Stochastic Model for Langerhans cells and HIV Dynamics in Vivo

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Abstract

Many aspects of the complex interaction between HIV and the human immune system remain elusive. Our objective is to study these interactions, focusing on the specific roles of langerhans cells (LCs) in HIV infection. In patients infected with HIV, a large amount of virus is associated with LCs in lymphoid tissue. To assess the influence of LCs on HIV viral dynamics during anti-retroviral therapy, we present and analyse a stochastic model describing the dynamics of HIV, CD4+ T-cells, and LCs interactions under therapeutic intervention in vivo. We perform sensitivity analyses on the model to determine which parameters and/or which interaction mechanisms strongly affect infection dynamics.

Keywords: HIV infection, Latent period, Langerhans cells, CD4+ T cells, Stochastic model, Therapeutic intervention.

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1 Introduction

HIV is a devastating human pathogen that causes serious immunological diseases in humans around the world. The virus is able to remain latent in an infected host for many years, allowing for the long-term survival of the virus and inevitably prolonging the infection process [3]. The location and mechanisms of HIV latency are under investigation and remain important topics in the study of viral pathogenesis. Given that HIV is a blood-borne pathogen, a number of cell types have been proposed to be the sites of latency, including resting memory CD4 + T cells, peripheral blood monocytes, dendritic cells (including langerhans cells) and macrophages in the lymph nodes, and haematopoietic stem cells in the bone marrow [16]. This study updates the latest advances in the study of HIV interactions with langerhans cells, and highlights the potential role of these cells as viral reservoirs and the effects of the HIV-host-cell interactions on viral pathogenesis.

Despite advances in our understanding of HIV and the human immune response in the last 25 years, much of this complex interaction remains elusive. CD4+ T-cells are targets of HIV, and are also important for the establishment and maintenance of an adaptive immune response [7]. The skin and mucosa are the first line of defense of the organism against external agents, not only as a physical barrier between the body and the environment but also as the site of initiation of immune reactions. The immunocompetent cells which act as antigen-presenting cells are Langerhans cells (LCs). Infection of LCs by HIV is relevant for several reasons. Firstly, LCs of mucosal epithelia may be among the first cells to be infected following mucosal HIV exposure and Secondly, LCs may serve as a reservoir for continued infection of CD4+ T cells, especially in lymph nodes where epidermal LCs migrate following antigenic activation[11].

Many indirect and/or direct experimental data have shown that LCs may be a privileged target, reservoir and vector of dissemination for the HIV from the inoculation sites (mucosa) to lymph nodes where the emigrated infected LCs could infect T lymphocytes [17]. Originated from the bone marrow, LCs migrate to the peripheral epithelia (skin, mucous membranes) where they play a primordial role in the induction of an immune response and are especially active in stimulating naive T lymphocytes in the primary response through a specific cooperation with CD4-positive lymphocytes after migration to proximal lymph nodes [15]. Apart from many plasma membrane determinants, LCs also express CD4 molecules which make them susceptible targets and reservoirs for HIV [4]. Once infected, these cells due to their localization in areas at risk (skin, mucous membranes), their capacity to migrate from the epidermal compartment to lymph nodes and their ability to support viral replication

without major cytopathic effects, could play a role of vector in the dissemination of virus from the site of inoculation to the lymph nodes and thereby to contribute to the infection of T lymphocytes [4].

Langerhans cells (LCs) which are members of the dendritic cells family and are professional antigen-presenting cells, reside in epithelial surfaces such as the skin and act as one of the primary, initial targets for HIV infection [14]. They specialize in antigen presentation and belong to the skin immune system (SIS) and play a major role in HIV pathogenesis. As part of the normal immune response, LCs capture virions at the site of transmission in the mucosa(peripheral tissues), and migrate to the lymphoid tissue where they present to naive T cells and hence are responsible for large-scale infection of CD4+ T lymphocytes [14]. These cells play an important role in the transmission of HIV to CD4+ cells [6], thus, LC - CD4+ cell interactions in lymphoid tissue, which are critical in the generation of immune responses, are also a major catalyst for HIV replication and expansion. This replication independent mode of HIV transmission, known as trans-infection, greatly increases T cell infection in vitro and is thought to contribute to viral dissemination in vivo [10].

The Langerhans cell is named after Paul Langerhans, a German physician and anatomist, who discovered the cells at the age of 21 in 1868 while he was a medical student [13]. The uptake HIV by professional antigen presenting cells (APCs) and subsequent transfer of virus to CD4+ T cells can result in explosive levels of virus replication in the T cells. This could be a major pathogenic process in HIV infection and development of AIDS. This process of trans (Latin; to the other side) infection of virus going across from the APC to the T cell is in contrast to direct, cis (Latin; on this side) infection of T cells by HIV [12]. Langerhans cell results in a burst of virus replication in the T cells that is much greater than that resulting from direct, cis infection of either APC or T cells, or trans infection between T cells. This consequently shows that Langerhans cells may be responsible for the quick spread of HIV infection.

The individual cells of the immune system are highly interactive, and the overall function of the system is a product of this multitude of interactions. The interplay between HIV and the immune system is particularly complicated, as HIV directly interacts with many immune cells, altering their functions, ultimately subverting the system at its core [7]. Because of this complexity, the immune response and its interaction with HIV are naturally suited to a mathematical modelling approach. Elucidating the mechanisms of LC-HIV-CD4+ T cells interactions is crucial in uncovering more details about host-HIV dynamics during HIV infection. To explore the role of LCs in HIV infection, we first develop a stochastic model of HIV dynamics in vivo before therapy. Next,

we introduce therapeutic intervention and finally investigate which parameters and/or which interaction mechanisms strongly affect the infection dynamics.

The organization of this paper is as follows: In Section 2, we formulate our stochastic model describing the interaction of HIV and the immune system and obtain a partial differential equation for the joint probability generating function of the numbers of healthy immune cells,the HIV infected immune cells, and the free HIV particles at any time t. The marginal probability distributions for the variables and the population measures which include the expectation of the variables are also derived in Section 2. HIV dynamic model incorporating therapy is derived and model analysis discussed in section 3. Some concluding remarks follow in Section 4.

2 The role of LC in HIV Infection in Vivo

In HIV infection, LCs play a dual role of promoting immunity while also facilitating infection. During antigen presentation, LC-associated virus, migrate to the lymphoid tissue where they present to naive T cells and hence facilitating infection of CD4+ T-cells [1]. Taken together, these interactions suggest that LC dynamics are particularly important to HIV infection. Several mechanisms have been proposed to trigger progression from the chronic phase of infection to AIDS. Many have hypothesized that progressive alteration of the immune system results in the transition to AIDS [2],[5].

To study the roles of LCs during HIV infection, we present a mathematical model of HIV infection and accompanying immune response. specifically, we develop a stochastic model focusing on the HIV-LC-CD4+ cell dynamics in Vivo. Our model analysis allows us to predict the importance of LC mechanisms and their role in triggering progression to AIDS. In particular, our model predicts which mechanisms of LC dysfunction are most significant in the transition to AIDS. A typical life-cycle of HIV virus and immune system interaction is shown in Figure 1.
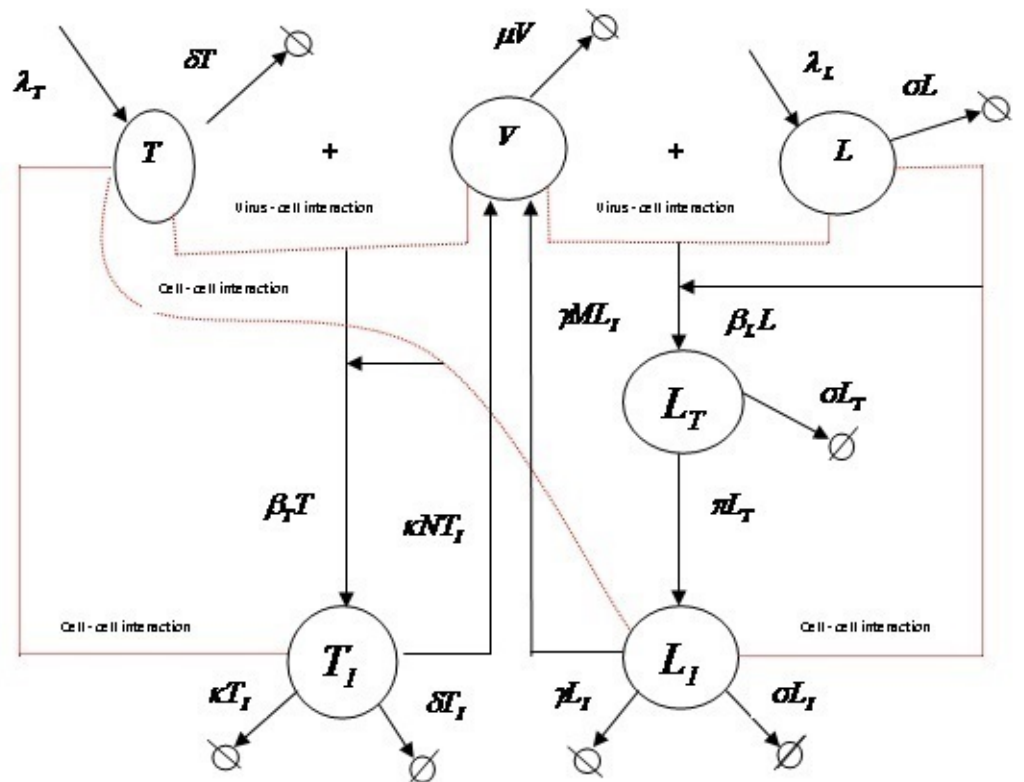
Figure 1: The interaction of HIV virus and the immune system

2.1   Variables and parameters for the model

The variables and parameters in the model are described as in tables 1 and 2:

Table 1: Variables for the Stochastic model

Variable	Description
$T(t)$	The concentration of healthy (susceptible)CD4+ cells at time t
$T_I(t)$	The concentration of infected CD4+ cells at time t
$L(t)$	The concentration of healthy (susceptible) Langerhans cells at time t
$L_T(t)$	The concentration of latently infected Langerhans cells at time t
$L_I(t)$	The concentration of infected Langerhans cells at time t
$V(t)$	The concentration of virus particles at time t

Table 2: Parameters for the stochastic model

Parameter	Description
λ_T	The total rate of production of healthy CD4+ cells per unit time
λ_L	The total rate of production of Langerhans cells per unit time
δ	The per capita death rate of healthy CD4+ cells
σ	The per capita death rate of healthy Langerhans cells
β_1	The transmission coefficient between uninfected CD4+ cells and infective virus particles
β_2	The transmission coefficient between uninfected CD4+ cells and IV infected langerhans cells
β_3	The transmission coefficient between uninfected langerhans cells and infective virus particles
β_4	The transmission coefficient between uninfected langerhans cells and HIV infected langerhans cells
κ	per capita death rate of infected CD4+ cells
τ	Intracellular delay time
γ	per capita death rate of infected langerhans cells
μ	The per capita death rate of infective virus particles
N	The average number of infective virus particles produced by an infected CD4+ cell in the absence of treatment during its entire infectious lifetime
M	The average number of infective virus particles produced by an infected langerhans cell in the absence of treatment during its entire infectious lifetime

From the assumptions above and by using the population change scenarios and parameters in tables 2 and applying probability arguments, we now summarize

the events that occur during the interval $(t, t+\Delta)$ together with their transition probabilities in table 3.

Possible transitions in host interaction of HIV and Immune system Cells and corresponding probabilities			
Event	Population components (T, T_I, L, L_I, V) at t	Population components (T, T_I, L, L_I, V) at $(t, t+\Delta)$	probability of transition
Production of healthy CD4+ cell	$(x-1, x_I, y, y_I, v)$	(x, x_I, y, y_I, v)	$\lambda_T \Delta t$
Death of healthy CD4+ cell	$(x+1, x_I, y, y_I, v)$	(x, x_I, y, y_I, v)	$\delta(x+1)\Delta t$
Infection of healthy CD4+ cell	$(x+1, x_I-1, y, y_I, v+1)$	(x, x_I, y, y_I, v)	$\beta_1(x+1)(v+1)e^{-\rho\tau}\Delta t$ $+ \beta_2(x+1)(y_I)e^{-\rho\tau}\Delta t$
Production of Langerhans cell	$(x, x_I, y-1, y_I, v)$	(x, x_I, y, y_I, v)	$\lambda_L \Delta t$
Death of Langerhans cell	$(x, x_I, y+1, y_I, v)$	(x, x_I, y, y_I, v)	$\sigma(y+1)\Delta t$
Infection of Langerhans cell	$(x, x_I, y+1, y_I-1, v+1)$	(x, x_I, y, y_I, v)	$\beta_3(y+1)(v+1)\Delta t$ $+\beta_4(y+1)(y_I)\Delta t$
Production of virons from the infected cell	$(x, x_I+1, y, y_I+1, v-1)$	(x, x_I, y, y_I, v)	$\kappa N(x_I+1)\Delta t + \gamma M(y_I+1)\Delta t$
Death of virons	$(x, x_I, y, y_I, v+1)$	(x, x_I, y, y_I, v)	$\mu(v+1)\Delta t$

Table 3: In - Host interaction of HIV

The change in population size during the time interval Δt, which is assumed to be sufficiently small to guarantee that only one such event can occur in $(t, t + \Delta t)$, is governed by the following conditional probabilities;

$$
\begin{aligned}
P_{x,x_I,y,y_I,v}(t + \Delta t) = \ & \{1 - (\lambda_T \Delta t + \lambda_L \Delta t + \delta x \Delta t + \sigma y \Delta t \\
& + \ \beta_1 xv \Delta t + \beta_2 xy_I \Delta t + +\beta_3 yv \Delta t + \beta_4 yy_I \Delta t \\
& + \ \kappa x_I \Delta t + \gamma y_I \Delta t + \mu v \Delta t) + o(\Delta t)\} P_{x,x_I,y,y_I,v}(t) \\
& + \ \{\lambda_T \Delta t + o(\Delta t)\} P_{x-1,x_I,y,y_I,v}(t) \\
& + \ \{\lambda_L \Delta t + o(\Delta t)\} P_{x,x_I,y-1,y_I,v}(t) \\
& + \ \{\delta(x + 1)\Delta t + o(\Delta t)\} P_{x+1,x_I,y,y_I,v}(t) \\
& + \ \{\sigma(y + 1)\Delta t + o(\Delta t)\} P_{x,x_I,y+1,y_I,v}(t) \\
& + \ \{[\beta_1(x + 1)(v + 1) + \beta_2(x + 1)(y_I)]e^{-\rho\tau}\Delta t + o(\Delta t)\} P_{x+1,x_I-1,y,y_I,v+1}(t) \\
& + \ \{[\beta_3(y + 1)(v + 1) + \beta_4(y + 1)(y_I)]\Delta t + o(\Delta t)\} P_{x,x_I,y+1,y_I-1,v+1}(t) \\
& + \ \{\kappa N(x_I + 1)\Delta t + o(\Delta t)\} P_{x,x_I+1,y,y_I,v-1}(t) \\
& + \ \{\gamma M(y_I + 1)\Delta t + o(\Delta t)\} P_{x,x_I,y,y_I+1,v-1}(t) \\
& + \ \{\mu(v + 1)\Delta t + o(\Delta t)\} P_{x,x_I,y,y_I,v+1}(t)
\end{aligned}
\tag{1}
$$

Re-arranging equation 1, then dividing through by Δt, and taking the limit as $\Delta t \Rightarrow 0$ we have the following difference differential equation.

$$
\begin{aligned}
P'_{x,x_I,y,y_I,v}(t) = \ & -\{\lambda_T + \lambda_L + \delta x + \sigma y + \beta_1 xv + \beta_2 xy_I \\
& + \ \beta_3 yv + \beta_4 yy_I + \kappa x_I + \gamma y_I + \mu v\} P_{x,x_I,y,y_I,v}(t) \\
& + \ \lambda_T P_{x-1,x_I,y,y_I,v}(t) + \lambda_L P_{x,x_I,y-1,y_I,v}(t) \\
& + \ \delta(x + 1)P_{x+1,x_I,y,y_I,v}(t) + \sigma(y + 1)P_{x,x_I,y+1,y_I,v}(t) \\
& + \ \{\beta_1(x + 1)(v + 1) + \beta_2(x + 1)(y_I)\}e^{-\rho\tau}P_{x+1,x_I-1,y,y_I,v+1}(t) \\
& + \ \{\beta_3(y + 1)(v + 1) + \beta_4(y + 1)(y_I)\}P_{x,x_I,y+1,y_I-1,v+1}(t) \\
& + \ \kappa N(x_I + 1)P_{x,x_I+1,y,y_I,v-1}(t) + \gamma M(y_I + 1)P_{x,x_I,y,y_I+1,v-1}(t) \\
& + \ \mu(v + 1)P_{x,x_I,y,y_I,v+1}(t)
\end{aligned}
\tag{2}
$$

This is also called the Master equation or the Forward Kolmogorov Partial differential equation for $P_{x,x_I,y,y_I,v}(t)$, with initial condition

$$
P'_{0,0,0,0,0}(t) = -(\lambda_T + \lambda_L)P_{0,0,0,0,0}(t) + \delta P_{1,0,0,0,0}(t) + \sigma P_{0,0,1,0,0}(t) + \mu P_{0,0,0,0,1}(t)
$$

For detailed description and derivation of the model we refer the reader to [9]

2.2 The Probability Generating Function

Now we apply the Generating function method. Multiplying equation 2 by $z_1^x z_2^y z_3^{x_I} z_4^{y_I} z_5^v$ and summing over x, y, x_I, y_I and v, then applying the properties of generating function, we obtain

$$
\begin{aligned}
\frac{\partial G}{\partial t} &= -(\lambda_T + \lambda_L)G - \delta z_1 \frac{\partial G}{\partial z_1} - \sigma z_2 \frac{\partial G}{\partial z_2} - \kappa z_3 \frac{\partial G}{\partial z_3} - \gamma z_4 \frac{\partial G}{\partial z_4} - \mu z_5 \frac{\partial G}{\partial z_5} \\
&- \beta_1 z_1 z_5 \frac{\partial^2 G}{\partial z_1 \partial z_5} - \beta_2 z_1 z_4 \frac{\partial^2 G}{\partial z_1 \partial z_4} - \beta_3 z_2 z_5 \frac{\partial^2 G}{\partial z_2 \partial z_5} - \beta_4 z_2 z_4 \frac{\partial^2 G}{\partial z_2 \partial z_4} \\
&+ \lambda_T z_1 G + \lambda_L z_2 G + \delta \frac{\partial G}{\partial z_1} + \sigma \frac{\partial G}{\partial z_2} + z_5 N \kappa \frac{\partial G}{\partial z_3} + z_5 M \gamma \frac{\partial G}{\partial z_4} + \mu \frac{\partial G}{\partial z_5} \\
&+ z_3 \beta_1 e^{-\rho\tau} \frac{\partial^2 G}{\partial z_1 \partial z_5} + z_3 \beta_2 e^{-\rho\tau} \frac{\partial^2 G}{\partial z_1 \partial z_4} + z_4 \beta_3 \frac{\partial^2 G}{\partial z_2 \partial z_5} + z_4 \beta_4 \frac{\partial^2 G}{\partial z_2 \partial z_4}
\end{aligned}
$$

On simplification we have,

$$
\begin{aligned}
\frac{\partial G}{\partial t} &= \{(z_1 - 1)\lambda_T + (z_2 - 1)\lambda_L\}G + (1 - z_1)\delta \frac{\partial G}{\partial z_1} + (1 - z_2)\sigma \frac{\partial G}{\partial z_2} \\
&+ (N z_5 - z_3)\kappa \frac{\partial G}{\partial z_3} + (M z_5 - z_4)\gamma \frac{\partial G}{\partial z_4} + (1 - z_5)\mu \frac{\partial G}{\partial z_5} \\
&+ \beta_1(z_3 e^{-\rho\tau} - z_1 z_5)\frac{\partial^2 G}{\partial z_1 \partial z_5} + \beta_2(z_3 e^{-\rho\tau} - z_1 z_4)\frac{\partial^2 G}{\partial z_1 \partial z_4} \quad (3) \\
&+ \beta_3(z_4 - z_2 z_5)\frac{\partial^2 G}{\partial z_2 \partial z_5} + \beta_4(z_4 - z_2 z_4)\frac{\partial^2 G}{\partial z_2 \partial z_4}
\end{aligned}
$$

This is called Lagrange partial differential equation for the probability generating function (pgf)

2.3 The marginal generating functions

Recall that

$$
G(z_1, 1, 1, t) = \sum_{x=0}^{\infty} \sum_{y=0}^{\infty} \sum_{v=0}^{\infty} P_{x,y,v}(t) z_1^x
$$

Assuming $z_2 = z_3 = z_4 = z_5 = 1$ and solving equation 3, we obtain the marginal partial generating function for Healthy CD4+ cells.

$$
\frac{\partial G(z_1, 1, 1, 1, 1; t)}{\partial t} = (z_1 - 1)\lambda_T G + (1 - z_1)\delta \frac{\partial G}{\partial z_1}
$$

$$+ \quad \beta_1(e^{-\rho\tau} - z_1)\frac{\partial^2 G}{\partial z_1 \partial z_5} + \beta_2(e^{-\rho\tau} - z_1)\frac{\partial^2 G}{\partial z_1 \partial z_4}$$

Assuming $z_1 = z_3 = z_4 = z_5 = 1$ and solving equation 3, we obtain the marginal partial generating function for Healthy Langerhans cells.

$$\frac{\partial G(1, z_2, 1, 1, 1; t)}{\partial t} = (z_2 - 1)\lambda_L G + (1 - z_2)\sigma\frac{\partial G}{\partial z_2}$$

$$+ \quad \beta_3(1 - z_2)\frac{\partial^2 G}{\partial z_2 \partial z_5} + \beta_4(1 - z_2)\frac{\partial^2 G}{\partial z_2 \partial z_4}$$

Assuming $z_1 = z_2 = z_4 = z_5 = 1$ and solving equation 3, we obtain the marginal partial generating function for Infected CD4+ cells.

$$\frac{\partial G(1, 1, z_3, 1, 1; t)}{\partial t} = (N - z_3)\kappa\frac{\partial G}{\partial z_3} + \beta_1(z_3 e^{-\rho\tau} - 1)\frac{\partial^2 G}{\partial z_1 \partial z_5} + \beta_2(z_3 e^{-\rho\tau} - 1)\frac{\partial^2 G}{\partial z_1 \partial z_4}$$

Assuming $z_1 = z_2 = z_3 = z_5 = 1$ and solving equation 3, we obtain the marginal partial generating function for Infected Langerhans cells.

$$\frac{\partial G(1, 1, 1, z_4, 1; t)}{\partial t} = (M - z_4)\gamma\frac{\partial G}{\partial z_4} + \beta_3(z_4 - 1)\frac{\partial^2 G}{\partial z_2 \partial z_5}$$

Assuming $z_1 = z_2 = z_3 = z_4 = 1$ and solving equation 3, we obtain the marginal partial generating function for virus population.

$$\frac{\partial G(1, 1, 1, 1, z_5; t)}{\partial t} = (Nz_5 - 1)\kappa\frac{\partial G}{\partial z_3} + (Mz_5 - 1)\gamma\frac{\partial G}{\partial z_4} + (1 - z_5)\mu\frac{\partial G}{\partial z_5}$$

$$+ \quad \beta_1(e^{-\rho\tau} - z_5)\frac{\partial^2 G}{\partial z_1 \partial z_5} + \beta_3(1 - z_5)\frac{\partial^2 G}{\partial z_2 \partial z_5}$$

2.4   Numbers of Cells and the Virons

As we know from probability generating function

$$\frac{\partial G_x}{\partial z} = \sum_{x=0}^{\infty} x P_x(t) z^{x-1}$$

Letting $z = 1$, we have

$$\frac{\partial G_x}{\partial z}\Big|_{z=1} = \sum_{x=0}^{\infty} x P_x(t) z^{x-1} = E[X]$$

Differentiating the partial differential equation of the pgf, we get the moments of $T(t), L(t), T_I(t), L_I(t)$ and $V(t)$.

Differentiating equation 3 with respect to z_1, and setting z=1, we have

$$\frac{\partial}{\partial t}E[T(t)] \;=\; \lambda_T - \delta E[T(t)] - \beta_1 E[T(t)V(t)] - \beta_2 E[T(t)L_I(t)]$$

Differentiating equation 3 with respect to z_2, and setting z = 1, we have

$$\frac{\partial}{\partial t}E[L(t)] \;=\; \lambda_L - \sigma E[L(t)] - \beta_3 E[L(t)V(t)] - \beta_4 E[L(t)L_I(t)]$$

Differentiating equation 3 with respect to z_3, and setting z = 1, we have

$$\frac{\partial}{\partial t}E[T_I(t)] = -\kappa E[T_I(t)] + \beta_1 e^{-\rho\tau} E[T(t)V(t)] + \beta_2 e^{-\rho\tau} E[T(t)L_I(t)]$$

Differentiating equation 3 with respect to z_4, and setting z = 1, we have

$$\frac{\partial}{\partial t}E[L_I(t)] = -\gamma E[L_I(t)] + \beta_3 E[L(t)V(t)]$$

Differentiating equation 3 with respect to z_5, and setting z = 1, we have

$$\frac{\partial}{\partial t}E[V(t)] = N\kappa E[T_I(t)] + M\gamma E[L_I(t)] - \mu E[V(t)] - \beta_1 E[T(t)V(t)] - \beta_3 E[L(t)V(t)]$$

Therefore the moments of $T(t), L(t), T_I(t), L_I(t)$ and $V(t)$ from the pgf before introduction of treatment are

$$
\begin{aligned}
\frac{\partial}{\partial t}E[T(t)] \;&=\; \lambda_T - \delta E[T(t)] - \beta_1 E[T(t)V(t)] - \beta_2 E[T(t)L_I(t)]\\
\frac{\partial}{\partial t}E[L(t)] \;&=\; \lambda_L - \sigma E[L(t)] - \beta_3 E[L(t)V(t)] - \beta_4 E[L(t)L_I(t)]\\
\frac{\partial}{\partial t}E[T_I(t)] \;&=\; -\kappa E[T_I(t)] + \beta_1 e^{-\rho\tau} E[T(t)V(t)] + \beta_2 e^{-\rho\tau} E[T(t)L_I(t)]\\
\frac{\partial}{\partial t}E[L_I(t)] \;&=\; -\gamma E[L_I(t)] + \beta_3 E[L(t)V(t)] \qquad\qquad\qquad (4)\\
\frac{\partial}{\partial t}E[V(t)] \;&=\; N\kappa E[T_I(t)] + M\gamma E[L_I(t)] - \mu E[V(t)] - \beta_1 E[T(t)V(t)] - \beta_3 E[L(t)V(t)]
\end{aligned}
$$

3   HIV dynamics under Therapeutic intervention

Introducing the effect of treatment, we have the following forward Kolmogorov partial differential equations (Master equation) for $P_{x,x_I,y,y_I,v}(t)$

$$
\begin{aligned}
P'_{x,x_I,y,y_I,v}(t) &= -\{\lambda_T + \lambda_L + \delta x + \sigma y + (1-\alpha)\beta_1 xv + (1-\alpha)\beta_2 xy_I + (1-\alpha)\beta_3 yv + (1-\alpha)\beta_4 yy_I \\
&+ (1-\omega)\kappa x_I + (1-\omega)\gamma y_I + \mu v\}P_{x,x_I,y,y_I,v}(t) + \lambda_T P_{x-1,x_I,y,y_I,v}(t) + \lambda_L P_{x,x_I,y-1,y_I,v}(t) \\
&+ \delta(x+1)P_{x+1,x_I,y,y_I,v}(t) + \sigma(y+1)P_{x,x_I,y+1,y_I,v}(t) \\
&+ \{\beta_1(x+1)(v+1) + \beta_2(x+1)(y_I)\}(1-\alpha)e^{-\rho\tau}P_{x+1,x_I-1,y,y_I,v+1}(t) \\
&+ \{\beta_3(y+1)(v+1) + \beta_4(y+1)(y_I)\}(1-\alpha)P_{x,x_I,y+1,y_I-1,v+1}(t) \\
&+ (1-\omega)\kappa N(x_I+1)P_{x,x_I+1,y,y_I,v-1}(t) + (1-\omega)\gamma M(y_I+1)P_{x,x_I,y,y_I+1,v-1}(t) \\
&+ \mu(v+1)P_{x,x_I,y,y_I,v+1}(t)
\end{aligned} \tag{5}
$$

With initial condition

$$
P'_{0,0,0,0,0}(t) = -(\lambda_T + \lambda_L)P_{0,0,0,0,0}(t) + \delta P_{1,0,0,0,0}(t) + \sigma P_{0,0,1,0,0}(t) + \mu P_{0,0,0,0,1}(t)
$$

Solving the master equation using generating function, the Lagrange partial differential equation becomes:-

$$
\begin{aligned}
\frac{\partial G}{\partial t} &= \{(z_1-1)\lambda_T + (z_2-1)\lambda_L\}G + (1-z_1)\delta\frac{\partial G}{\partial z_1} + (1-z_2)\sigma\frac{\partial G}{\partial z_2} \\
&+ (Nz_5-z_3)(1-\omega)\kappa\frac{\partial G}{\partial z_3} + (Mz_5-z_4)(1-\omega)\gamma\frac{\partial G}{\partial z_4} + (1-z_5)\mu\frac{\partial G}{\partial z_5} \\
&+ (1-\alpha)\beta_1(z_3 e^{-\rho\tau} - z_1 z_5)\frac{\partial^2 G}{\partial z_1 \partial z_5} + (1-\alpha)\beta_2(z_3 e^{-\rho\tau} - z_1 z_4)\frac{\partial^2 G}{\partial z_1 \partial z_4} \\
&+ (1-\alpha)\beta_3(z_4 - z_2 z_5)\frac{\partial^2 G}{\partial z_2 \partial z_5} + (1-\alpha)\beta_4(z_4 - z_2 z_4)\frac{\partial^2 G}{\partial z_2 \partial z_4}
\end{aligned} \tag{6}
$$

Solving the pgf of the In-host HIV dynamics with therapeutic intervention, we have the moments of $T(t), L(t), T_I(t), L_I(t)$ and $V(t)$.

$$
\frac{\partial}{\partial t}E[T(t)] = \lambda_T - \delta E[T(t)] - (1-\alpha)\beta_1 E[T(t)V(t)] - (1-\alpha)\beta_2 E[T(t)L_I(t)]
$$

$$
\frac{\partial}{\partial t}E[L(t)] = \lambda_L - \sigma E[L(t)] - (1-\alpha)\beta_3 E[L(t)V(t)] - (1-\alpha)\beta_4 E[L(t)L_I(t)]
$$

$$
\frac{\partial}{\partial t}E[T_I(t)] = -\kappa E[T_I(t)] + (1-\alpha)\beta_1 e^{-\rho\tau}E[T(t)V(t)] + (1-\alpha)\beta_2 e^{-\rho\tau}E[T(t)L_I(t)]
$$

$$\frac{\partial}{\partial t}E[L_I(t)] = -\gamma E[L_I(t)] + (1-\alpha)\beta_3 E[L(t)V(t)] \tag{7}$$

$$\frac{\partial}{\partial t}E[V(t)] = (1-\omega)N\kappa E[T_I(t)] + (1-\omega)M\gamma E[L_I(t)] - \mu E[V(t)]$$
$$- (1-\alpha)\beta_1 E[T(t)V(t)] - (1-\alpha)\beta_3 E[L(t)V(t)]$$

3.1   Simulation results

3.2   Variables and parameter values

The initial variable values and parameter values for the model are described in tables 4 and 5 below:

Table 4: Variables for the Stochastic model

Variable	Description	Initial condition
$T(t)$	The concentration of healthy (susceptible)CD4+ cells at time t	100
$T_I(t)$	The concentration of infected CD4+ cells at time t	0.02
$L(t)$	The concentration of healthy (susceptible) Langerhans cells at time t	200
$L_I(t)$	The concentration of infected Langerhans cells at time t	0.1
$V(t)$	The concentration of virus particles at time t	0.001

Using the parameter values and initial conditions defined in Tables 4 and 5, we illustrate the general dynamics of the CD4- T cells and HIV virus for by performing sensitivity analysis on the effect of intracellular delay and drug efficacy.
From the simulations, it is clear that in the primary stage of HIV infection, drastic decrease in the levels of healthy immune cells occur but the number of free virons and infected LCs increase with time, see figures 2 and 3.

With 60% drug efficacy, the virus population drops and stabilizes after some time t, but the number of infected LCs increase with time, see figures 4 and 5.

An increase in efficacy for the current HIV drugs, a patient will have low, undetectable viral load levels but the population of infected LCs is still at large, see figures 6 and 7.

Table 5: Parameters for the stochastic model

| Parameter	Parameter description	Estimate
$(1 - \alpha)$	The reverse transcriptase inhibitor drug effect	0.5
$(1 - \omega)$	The protease inhibitor drug effect	0.5
λ_T	The total rate of production of healthy CD4+ cells per unit time	10
λ_L	The total rate of production of Langerhans cells per unit time	10
δ	The per capita death rate of healthy CD4+ cells	0.02
σ	The per capita death rate of healthy Langerhans cells	0.001
β_1	The transmission coefficient between uninfected CD4+ cells and infective virus particles	0.24e-4
β_2	The transmission coefficient between uninfected CD4+ cells and HIV infected langerhans cells	0.04e-4
β_3	The transmission coefficient between uninfected langerhans cells and infective virus particles	0.45e-4
β_4	The transmission coefficient between uninfected langerhans cells and HIV infected langerhans cells	0.14e-4
κ	per capita death rate of infected CD4+ cells	0.5
ρ	The death rate of infected but not yet virus producing cell	0.5
τ	Intracellular delay time	0.5
γ	per capita death rate of infected langerhans cells	0.001
μ	The per capita death rate of infective virus particles	3
N	The average number of infective virus particles produced by an infected CD4+ cell in the absence of treatment during its entire infectious lifetime	1000
M	The average number of infective virus particles produced by an infected langerhans cell in the absence of treatment during its entire infectious lifetime	500
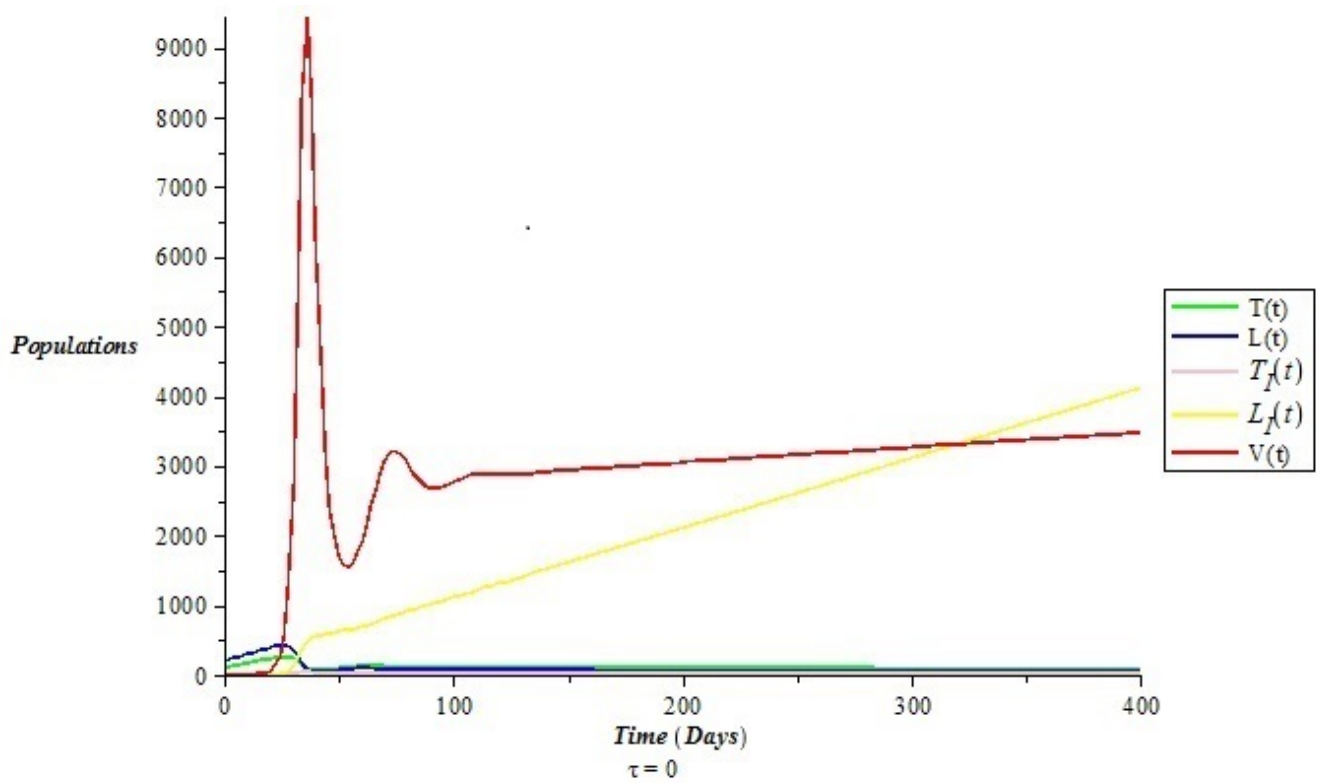
Figure 2: Cells and HIV population dynamics before therapeutic intervention. *Shows the population dynamics when $\tau = 0$*
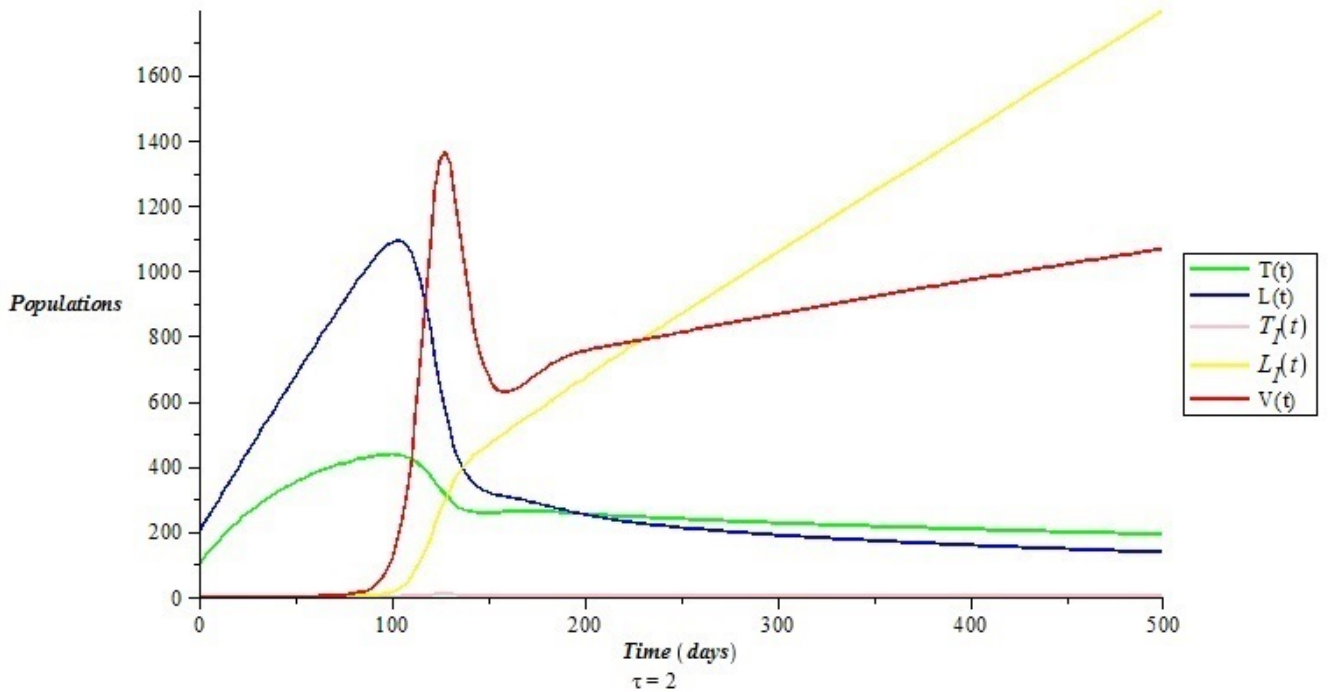

Figure 3: Cells and HIV population dynamics before therapeutic intervention. *Shows the population dynamics when $\tau = 2$*
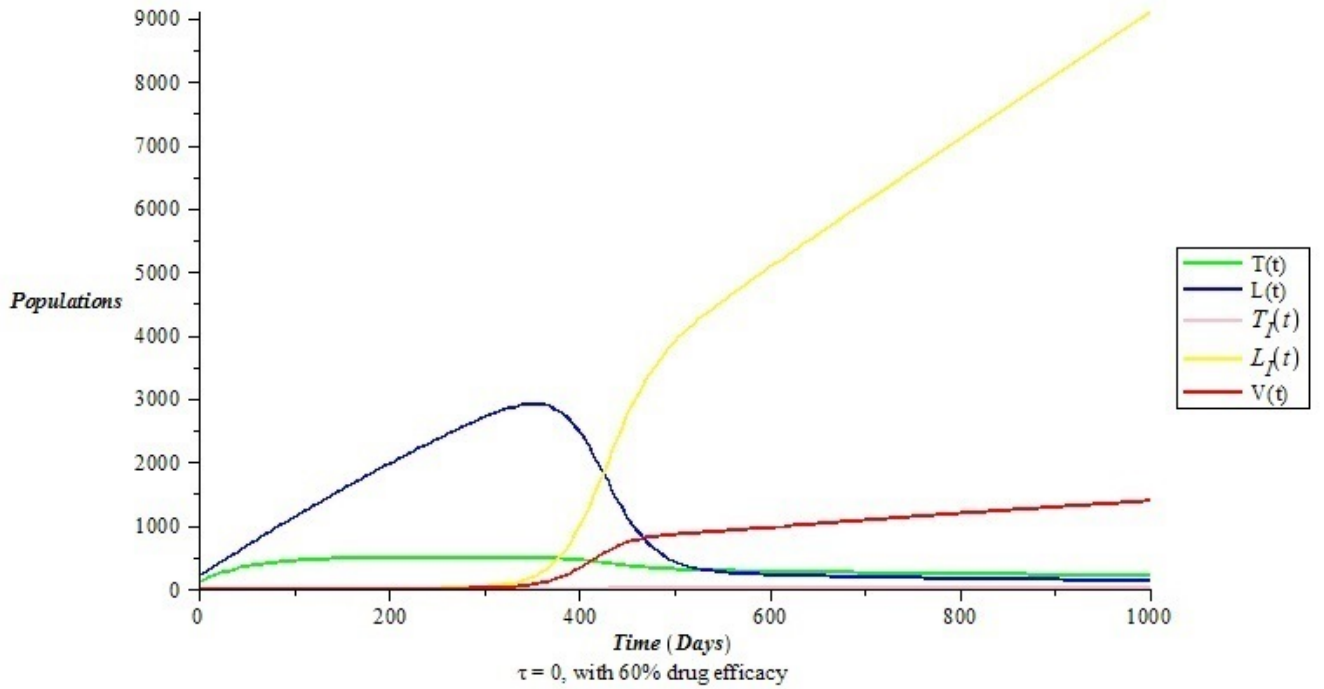
Figure 4: Cells and HIV population dynamics under therapeutic intervention. *Shows the population dynamics with drug efficacy of 60% and when $\tau = 0$*
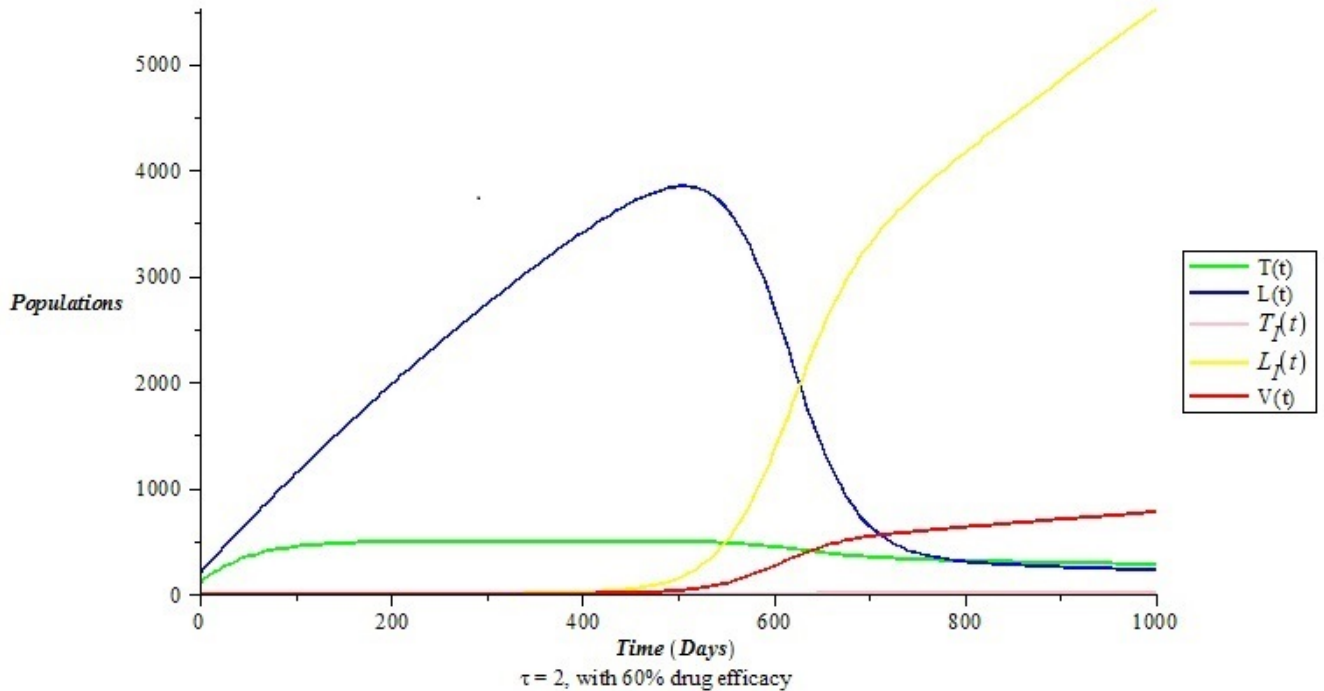

Figure 5: Cells and HIV population dynamics under therapeutic intervention. *Shows the population dynamics with drug efficacy of 60% and when $\tau = 2$*
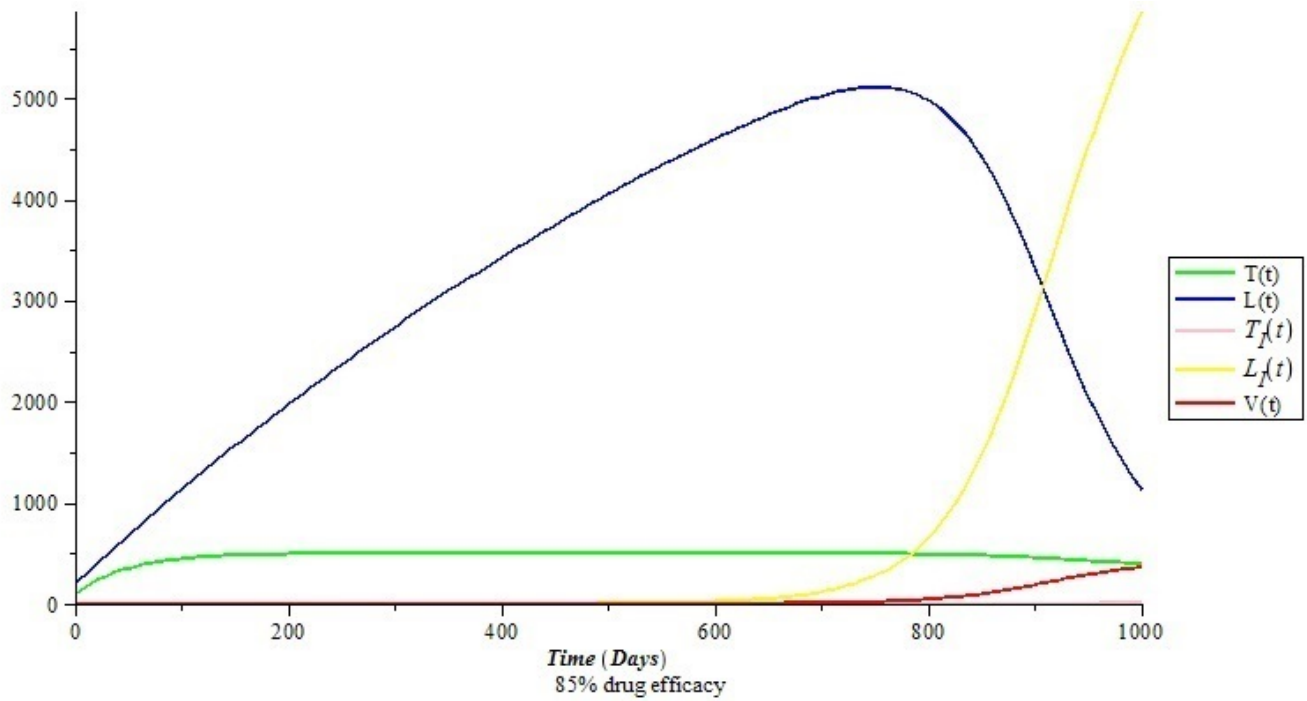
Figure 6: Cells and HIV population dynamics under therapeutic intervention.*Shows the population dynamics with drug efficacy of 85%*
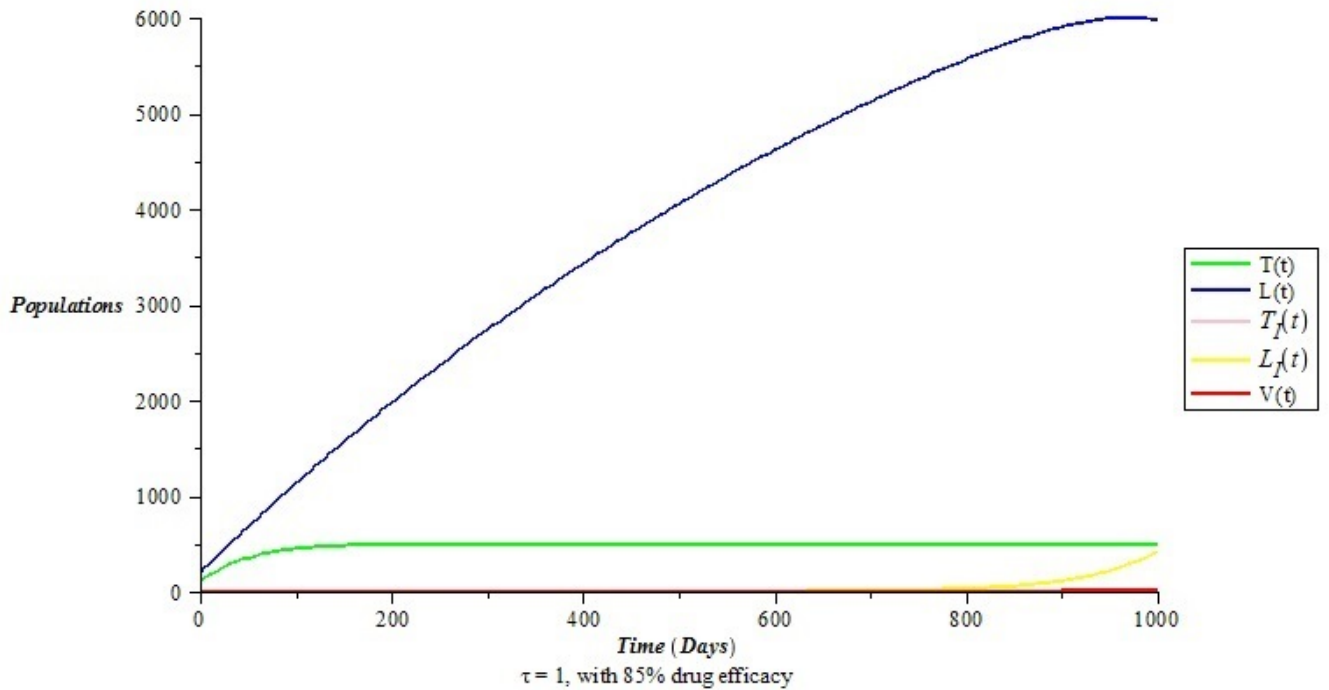

Figure 7: Cells and HIV population dynamics under therapeutic intervention.*Shows the population dynamics with drug eficacy of 85% and when $\tau = 1$*

4   Discussion

In this study, we derived and analyse a stochastic model describing the dynamics of HIV, CD4+ T-cells, and LCs interactions under therapeutic intervention in vivo. This model included dynamics of five compartments- the number of healthy CD4 cells, the number of infected CD4 cells, the number of healthy langerhans cells, the number of infected langerhans cells and the HIV virons. The model describes HIV infection before and during therapy. We derived equations for the the joint probability generating function of the numbers of healthy immune cells,the HIV infected immune cells, and the free HIV particles at any time t, and obtained the moment structures of the healthy immune cells, infected immune cells and the virus particles over time t. We simulated the mean number of the healthy immune cells, the infected immune cells and the virus particles before and after combined therapeutic treatment at any time t.

Our analysis show that eradication of HIV is not possible without clearance of latently infected langerhans cells. Therefore, understanding HIV therapeutic treatment dynamics in vivo is critical to eliminating the virus, which shows that LCs are important in determining the disease progression. Our model analysis suggest that, therapies should be developed to block the binding of HIV onto langerhans cells. Such therapies will have the potential to dramatically accelerate viral decay. We conclude that to control the concentrations of the virus and the infected cells in HIV infected person, a strategy should aim to improve the drug efficacy, hence the efficacy of the protease inhibitor and the reverse transcriptase inhibitor and also the intracellular delay play crucial role in preventing the progression of HIV [8]. These findings illustrates the role of LCs as a central hub of interaction and information exchange during HIV infection. Our model produces interesting feature that, classification of HIV disease states should not be based on CD4+ cells as the only immune cells infected by the virus. The most reliable HIV state classification criteria should be the CDC/WHO classification.

In our work, the dynamics of mutant virus was not considered and also our study only included dynamics of only five compartments (healthy immune cells, infected immune cells and free virus particles- ignoring the latency of infected immune cells) of which extensions are recommended for further extensive research. In a follow-up work, we intend to obtain real data in order to test the efficacy of our models as we have done here with simulated data.

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