Antigen Variation

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ABSTRACT
This research involves the formulation of mathematical models representing the dynamics between CD4+ T cell depletion and antigen variation, subject to the initial conditions. The study considered some assumptions where the interaction of the HIV cells with the immune cells leads to the depletion of the immune system. The study further considers that immune cells and the HIV cells grow logistically, excluding a constant supply of the T immune cells from the thymus. Moreover, the HIV cells are considered autonomous external invaders. The steady-state solution of the system was obtained, linearisation of the system was carried out, and characteristic eigenvalues were obtained. In addition, numerical simulation using Wolfram Mathematica, version 12, on the models was performed, where the impact of the pertinent parameters on the system was considered. The results showed that increases in viral replication rate accelerate immune cell depletion and destabilise the system, while higher immune response rates promote stability and delay progression toward immune collapse.

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Received: October 27, 2025; **Accepted:** October 31, 2025; **Published:** November 13, 2025

Keywords: Mathematical Modeling, HIV, Immune System, T Cells, Growth Rate, Carrying Capacity

Introduction
T lymphocytes, or T cells, constitute a critical subset of leukocytes responsible for orchestrating cellular immunity. Originating from haematopoietic stem cells in the bone marrow, immature T cells migrate to the thymus, where they undergo a tightly regulated process of maturation and differentiation. Within the thymic microenvironment, they develop into distinct functional lineages, including helper ($CD4^+$), regulatory, cytotoxic ($CD8^+$), and memory T cells. Upon maturation, these cells are released into peripheral tissues and circulate through the bloodstream and lymphatic system, forming a highly diverse repertoire capable of recognising an extensive array of antigens through their unique T-cell receptors [1]. $CD4^+$ T cells, commonly termed helper T cells, do not exert direct cytotoxic effects on pathogens; rather, they coordinate and potentiate immune responses by activating other immune effector cells. In contrast, $CD8^+$ T cells, distinguished by the CD8 surface glycoprotein, mediate cytotoxic activity and secrete effector molecules that eliminate virus-infected or otherwise compromised cells [2]. Mature $CD4^+$ T cells, defined by surface expression of the CD4 co-receptor, play a central regulatory role in adaptive immunity, functioning as pivotal modulators of immune activation and homeostasis. Jahan and Munshi [3]. A properly functioning immune system requires the selection of T cells with receptors that recognise antigens in the context of self–MHC molecules while remaining tolerant to self-antigens. This critical selection process primarily occurs in the thymus, where immature lymphocytes assemble their surface receptors, Starr et al. [4]. Achieving self-tolerance while retaining the capacity to mount effective immune responses against invading pathogens is a highly regulated process that ensures balance within the immune system [5]. Regulatory T (Treg) cells, a subset of CD4+ T cells, play an essential role in maintaining this balance by suppressing potentially harmful activities of helper T (Th) cells, thereby modulating adaptive immune responses against pathogens and cancer, Corthay [6]. CD4+ T cells are a distinct and indispensable component of the adaptive immune system, vital for orchestrating controlled and efficient immune responses to infections; their normal function is crucial for survival [7]. The significance of CD4+ T cells is exemplified by the human immunodeficiency virus (HIV), which primarily targets these cells, though it can also infect other immune cells expressing CD4 receptors, such as macrophages, Murphy and Kenneth [8]. The depletion of functional CD4+ T cells during advanced HIV infection results in acquired immunodeficiency syndrome (AIDS). Early detection of HIV in blood or body fluids, coupled with consistent adherence to antiretroviral therapy, can prevent progression to AIDS and enable recovery of CD4+ cell counts. Interestingly, a minority of individuals known as “elite controllers” or “long-term non-progressors” can naturally suppress viral replication and maintain stable T cell levels without therapy [9].

Since its discovery in the early 1980s, HIV has spread globally in successive waves, affecting nearly every region of the world [10]. It is estimated that over 60 million people have been infected, with more than one-third succumbing to the disease [11]. The immune system combats foreign antigens through both cellular and humoral responses, aiming to eliminate invading pathogens and maintain homeostasis [12].

The human immunodeficiency virus (HIV) is a pathogen that targets and weakens the immune system. HIV infection leads to acquired immunodeficiency syndrome (AIDS), the advanced stage of the disease in which the immune system becomes severely compromised and unable to effectively defend the body against certain infections [1]. Individuals living with HIV are diagnosed with AIDS when their CD4+ T cell count drops below 200 cells/mm³ or when they develop specific opportunistic infections [1].

HIV/AIDS remains a major global public health challenge. Effective treatment adherence and prevention strategies are critical for controlling its spread. In 2021, an estimated 38.4 million people worldwide were living with HIV, with approximately 1.5 million new infections and 650,000 AIDS-related deaths. At the same time, 28.7 million people were receiving antiretroviral therapy [2]. ART, typically available as a once-daily one- or two-pill regimen, can be initiated early after infection to suppress viral replication. Individuals who achieve immune reconstitution and maintain long-term viral suppression can have a near-normal life expectancy. Furthermore, people with undetectable viral loads cannot sexually transmit HIV to others [5].

Pre-exposure prophylaxis (PREP) is an HIV prevention strategy that uses antiretroviral drugs to reduce the risk of infection. Currently, two oral PREP formulations are approved: a combination of tenofovir and emtricitabine (TDF/FTC, brand name Truvada) and a combination of tenofovir alafenamide and emtricitabine (F/TAF, brand name Descovy) [8]. When taken consistently, oral PREP can reduce the risk of sexual HIV transmission by about 99% and the risk associated with injection drug use by at least 74% [9].

However, adherence to oral PREP can be difficult due to the need for daily dosing, pill fatigue, limited availability, and accessibility barriers. To address these challenges, an injectable form of PREP has been developed, which only requires administration every two months, thereby reducing the risk of missed doses and improving adherence [10].

In recent years, numerous mathematical modelling studies have explored the population-level impact of PREP use [8]. For example, Moya et al. developed a model examining the role of PREP and post-exposure prophylaxis (PEP) under varying diagnostic and detectability conditions, while Moya and Rodrigues introduced a fractional-order model comparing oral and injectable PREP modalities [13,14]. Kirschner constructed a model to study HIV transmission among men who have sex with men (MSM) in South Korea, evaluating the effects of early ART, early diagnosis, and PREP interventions [12]. In a similar vein, Omondi and Ochieng proposed a sex- and behaviour-stratified model that incorporated PREP dynamics. Li & Zhang modelled the long-term (20-year) effects of PREP and other biomedical interventions, while Silva & Torres demonstrated through their model that PREP substantially reduces HIV transmission. Other studies have broadened the scope of modelling: Nabil & Hamaizia examined HIV cancer cell interactions using a three-dimensional discrete-time model, and Bolaji & Akinyemi developed a model of HIV tuberculosis co-infection, suggesting that early tuberculosis treatment could significantly reduce HIV incidence in affected populations. However, in this study we will formulate a mathematical model to investigate the dynamics between CD4+ T cell depletion and antigen variation and perform numerical simulation using Wolfram Mathematica in order to ascertain the pertinent parameter impacts on the dynamic system following the ideas developed by Eli and Bunonyo, Kubugha and Ebiwareme, Bunonyo and Ebiwareme, and Bunonyo et al. [15-18].

Assumptions
In section, we will consider some basic assumption in order to guide our formulation. The assumptions are:

- **Antigenic Variation:** HIV rapidly mutates, changing its surface proteins and making it difficult for T cells to recognize.
- **CD4+ T Cell Depletion:** HIV directly kills CD4+ T cells, weakening the immune system
- **Immune Evasion:** HIV produces proteins that interfere with T cell function, suppressing the immune response.
- **Chronic Inflammation:** HIV causes chronic inflammation, leading to tissue damage and organ dysfunction.
- **Cell-to-Cell Transmission:** HIV can spread directly from cell to cell, allowing it to evade the immune system and antiretroviral therapies.
- **Immune Evasion:** HIV uses various mechanisms to evade the immune system, including antigen variation and immune suppression.

Models Formulation
Following the above mentioned assumptions and Eli and Bunonyo, Kubugha and Ebiwareme, Bunonyo and Ebiwareme, and Bunonyo et al., the dynamic system is formulated as [15-18].

$$\frac{dx}{dt} = \beta_1 x\left(1 - \frac{x}{k_1}\right) - \alpha_1 xy \tag{1}$$

$$\frac{dy}{dt} = \beta_2 y\left(1 - \frac{y}{k_2}\right) \tag{2}$$

At steady state, $x \to x_e$ and $y \to y_e$, then

$$\frac{dx_e}{dt} = 0 \text{ and } \frac{dy_e}{dt} = 0 \tag{3}$$

Applying equation (3) in equations (1) and (2), then we have:

$$\beta_1 x_e\left(1 - \frac{x_e}{k_1}\right) - \alpha_1 x_e y_e = 0 \tag{4}$$

$$\beta_2 y_e\left(1 - \frac{y_e}{k_2}\right) = 0 \tag{5}$$

Simplifying equations (4) and (5), we have:

$$\beta_1 x_e\left(1 - \frac{x_e}{k_1}\right) - \alpha_1 x_e y_e = 0 \tag{6}$$

$$\beta_2 y_e\left(1 - \frac{y_e}{k_2}\right) = 0 \tag{7}$$

Simplifying equations (6) and (7), we have the following:

$$\left(\beta_1\left(1 - \frac{x_e}{k_1}\right) - \alpha_1 y_e\right) x_e = 0 \tag{8}$$

$$\beta_2\left(1 - \frac{y_e}{k_2}\right) y_e = 0 \tag{9}$$

The trivial steady state solutions are:

$$x_e = 0 \text{ and } y_e = 0 \tag{10}$$

The nontrivial steady state solutions are when , then equations (9) and (10) reduces to:

$$\beta_1\left(1 - \frac{x_e}{k_1}\right) - \alpha_1 y_e = 0 \tag{11}$$

$$\beta_2\left(1-\frac{y_e}{k_2}\right)=0 \tag{12}$$

Simplifying equations (11) and (12), we have the following:

$$\beta_1 k_1-\beta_1 x_e-\alpha_1 k_1 y_e=0 \tag{13}$$

$$\beta_2 k_2-\beta_2 y_e=0 \tag{14}$$

From equation (14), we have:

$$y_e=k_2 \tag{15}$$

Substituting equation (15) into equation (13), we have

$$\beta_1 k_1-\beta_1 x_e-\alpha_1 k_1 k_2=0 \tag{16}$$

Solving equation (16), we have:

$$x_e=\frac{k_1}{\beta_1}\left(\beta_1-\alpha_1 k_2\right) \tag{17}$$

To perform the linearization of the system, we let equations (11) and (12) be $F\left(x_e,y_e\right)$ and $G\left(x_e,y_e\right)$ respectively:

$$F\left(x_e,y_e\right)=\beta_1 x_e-\frac{\beta_1 x_e^2}{k_1}-\alpha_1 x_e y_e \tag{18}$$

$$G\left(x_e,y_e\right)=\beta_2 y_e-\frac{\beta_2 y_e^2}{k_2} \tag{19}$$

Differentiating equations (18) and (19) partially, we have:

$$J_{11}=\frac{\partial F}{\partial x_e}=\beta_1-\frac{2\beta_1 x_e}{k_1}-\alpha_1 y_e \tag{20}$$

$$J_{12}=\frac{\partial F}{\partial y_e}=-\alpha_1 x_e \tag{21}$$

$$J_{21}=\frac{\partial G}{\partial x_e}=0 \tag{22}$$

$$J_{22}=\frac{\partial G}{\partial y_e}=\beta_2-\frac{2\beta_2 y_e}{k_2} \tag{23}$$

Case I: Linearization at the trivial steady state solution $E_0\left(x_e,y_e\right)=(0,0)$ equations (20)-(23) becomes

$$J_{11}=\frac{\partial F}{\partial x_e}=\beta_1 \tag{24}$$

$$J_{12}=\frac{\partial F}{\partial y_e}=0 \tag{25}$$

$$J_{21}=\frac{\partial G}{\partial x_e}=0 \tag{26}$$

$$J_{22}=\frac{\partial G}{\partial y_e}=\beta_2 \tag{27}$$

Then, the Jacobian matrix of equations (24)-(27) becomes

$$J\left(E_0\right)=\begin{pmatrix}\beta_1 & 0\\ 0 & \beta_2\end{pmatrix} \tag{28}$$

The characteristic equation can be simplified as:

$$\left|\begin{pmatrix}\beta_1 & 0\\ 0 & \beta_2\end{pmatrix}-\begin{pmatrix}\lambda & 0\\ 0 & \lambda\end{pmatrix}\right|=0 \tag{29}$$

Simplifying equation (29), we have:

$$\lambda=\beta_1 \text{ and } \beta_2 \tag{30}$$

Case II: Linearization at the nontrivial steady state solution $E_1\left(x_e,y_e\right)=\left(\frac{k_1}{\beta_1}\left(\beta_1-\alpha_1 k_2\right),k_2\right)$ equations (25)-(28) becomes

$$J_{11}=\frac{\partial F}{\partial x_e}=\alpha_1 k_2-\beta_1 \tag{31}$$

$$J_{12}=\frac{\partial F}{\partial y_e}=\frac{\alpha_1 k_1}{\beta_1}\left(\alpha_1 k_2-\beta_1\right) \tag{32}$$

$$J_{21}=\frac{\partial G}{\partial x_e}=0 \tag{33}$$

$$J_{22}=\frac{\partial G}{\partial y_e}=-\beta_2 \tag{34}$$

Then, the Jacobian matrix of equations (31)-(34) becomes

$$J\left(E_1\right)=\begin{pmatrix}\alpha_1 k_2-\beta_1 & \frac{\alpha_1 k_1}{\beta_1}\left(\alpha_1 k_2-\beta_1\right)\\ 0 & -\beta_2\end{pmatrix} \tag{35}$$

The characteristics polynomial is:

$$\left|J\left(E_1\right)-\lambda I\right|=0 \tag{36}$$

Simplifying equation (40), we have:

$$\left|\begin{pmatrix}\alpha_1 k_2-\beta_1-\lambda_1 & \frac{\alpha_1 k_1}{\beta_1}\left(\alpha_1 k_2-\beta_1\right)\\ 0 & -\beta_2-\lambda_2\end{pmatrix}\right|=0 \tag{37}$$

Solving equation (37), we have:

$$\left(\left(\alpha_1 k_2-\beta_1\right)-\lambda\right)\left(\beta_2+\lambda\right)=0 \tag{38}$$

$$\lambda^2+\lambda\left(\left(\beta_1+\beta_2\right)-\alpha_1 k_2\right)+\beta_2\left(\beta_1-\alpha_1 k_2\right)=0 \tag{39}$$

Solving equation (38), we have:

$$\lambda_1=\left(\alpha_1 k_2-\beta_1\right), \text{ and } \lambda_2=-\beta_2 \tag{40}$$

Results

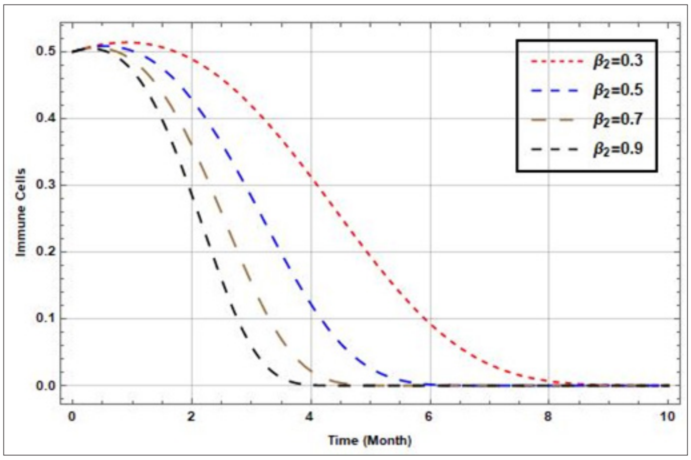

Figure 1: The Effect of Increase in HIV Cells Growth Rate on the Immune System

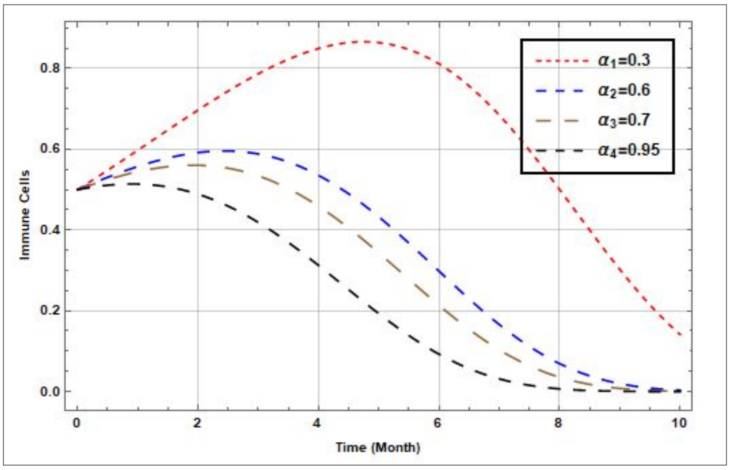

Figure 2: The Effect of Increase in Interaction Rate of HIV Cells on the Immune System

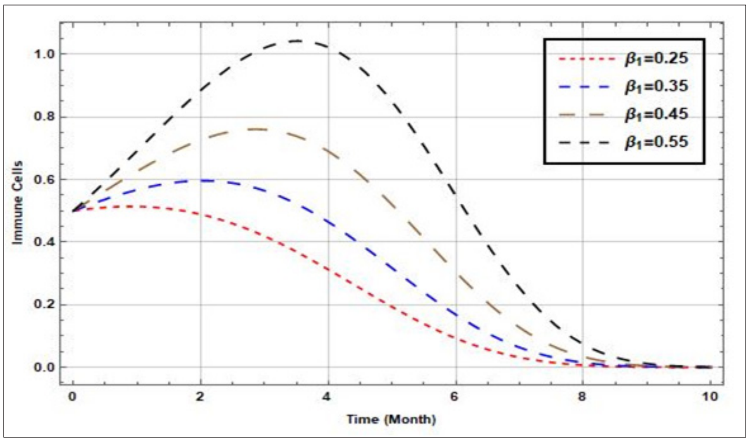

Figure 3: The Effect of Increase Grote Rate of HIV Cells on the Immune System

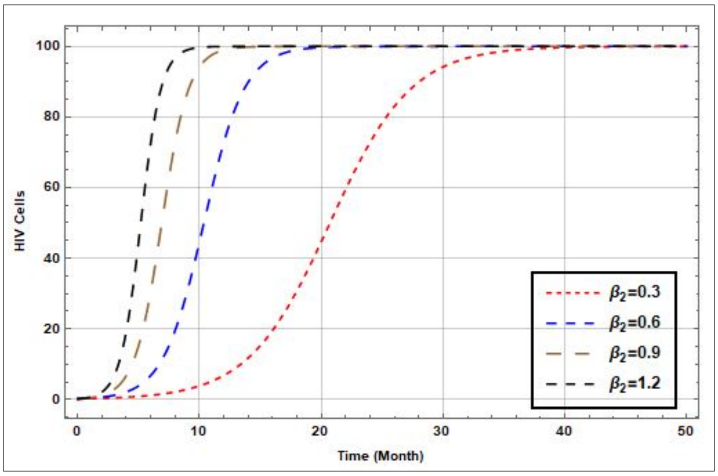

Figure 4: The Effect of Increase in Interaction Rate of HIV Cells on the Immune System

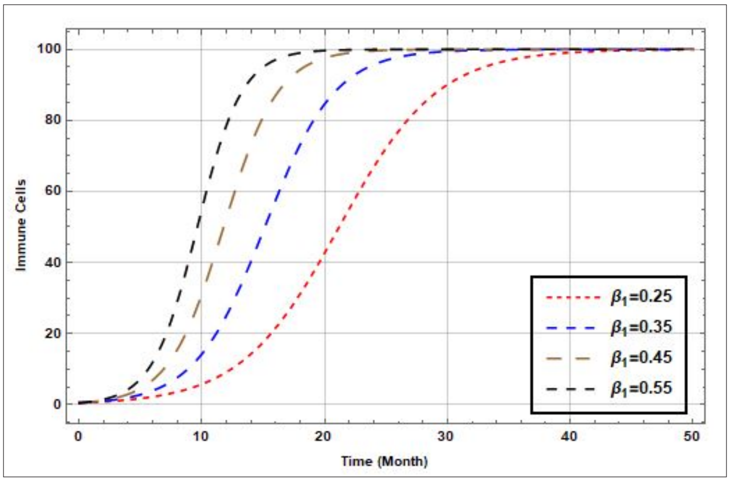

Figure 5: The Effect of Increase in Interaction Rate of HIV cells on the Immune System

Discussion

Figure 1 illustrates a rapid decrease of immune cell over time for different growth rate of the HIV cells which control the rate of immune cells. Biologically, this means immune cells start at a certain level but diminish as months pass, and the higher the growth rate of the HIV cells the faster this happens. This parameter represent, drug toxicity, or autoimmune attack severity that influences immune cell loss. The implication is that when β_2 is high, immune cells are destroyed more quickly, which could mean a faster disease progression, worse treatment side effects, or a stronger immune system attack on itself.

Figure 2 Demonstrates how immune cell levels change over time based on the parameter α_1, which controls both the growth and decline phases of the immune cells. Biologically, influences how strongly immune cells proliferate initially and how quickly they later decrease. Lower values of allow α_1 immune cells to expand more robustly and sustain higher levels for longer α_1, while higher α_1 values result in weaker immune growth and faster depletion. Clinically, understanding and managing α_1 is essential for modulating immune responses effectivelyboosting it when a strong, sustained immune defense is needed or limiting it to prevent premature immune exhaustion or damage. This insight helps tailor treatments to maintain optimal immune function over time.

Figure 3 illustrate how immune cell levels change over time based on the parameter β_1 , which controls both the growth and decline phases of the immune cells. Biologically, influences how strongly immune cells proliferate initially and how quickly they later decrease. Lower values of β_1 allow immune cells to expand more robustly and sustain higher levels for longer β_1, while higher β_1 values result in weaker immune growth and faster depletion. Clinically, understanding and managing is essential for modulating immune responses effectivelyboosting it when a strong, sustained immune defense is needed or limiting it to prevent premature immune exhaustion or damage. This insight helps tailor treatments to maintain optimal immune function over time.

Figure 4 shows a rapid growth of the disease-free equilibrium over time, as β_2 increases; we observe local stability of the HIV cells. Biologically, the influencesof HIV cells initially grow quickly and they later become stable as time increases. Higher values β_2 of allow immune cells to be stable.

Figure 5 Show a rapid growth of the disease-free equilibrium over time, as β_1 increases, we observe local stability of the HIV cells. Biologically, the influences of HIV cells initially grow quickly and they later become stable as time increases. Higher values of β_1 allow immune cells to be stable.

Conclusion

Mathematical models for dynamics between CD4+ T cell depletion and antigen variation can help researchers and clinicians to better understand the dynamics of the disease, predict the impact of interventions, and formulate a new strategy for the management of the infection.

Nomenclature

β_1 **:** The growth rate of Immune cells x
β_2 **:** The growth rate of the HIV cells y
K_1 **:** The carrying capacity of Immune cells x
K_2 **:** The carrying capacity of the HIV cells y
α_1 **:** The elimination rate of immune cells for interacting with HIV cells y

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