

Research Article

Stochastic Model for In-Host HIV Dynamics with Therapeutic Intervention

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Untangling the dynamics between HIV and CD4 cellular populations and molecular interactions can be used to investigate the effective points of interventions in the HIV life cycle. With that in mind, we propose and show the usefulness of a stochastic approach towards modeling HIV and CD4 cells' dynamics *in vivo* by obtaining probability generating function, the moment structures of the healthy CD4 cell and the virus particles at any time t , and the probability of HIV clearance. The unique feature is that both therapy and the intracellular delay are incorporated into the model. Our analysis shows that, when it is assumed that the drug is not completely effective as is the case of HIV *in vivo*, the probability of HIV clearance depends on two factors: the combination of drug efficacy and length of the intracellular delay and also the education of the infected patients. Comparing simulated data before and after treatment indicates the importance of combined therapeutic intervention and intracellular delay in having low, undetectable viral load in HIV-infected person.

1. Introduction

Since HIV pandemic first became visible, enormous mathematical models have been developed to describe the immunological response to infection with human immunodeficiency virus (HIV). Mathematical modeling has proven to be valuable in understanding the dynamics of infectious diseases with respect to host-pathogen interactions. When HIV enters the body, it targets all the cells with CD4 receptors including the CD4 T cells. The knowledge of principal mechanisms of viral pathogenesis, namely, the binding of the retrovirus to the gp120 protein on the CD4 cell, the entry of the viral RNA into the target cell, the reverse transaction of viral RNA to viral DNA, the integration of the viral DNA with that of the host, and the action of viral protease in cleaving viral proteins into mature products, has led to the design of drugs (chemotherapeutic agents) to control the production of HIV.

Chronic HIV-infection causes gradual depletion of the CD4 T-cell pool and, thus, progressively compromises the host's immune response to opportunistic infections, leading

to acquired immunodeficiency syndrome (AIDS) [1]. With the spread of the HIV-AIDS pandemic and in the absence of an "effective" vaccine or cure, therapeutic interventions are still heavily relied on. Several research studies have been carried out in the recent past, both theoretically and experimentally, to analyse the impact of therapy on the viral load in HIV-infected persons in order to ascertain the effectiveness of the treatment (see, e.g., [2–8]). Their utility lies in the ability to predict an infected steady state and examining the effects that the changes in parameters have on the outcome of the system over time to determine which parameters are most important in disease progression, and further determine critical threshold values for these parameters.

In HIV-infected individuals, the infection exhibits a long asymptomatic phase (after the initial high infectious phase) of approximately 10 years on average before the onset of AIDS. During this incubation period, which some call the clinical latency period, the individuals appear to be well and may contribute significantly to the spread of the epidemic in a community [9]. Some clinical markers such as the

CD4 cell count and the RNA viral load (viraemia) provide information about the progression of the disease in infected individuals. Also, the clinical latency period of the disease may provide a sufficiently long period during which one can attempt an effective suppressive therapeutic intervention in HIV infections. Various biological reasons lead to the introduction of time delays in models of disease transmission. Time delays are used to model the mechanisms in the disease dynamics (see, e.g., [10, 11]).

Intracellular delays and the target-cell dynamics such as mitosis are two key factors that play an important role in the viral dynamics. Mitosis in healthy or infected target-cell population are typically modelled by a logistic term [2, 12–16]. Intracellular delays have been incorporated into the incidence term in finite or distributed form [4, 17–23]. In [13, 16], in-host viral models with a logistic growth term without intracellular delays are investigated, and it is shown that sustained oscillations can occur through Hopf bifurcation when the intrinsic growth rate increases. It is shown in [17, 23], in in-host models with both a logistic growth term and intracellular delay, that Hopf bifurcations can occur when the intracellular delay increases. In [19], using in-host models with a general form of target-cell dynamics and general distributions for intracellular delays, it is shown that the occurrence of Hopf bifurcation in these models critically depends on the form of target-cell dynamics. More specifically, it is proved in [20] that, if the target-cell dynamics are such that no Hopf bifurcations occur when delays are absent, introducing intracellular delays in the model will not lead to Hopf bifurcations or periodic oscillations.

To incorporate the intracellular delay phase of the virus life cycle, [24] assumed that virus production occurs after the virus entry by a constant delay τ . They came up with a basic in-host compartmental model of the viral dynamics containing three compartments: $x(t)$, $y(t)$, and $v(t)$ denoting the populations of uninfected target cells, infected target cells that produce virus, and free virus particles, respectively. They further assumed that parameters δ , α , and μ are turnover rates of the x , y , and v compartments, respectively. Uninfected target cells are assumed to be produced at a constant rate λ . They assumed also that cells infected at time t will be activated and produce viral materials at time $t + \tau$. In their model, constant s is the death rate of infected but not yet virus-producing cells, and $e^{-s\tau}$ describes the probability of infected target cells surviving the period of intracellular delay from $t - \tau$ to t . Constant κ denotes the average number of virus particles that each infected cell produces. Preceding assumptions lead to the following system of differential equations:

$$\begin{aligned} \frac{dx}{dt} &= \lambda - \delta x(t) - \beta x(t) v(t), \\ \frac{dy}{dt} &= \beta x(t - \tau) v(t - \tau) e^{-s\tau} - \alpha y(t), \\ \frac{dv}{dt} &= \kappa y(t) - \mu v(t). \end{aligned} \quad (1)$$

System (1) can be used to model the infection dynamics of HIV, HBV, and other viruses [2, 12–14, 25, 26]. It can also be

considered as a model for the HTLV-I infection if $x(t)$, $y(t)$, and $v(t)$ are regarded as healthy, latently infected, and actively infected CD4 T cells [14, 15]. For detailed description and derivation of the model, as well as the incorporation of intracellular delays, we refer the reader to [24].

From the literature, many researchers have employed deterministic models to study HIV internal dynamics, ignoring the stochastic effects. We consider a stochastic model for the interaction of HIV virus and the immune system in an HIV-infected individual undergoing a combination-therapeutic treatment. Our aim in this paper is to use a stochastic model obtained by extending the model of [24] to determine the probability distribution, variance and covariance structures of the uninfected CD4+ cells, infected CD4 cells, and the free HIV particles in an infected individual at any time t by examining the combined antiviral treatment of HIV. Based on the model, we obtain joint probability distribution, expectations, variance and covariance structures of variables representing the numbers of uninfected CD4 cells, the HIV-infected CD4 T cells, and the free HIV particles at any time t and derive conclusions for the reduction or elimination of HIV in HIV-infected individuals, which is one of the main contributions of this paper.

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 probability generating function of the numbers of uninfected CD4 cells, the HIV-infected CD4 T cells, and the free HIV particles at any time t , also moments for the variables are derived here. In Section 3, we derive the moments of the variables in a therapeutic environment and probability of extinction of HIV virus and also provide a numerical illustration to demonstrate the impact of intercellular delay and therapeutic intervention in controlling the progression of HIV. Some concluding remarks follow in Section 4.

2. HIV and CD4 Cells Dynamics before Therapeutic Intervention

To study the interaction of HIV virus and the immune system, we propose a stochastic model by extending the deterministic model presented in the literature. A stochastic process is defined by the probabilities with which different events happen in a small time interval Δt . In our model, there are two possible events (production and death/removal) for each population (uninfected cells, infected cells, and the free virions). The corresponding rates in the deterministic model are replaced in the stochastic version by the probabilities that any of these events occur in a small time interval Δt .

(1) *The Interaction of HIV Virus and the CD4 T-Cells.* A typical life-cycle of HIV virus and immune system interaction is shown in Figure 1.

Let $X(t)$ be the size of the healthy cells population at time t , $Y(t)$ be the size of infected cell population at time t , and $V(t)$ be the size of the virions population at time t . In the model to be formulated, it is now assumed that

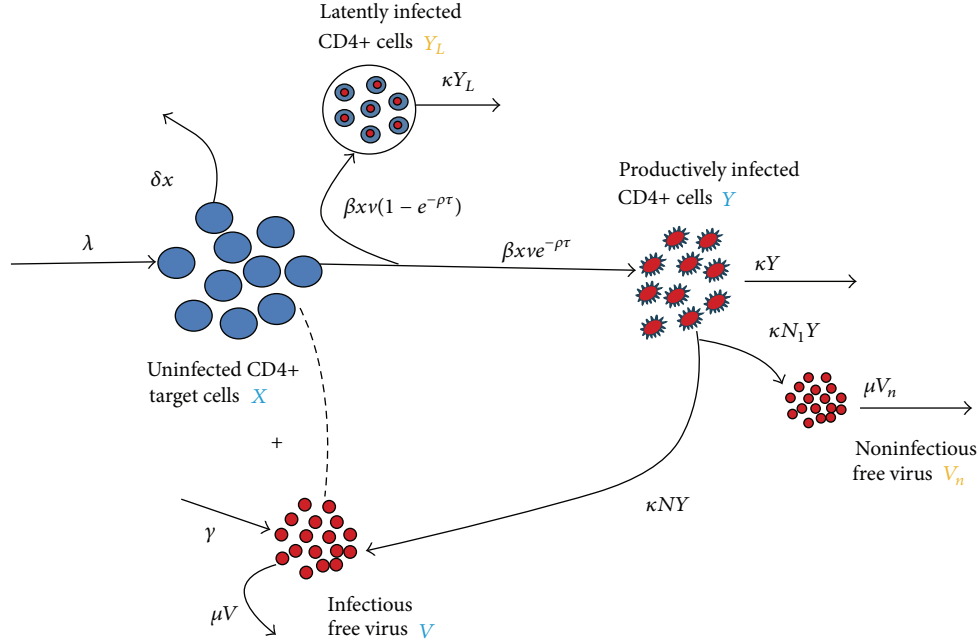


FIGURE 1: The interaction of HIV virus and the CD4+ T cells.

instead of rates of births and deaths, there is a possibility of stochastic births or deaths of the healthy cells, infected cells and the virus particles. Thus, $X(t)$, $Y(t)$, and $V(t)$ are time-dependent random variables. This epidemic process can be modeled stochastically by letting the nonnegative integer values process $X(t)$, $Y(t)$, and $V(t)$, respectively, represent the number of healthy cells, infected cells, and virions of the disease at time t . Then, $\{(X(t), Y(t), V(t)) : t \geq 0\}$ can be modeled as continuous time multivariate Markov chain. Let the probability of there being x healthy cells, y infected cells, and v virions in an infected person at time t be denoted by the following joint probability function: $P_{x,y,v}(t) = P[X(t) = x, Y(t) = y, V(t) = v]$, for $x, y, v = 0, 1, 2, 3, \dots$

The standard argument using the forward Chapman-Kolmogorov differential equations is used to obtain the joint probability function $P_{x,y,v}(t)$, by considering the joint probability $P_{x,y,v}(t, t + \Delta t)$. This joint probability is obtained as the sum of the probabilities of the following mutually exclusive events.

(2) *Population Change Scenarios.* Consider the following points.

- (1) There were x healthy cells, y infected cells, and v virions by time t , and nothing happens during the time interval $(t, t + \Delta t)$.
- (2) There were $x - 1$ healthy cells, y infected cells, and v virions by time t , and one healthy cell is produced from the thymus during the time interval $(t, t + \Delta t)$.
- (3) There were $x + 1$ healthy cells, y infected cells, and v virions by time t , and one healthy cell dies or is infected by HIV virus during the time interval $(t, t + \Delta t)$.

- (4) There were x healthy cells, $y - 1$ infected cells, and v virions by time t , and one healthy cell is infected by HIV virus during the time interval $(t, t + \Delta t)$.
- (5) There were x healthy cells, $y + 1$ infected cells, and v virions by time t and one infected cell dies (HIV-infected cell bursts or undergoes a lysis) during the time interval (t, τ) .
- (6) There were x healthy cells, y infected cells, and $v - 1$ virions by time t and one virion is produced (HIV-infected cell undergoes a lysis or the individual engages in risky behaviour) during the time interval $(t, t + \Delta t)$.
- (7) There were x healthy cells, y infected cells, and $v + 1$ virions by time t , and one virion dies during the time interval $(t, t + \Delta t)$.

We incorporate a time delay between infection of a cell and production of new virus particles, we let τ be the time lag between the time the virus contacts a target CD4 T cell and the time the cell becomes productively infected (including the steps of successful attachment of the virus to the cell and penetration of virus into the cell); this means the recruitment of virus producing cells at time t is given by the density of cells that were newly infected at time $t - \tau$ and are still alive at time t . If we also let ρ be the death rate of infected but not yet virus producing cell, then the probability that the infected cell will survive to virus producing cell during the short time interval τ will be given by $e^{-\rho\tau}$.

(3) *Variables and Parameters for the Model.* The variables and parameters in the model are described as in Table 1.

Using the population change scenarios and parameters in Table 1, we now summarize the events that occur during

TABLE 1: (a) Variables for the stochastic model. (b) Parameters for the stochastic model.

(a)		
Variable	Description	Initial condition $t = 0$
$X(t)$	The concentration of uninfected CD4 cells at time t	100
$Y(t)$	The concentration of infected CD4 cells at time t	0.02
$V(t)$	The concentration of virus particles at time t	0.001

(b)		
Parameter symbol	Parameter description	Estimate
$(1 - \alpha)$	The reverse transcriptase inhibitor drug effect	0.5
$(1 - \omega)$	The protease inhibitor drug effect	0.5
λ	The total rate of production of healthy CD4 cells	10
δ	The per capita death rate of healthy CD4 cells	0.02
β	The transmission coefficient between uninfected CD4 cells and infective virus particles	0.000024
κ	Per capita death rate of infected CD4 cells	0.5
γ	The virus production rate due to risk behaviors	0.001
μ	The per capita death rate of infective virus particles	3
ρ	The death rate of infected but not yet virus producing cell	0.5
τ	Time lag during infection	0.5
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

the interval $(t, t + \Delta)$ together with their transition probabilities in Table 2.

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:

$$\begin{aligned}
 &P_{x,y,v}(t + \Delta t) \\
 &= \{1 - (\lambda \Delta t + \delta x \Delta t + \beta x v \Delta t + \mu v \Delta t + \kappa y \Delta t + \gamma \Delta t) \\
 &\quad + o(\Delta t)\} P_{x,y,v}(t) \\
 &\quad + \{\lambda \Delta t + o(\Delta t)\} P_{x-1,y,v}(t) \\
 &\quad + \{\delta(x+1) \Delta t + o(\Delta t)\} P_{x+1,y,v}(t) \\
 &\quad + \{\beta(x+1)(v+1) e^{-\rho \tau} \Delta t + o(\Delta t)\}
 \end{aligned}$$

$$\begin{aligned}
 &\times P_{x+1,y-1,v+1}(t) \\
 &\quad + \{\kappa N(y+1) \Delta t + o(\Delta t)\} P_{x,y+1,v-1}(t) \\
 &\quad + \{\gamma \Delta t + o(\Delta t)\} P_{x,y,v-1}(t) \\
 &\quad + \{\mu(v+1) \Delta t + o(\Delta t)\} P_{x,y,v+1}(t).
 \end{aligned} \tag{2}$$

Simplifying (2), we have the following forward Kolmogorov partial differential equations for $P_{x,y,v}(t)$:

$$\begin{aligned}
 P'_{x,y,v}(t) = & - \{\lambda + \delta x + \beta e^{-\rho \tau} x v + \mu v + \kappa N y + \gamma\} P_{x,y,v}(t) \\
 & + \lambda P_{x-1,y,v}(t) + \delta(x+1) P_{x+1,y,v}(t) \\
 & + \beta(x+1)(v+1) e^{-\rho \tau} P_{x+1,y-1,v+1}(t) \\
 & + N \kappa(y+1) P_{x,y+1,v-1}(t) + \gamma P_{x,y,v-1}(t) \\
 & + \mu(v+1) P_{x,y,v+1}(t).
 \end{aligned} \tag{3}$$

This will also be referred to as the Master equation or the Differential-Difference equation, with the condition

$$P'_{0,0,0}(t) = -(\lambda + \gamma) P_{0,0,0}(t) + \delta P_{1,0,0}(t) + \mu P_{0,0,1}(t). \tag{4}$$

2.1. The Probability Generating Function. The probability generating function of $(X(t), Y(t), V(t))$ is defined by

$$G(z_1, z_2, z_3, t) = \sum_{x=0}^{\infty} \sum_{y=0}^{\infty} \sum_{v=0}^{\infty} P_{x,y,v}(t) z_1^x z_2^y z_3^v. \tag{5}$$

Differentiating (5) with respect to t yields

$$\frac{\partial G(z_1, z_2, z_3, t)}{\partial t} = \sum_{x=0}^{\infty} \sum_{y=0}^{\infty} \sum_{v=0}^{\infty} P'_{x,y,v}(t) z_1^x z_2^y z_3^v. \tag{6}$$

Differentiating again (5) with respect to z_1, z_2 , and z_3 yields

$$\begin{aligned}
 &\frac{\partial^3 G(z_1, z_2, z_3, t)}{\partial z_1 \partial z_2 \partial z_3} \\
 &= \sum_{x=1}^{\infty} \sum_{y=1}^{\infty} \sum_{v=1}^{\infty} x y v P_{x,y,v}(t) z_1^{x-1} z_2^{y-1} z_3^{v-1} \\
 &= \sum_{x=0}^{\infty} \sum_{y=0}^{\infty} \sum_{v=0}^{\infty} (x+1)(y+1)(v+1) P_{x+1,y+1,v+1}(t) z_1^x z_2^y z_3^v.
 \end{aligned} \tag{7}$$

Multiplying (3) by $z_1^x z_2^y z_3^v$ and summing over x, y , and v , then applying (4), (5), (6), and (7) and on simplification we obtain

$$\begin{aligned}
 \frac{\partial G}{\partial t} = & \{(z_1 - 1) \lambda + (z_3 - 1) \gamma\} G \\
 & + (1 - z_1) \delta \frac{\partial G}{\partial z_1} + (z_3 - z_2) \kappa N \frac{\partial G}{\partial z_2} \\
 & + (1 - z_3) \mu \frac{\partial G}{\partial z_3} + \beta e^{-\rho \tau} (z_2 - z_1 z_3) \frac{\partial^2 G}{\partial z_1 \partial z_3}.
 \end{aligned} \tag{8}$$

TABLE 2: Transitions of in-host interaction of HIV.

Possible transitions in host interaction of HIV and immune system cells and corresponding probabilities			
Event	Population (X, Y, V) at t	Population (X, Y, V) at (t, t + Δ)	Probability of transition
Production of uninfected cell	(x - 1, y, v)	(x, y, v)	$\lambda \Delta t$
Death of uninfected cell	(x + 1, y, v)	(x, y, v)	$\delta(x + 1) \Delta t$
Infection of uninfected cell	(x + 1, y - 1, v + 1)	(x, y, v)	$\beta(x + 1)(v + 1)e^{-\rho\tau} \Delta t$
Production of virons from the bursting infected cell	(x, y + 1, v - 1)	(x, y, v)	$\kappa N(y + 1) \Delta t$
Introduction of virons due to reinfection because of risky behaviour	(x, y, v - 1)	(x, y, v)	$\gamma \Delta t$
Death of virons	(x, y, v + 1)	(x, y, v)	$\mu(v + 1) \Delta t$

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

Attempt to solve (8) gave us the following solution:

$$\begin{aligned}
 G(z_1, z_2, z_3, t) &= ae^{bt} \left\{ \{(z_1 - 1)\lambda + (z_3 - 1)\gamma\} F(z_1, z_2, z_3) \right. \\
 &\quad + (1 - z_1) \delta \frac{\partial F(z_1, z_2, z_3)}{\partial z_1} \\
 &\quad + (Nz_3 - z_2) \kappa \frac{\partial F(z_1, z_2, z_3)}{\partial z_2} \\
 &\quad + (1 - z_3) \mu \frac{\partial F(z_1, z_2, z_3)}{\partial z_3} \\
 &\quad \left. + \beta(e^{-\rho\tau} z_2 - z_1 z_3) \frac{\partial^2 F(z_1, z_2, z_3)}{\partial z_1 \partial z_3} \right\}, \quad (9)
 \end{aligned}$$

where a and b are constants.

Equation (9) is not solvable, even for any simple form of $F(z_1, z_2, z_3)$. However, it is possible to obtain the moment structure of $(X(t); Y(t); V(t))$ from (8).

2.2. The Marginal Generating Functions. Recall that

$$G(z_1, 1, 1, t) = \sum_{x=0}^{\infty} \sum_{y=0}^{\infty} \sum_{v=0}^{\infty} P_{x,y,v}(t) z_1^x. \quad (10)$$

Assuming that $z_2 = z_3 = 1$, $z_1 = z_3 = 1$, and $z_2 = z_1 = 1$ and solving (8), we obtain the marginal partial generating functions for $X(t)$, $Y(t)$, and $V(t)$, respectively,

$$\begin{aligned}
 \frac{\partial G(z_1; t)}{\partial t} &= \frac{\partial G(z_1, 1, 1; t)}{\partial t} \\
 &= (z_1 - 1) \lambda G + (1 - z_1) \delta \frac{\partial G}{\partial z_1} \\
 &\quad + \beta e^{-\rho\tau} (1 - z_1) \frac{\partial^2 G}{\partial z_1 \partial z_3}, \\
 \frac{\partial G(z_2; t)}{\partial t} &= \frac{\partial G(1, z_2, 1; t)}{\partial t} \\
 &= (1 - z_2) \kappa N \frac{\partial G}{\partial z_2} + \beta e^{-\rho\tau} (z_2 - 1) \frac{\partial^2 G}{\partial z_1 \partial z_3}, \\
 \frac{\partial G(z_3; t)}{\partial t} &= \frac{\partial G(1, 1, z_3; t)}{\partial t} \\
 &= (z_3 - 1) \gamma G + (z_3 - 1) \kappa N \frac{\partial G}{\partial z_2} + (1 - z_3) \mu \frac{\partial G}{\partial z_3} \\
 &\quad + \beta e^{-\rho\tau} (1 - z_3) \frac{\partial^2 G}{\partial z_1 \partial z_3}. \quad (11)
 \end{aligned}$$

2.3. Numbers of CD4 T Cells and the Virons. As we know from probability generating function,

$$\frac{\partial G_x}{\partial z} = \sum_{x=0}^{\infty} x P_x(t) z^{x-1}. \quad (12)$$

Letting $z = 1$, we have

$$\left. \frac{\partial G_x}{\partial z} \right|_{z=1} = \sum_{x=0}^{\infty} x P_x(t) z^{x-1} = E[X]. \quad (13)$$

Differentiating the partial differential equations of the pgf, we get the moments of $X(t)$, $Y(t)$, and $V(t)$.

Differentiating (11) with respect to z_1 , z_2 , and z_3 , respectively, and setting $z_1 = z_2 = z_3 = 1$, we have

$$\begin{aligned}\frac{\partial}{\partial t} E[X(t)] &= \lambda - \delta E[X(t)] - \beta E[X(t) V(t)], \\ \frac{\partial}{\partial t} E[Y(t)] &= -\kappa E[Y(t)] + \beta e^{-\rho\tau} E[X(t) V(t)], \\ \frac{\partial}{\partial t} E[V(t)] &= \gamma + N\kappa E[Y(t)] - \mu E[V(t)] - \beta E[X(t) V(t)].\end{aligned}\quad (14)$$

Therefore, the moments of $(X(t), Y(t), V(t))$ from the pgf before treatment are as follows:

$$\begin{aligned}\frac{\partial}{\partial t} E[X(t)] &= \lambda - \delta E[X(t)] - \beta E[X(t) V(t)], \\ \frac{\partial}{\partial t} E[Y(t)] &= -\kappa E[Y(t)] + \beta e^{-\rho\tau} E[X(t) V(t)], \\ \frac{\partial}{\partial t} E[V(t)] &= \gamma + N\kappa E[Y(t)] - \mu E[V(t)] - \beta E[X(t) V(t)].\end{aligned}\quad (15)$$

The corresponding deterministic model of HIV-host interaction as formulated in [24] is given as follows:

$$\begin{aligned}\frac{dx}{dt} &= \lambda - \delta x(t) - \beta x(t) v(t), \\ \frac{dy}{dt} &= \beta e^{-\rho\tau} x(t - \tau) v(t - \tau) - \kappa y(t), \\ \frac{dv}{dt} &= \gamma + N\kappa y(t) - \mu v(t) - \beta x(t) v(t).\end{aligned}\quad (16)$$

Comparing system of (15) with the system of (16), we see that expected values of the multivariate Markov process $[X(t), Y(t), V(t)]$ satisfies the corresponding deterministic model of the HIV-host interaction dynamics.

2.3.1. Simulation. Using the parameter values and initial conditions defined in Table 1, we illustrate the general dynamics of the CD4-T cells and HIV virus for model (15) during infection and in the absence of treatment.

The second graph in Figure 2 is the population dynamics after taking the logarithm of the cell populations in the first graph.

From the simulations, it is clear that in the primary stage of the infection (period before treatment), a dramatic decrease in the level of the CD4-T cells occurs and the number of the free virions increases with time. With the introduction of intracellular delay, the virus population drops as well as an increase in the CD4, cells but then they stabilize at some point and coexist in the host as shown in Figure 2.

3. HIV and CD4 Cells Dynamics under Therapeutic Intervention

Assume that at time $t = 0$, a combination therapy treatment is initiated in an HIV-infected individual. We assume that

the therapeutic intervention inhibits either the enzyme action of reverse transcriptase or that of the protease of HIV in an HIV-infected cell. An HIV-infected cell with the inhibited HIV-transcriptase may be considered a dead cell as it cannot participate in the production of the copies of any type of HIV. On the other hand, an HIV-infected cell in which the reverse transcription has already taken place and the viral DNA is fused with the DNA of the host, but the enzyme activity of HIV-protease is inhibited, undergoes a lysis releasing infectious free HIV and noninfectious free HIV. A noninfectious free HIV cannot successfully infect a CD4 cell. Accordingly, at any time t , the blood of the infected person contains virus producing HIV-infected cells, infectious free HIV, and noninfectious free HIV. A typical life cycle of HIV virus and immune system interaction with therapeutic intervention is shown in Figure 3.

Introducing the effect of treatment, the Lagrange partial differential equation becomes

$$\begin{aligned}\frac{\partial G}{\partial t} &= \{(z_1 - 1)\lambda + (z_3 - 1)\gamma\}G + (1 - z_1)\delta \frac{\partial G}{\partial z_1} \\ &+ (1 - \omega)(z_3 - z_2)\kappa N \frac{\partial G}{\partial z_2} + (1 - z_3)\mu \frac{\partial G}{\partial z_3} \\ &+ (1 - \alpha)\beta e^{-(1-\alpha)\rho\tau}(z_2 - z_1 z_3) \frac{\partial^2 G}{\partial z_1 \partial z_3}.\end{aligned}\quad (17)$$

3.1. The Marginal Generating Functions. Recall that

$$G(z_1, 1, 1, t) = \sum_{x=0}^{\infty} \sum_{y=0}^{\infty} \sum_{v=0}^{\infty} P_{x,y,v}(t) z_1^x. \quad (18)$$

Setting $z_2 = z_3 = 1$, $z_1 = z_3 = 1$, and $z_2 = z_1 = 1$ and solving (17), we obtain the marginal partial generating functions for $X(t)$, $Y(t)$, and $V(t)$, respectively, as:

$$\begin{aligned}\frac{\partial G(z_1; t)}{\partial t} &= \frac{\partial G(z_1, 1, 1; t)}{\partial t} \\ &= (z_1 - 1)\lambda G + (1 - z_1)\delta \frac{\partial G}{\partial z_1} \\ &+ (1 - \alpha)\beta e^{-(1-\alpha)\rho\tau}(1 - z_1) \frac{\partial^2 G}{\partial z_1 \partial z_3}, \\ \frac{\partial G(z_2; t)}{\partial t} &= \frac{\partial G(1, z_2, 1; t)}{\partial t} \\ &= (1 - \omega)(N - z_2)\kappa \frac{\partial G}{\partial z_2} \\ &+ (1 - \alpha)\beta e^{-(1-\alpha)\rho\tau}(z_2 - 1) \frac{\partial^2 G}{\partial z_1 \partial z_3},\end{aligned}$$

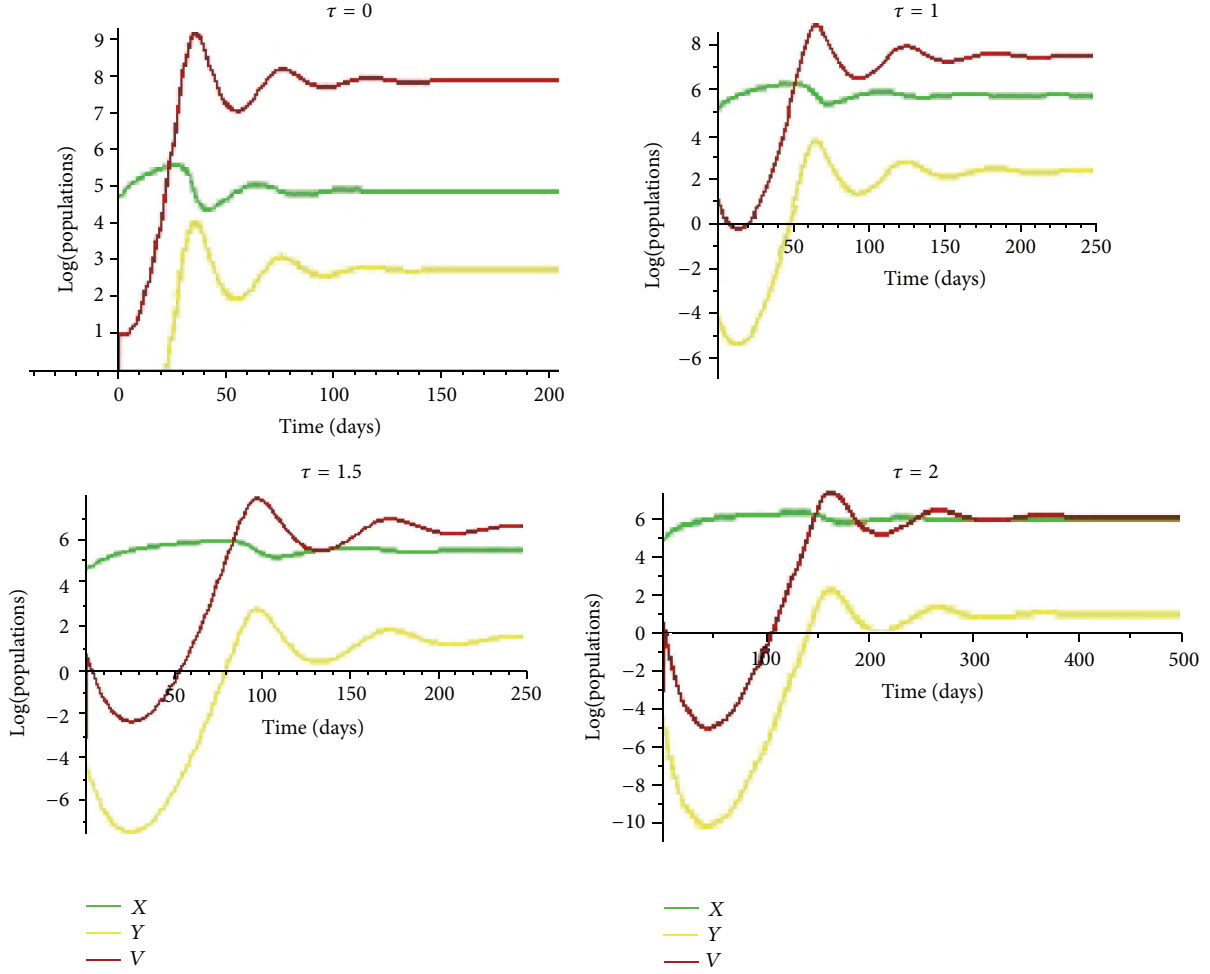


FIGURE 2: The figure shows the CD4 cells and HIV virus population dynamics before therapeutic intervention and when $\tau = 0, 1.5$, and 2 days. The other parameters and initial conditions are given in Tables 1 and 2.

$$\begin{aligned}
 \frac{\partial G(z_3; t)}{\partial t} &= \frac{\partial G(1, 1, z_3; t)}{\partial t} \\
 &= (z_3 - 1) \gamma G + (1 - \omega)(z_3 - 1) \kappa N \frac{\partial G}{\partial z_2} \\
 &\quad + (1 - z_3) \mu \frac{\partial G}{\partial z_3} \\
 &\quad + (1 - \alpha) \beta e^{-(1-\alpha)\rho\tau} (1 - z_3) \frac{\partial^2 G}{\partial z_1 \partial z_3}.
 \end{aligned} \tag{19}$$

3.2. Numbers of CD4+ T Cells and Virons under Therapeutic Intervention. From probability generating function one gets

$$\frac{\partial G_x}{\partial z} = \sum_{x=0}^{\infty} x P_x(t) z^{x-1}. \tag{20}$$

Letting $z = 1$, we have the expected number of target CD4+ T cells $X(t)$ as follows:

$$\begin{aligned}
 E[X(t)] &= \left. \frac{\partial G_x}{\partial z} \right|_{z=1} \\
 &= \sum_{x=0}^{\infty} x P_x(t) z^{x-1}.
 \end{aligned} \tag{21}$$

Differentiating the partial differential equations of the pgf, we get the moments of $X(t)$, $Y(t)$, and $V(t)$.

Differentiating (19) with respect to z_1 , z_2 , and z_3 , respectively, and setting $z_1 = z_2 = z_3 = 1$, we have

$$\begin{aligned}
 \frac{\partial}{\partial t} E[X(t)] &= \lambda - \delta E[X(t)] - (1 - \alpha) \beta E[X(t) V(t)], \\
 \frac{\partial}{\partial t} E[Y(t)] &= -\kappa E[Y(t)] + (1 - \alpha) \beta e^{-(1-\alpha)\rho\tau} E[X(t) V(t)], \\
 \frac{\partial}{\partial t} E[V(t)] &= \gamma + (1 - \omega) N \kappa E[Y(t)] - \mu E[V(t)] \\
 &\quad - (1 - \alpha) \beta E[X(t) V(t)].
 \end{aligned} \tag{22}$$

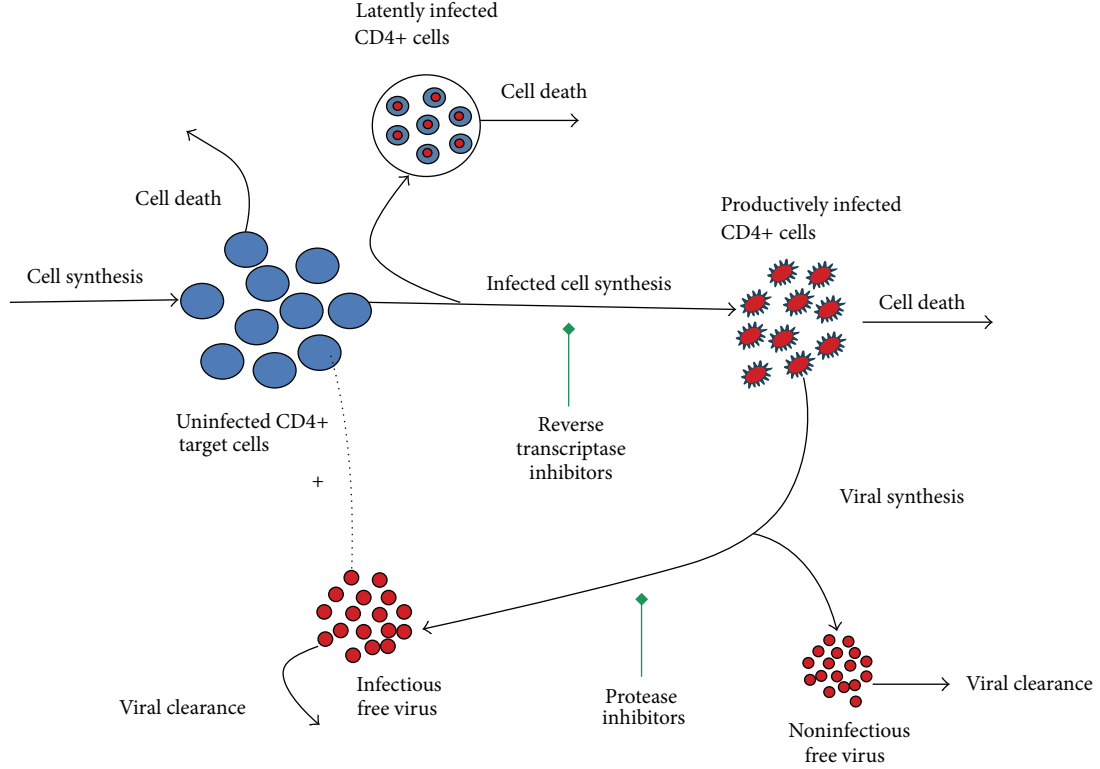


FIGURE 3: HIV-host interaction with treatment.

Therefore, the moments of $(X(t), Y(t), V(t))$ from the pgf with therapeutic intervention are

$$\begin{aligned}\frac{\partial}{\partial t} E[X(t)] &= \lambda - \delta E[X(t)] - (1 - \alpha) \beta E[X(t) V(t)], \\ \frac{\partial}{\partial t} E[Y(t)] &= -\kappa E[Y(t)] + (1 - \alpha) \beta e^{-(1-\alpha)\rho\tau} E[X(t) V(t)], \\ \frac{\partial}{\partial t} E[V(t)] &= \gamma + (1 - \omega) N \kappa E[Y(t)] \\ &\quad - \mu E[V(t)] - (1 - \alpha) \beta E[X(t) V(t)].\end{aligned}\quad (23)$$

3.2.1. Simulation. Using the parameter values and initial conditions defined in Table 1, we illustrate the general dynamics of the CD4-T cells and HIV virus for model (23) with therapeutic intervention and test the effect of intracellular delay and drug efficacy (perform sensitivity analysis).

With 60% drug efficacy, the virus stabilizes and coexists with the CD4 cells within the host as shown in the first graph in Figure 4.

Introducing intracellular time delay, $\tau = 0.5$, the CD4 cells increase and the virus population drops then stabilizes and again coexists within the host as illustrated in the second graph in Figure 4.

For $\tau = 1$ and with 60% drug efficacy, the dynamics change as shown in the last graph in Figure 4.

We now analyze drug effectiveness on the cell populations.

Figure 5 shows that, with improved HIV drug efficacy, a patient on treatment will have low, undetectable viral load with time. It also shows that the protease inhibitor drug efficacy is very important in clearing the virus. Also the figure shows that a combination of therapeutic intervention and intracellular delay is very important in lowering the viral load in an HIV-infected person.

3.3. The Probability of HIV Clearance. We now calculate the distribution of times to extinction for the virions reservoir. If we assume the drug given at fixed intervals to sustain its efficacy to be effective in producing noninfectious virus, then we can clear the infectious virus. Using reverse transcriptase (ART), the infected cell can be forced to become latently infected (nonvirus producing cell) hence clearing the virus producing cell reservoir. If we assume that no newly infected cells become productively infected in the short time $\tau(e^{-\rho\tau} = 0)$ or that treatment is completely effective ($\omega = 1$), we can obtain the extinction probability analytically. In this case, the infectious virus cell dynamics decouples from the rest of the model and can be represented as a pure immigration-and-death process with master equation

$$\begin{aligned}P'_v(t) &= -(\gamma + \kappa(1 - \omega)N)P_v(t) \\ &\quad - v(\mu + (1 - \alpha)e^{-\rho\tau}\beta)P_v(t) \\ &\quad + (v - 1)(\gamma + \kappa(1 - \omega)N)P_{v-1}(t) \\ &\quad + (v + 1)(\mu + (1 - \alpha)e^{-\rho\tau}\beta)P_{v+1}(t),\end{aligned}\quad (24)$$

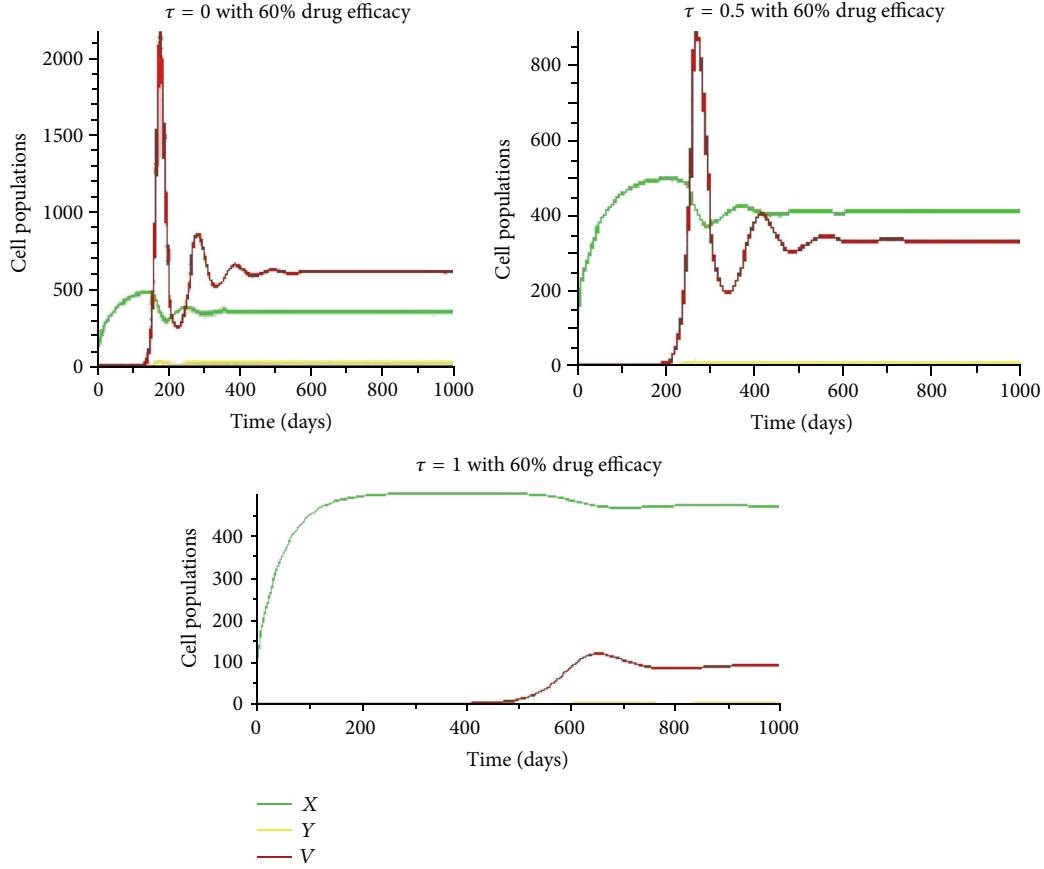


FIGURE 4: The figure shows the CD4 cells and HIV virus population dynamics with drug efficacy of 60% and $\tau = 0, 0.5$, and 1 days. The other parameters and initial conditions are given in Tables 1 and 2.

where $P_v(t)$ is the probability that, at time t , there are v HIV particles. This probability has the conditional probability generating function

$$G_v(z, t) |_{V(0)=v_0} = \exp \left\{ \frac{\theta}{\epsilon} (z-1) (1 - e^{-\theta t}) \right\} \left\{ z e^{-\theta t} + 1 - e^{-\theta t} \right\}^{v_0}, \quad (25)$$

where v_0 is the initial virus reservoir size, $\theta = \mu + (1 - \alpha)\beta e^{-\rho\tau}$ and $\epsilon = \gamma + (1 - \omega)\kappa N$. We noticed that this is a pgf of a random variable with a product of Poisson distribution $\exp\{(\theta/\epsilon)(z-1)(1 - e^{-\theta t})\}$ with mean $(\theta/\epsilon)(1 - e^{-\theta t})$ and a binomial distribution $\{z e^{-\theta t} + 1 - e^{-\theta t}\}^{v_0}$.

The probability of this population going extinct at t or before time t is given by

$$p_{\text{ext}}(t) |_{V(0)=v_0} = P(V = 0, t) |_{V(0)=v_0} = G_v(0, t) = P_0(t) = \exp \left\{ \frac{\theta}{\epsilon} (e^{-\theta t} - 1) \right\} \left\{ 1 - e^{-\theta t} \right\}^{v_0}. \quad (26)$$

The probability of extinction is the value of $G_v(z, t)$ when $t \rightarrow \infty$, that is,

$$\begin{aligned} p_{\text{ext}} &= P_0(\infty) \\ &= \lim_{t \rightarrow \infty} \left(\exp \left\{ \frac{\theta}{\epsilon} (e^{-\theta t} - 1) \right\} \left\{ 1 - e^{-\theta t} \right\}^{v_0} \right) \\ &= e^{-\theta/\epsilon} \\ &= e^{-((\mu + (1 - \alpha)\beta e^{-\rho\tau})/(\gamma + (1 - \omega)\kappa N))}. \end{aligned} \quad (27)$$

From (27), it is evident that probability of clearance of HIV is affected by the combination of drug efficacy and intracellular delay, death of the virions and education (counseling the HIV patients on the risk of involvement in risk behaviors).

4. Discussion and Recommendation

In this study, we derived and analyzed a stochastic model for in-host HIV dynamics that included combined therapeutic treatment and intracellular delay between the infection of a cell and the emission of viral particles. This model included dynamics of three compartments—the number of healthy CD4 cells, the number of infected CD4 cells, and the HIV virions—and it described HIV infection of CD4 T cells before

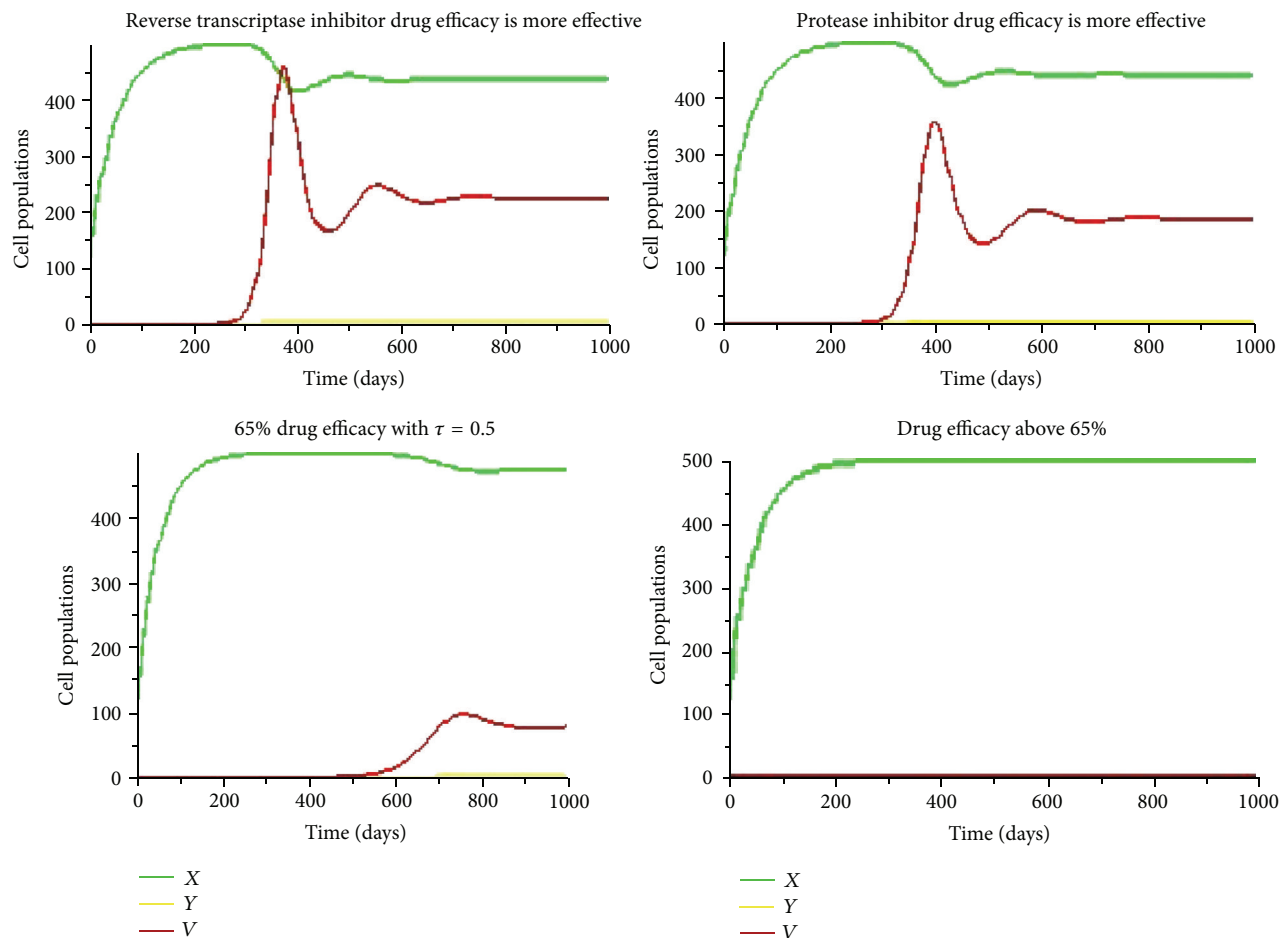


FIGURE 5: Shows the CD4 cells and HIV virus population dynamics with $\tau = 0.5$ days and different levels of drug efficacy. The other parameters and initial conditions are given in Tables 1 and 2.

and during therapy. We derived equations for the probability generating a function and using numerical techniques. In this paper we showed the usefulness of our stochastic approach towards modeling HIV dynamics by obtaining moment structures of the healthy CD4+ cell and the virus particles over time t . We simulated the mean number of the healthy CD4 cell, the infected cells, and the virus particles before and after combined therapeutic treatment at any time t . We will emphasize further usefulness of stochastic models in HIV dynamics in our future research.

Our analysis during treatment shows that, when it is assumed that the drug is not completely effective, as it is the case of HIV *in vivo*, the predicted rate of decline in plasma HIV virus concentration depends on three factors: the death rate of the viruses, the efficacy of therapy, and the length of the intracellular delay. Our model produces an interesting feature that the successfully treated HIV patients will have low, undetectable viral load. 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 cure rate (drug efficacy) and also to increase the intracellular delay τ . Therefore, 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.

The extinction probability model showed that the time it takes to have low, undetectable viral load (infectious virus) in an HIV-infected patient depends on the combination of drug efficacy and intracellular delay and also education of the infected patients. In our work, the dynamics of mutant virus were not considered, and also our study included dynamics of only three compartments (healthy CD4 cell, infected CD4 cells, and infectious HIV virus particles) 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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