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A COMPARISON OF DETERMINISTIC AND STOCHASTIC MODEL ON THE DYNAMICS OF HIV AND CD4$^+$ T-CELLS INTERACTIONS

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Abstract: This study aims to present a comparison of deterministic and stochastic approaches on the interaction of HIV and CD4$^+$ T-cells with effects of HAART treatment. A three-dimensional nonlinear model is formulated with randomness that is considered as a Brownian motion coming from the uncertainty of the death rate of cells and viruses. We establish sufficient conditions for stability of endemic and nonendemic solutions that associate with an early reproductive threshold value of HIV infection which is linearly negative depending on the HAART treatment parameters. Non-negative stochastic solutions are also analysed. Numerical simulations show that HAART parameters have a significant effect in reducing HIV infection. The smaller value of treatment parameter, the more infected cells, which is also indicated by a threshold value that is greater than one. It also results in high fluctuations in the stochastic solutions. If the treatment parameter increases due to regular treatment, the number of infected cells and viruses decreases. It also reduces high fluctuations in the stochastic solutions which on average follow the decreasing trend

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of deterministic solutions. These results provide an overview of the intervals of the number of viruses and infected cells produced before and after being given treatment.

Keywords: HIV; HAART; stochastic and deterministic models; non-negativity solution; Euler Maruyama method.

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1. INTRODUCTION

Acquired Immunodeficiency Syndrome (AIDS) is caused by a virus known as Human Immunodeficiency Virus (HIV). Since 1981, more than three decades, HIV still remains the public health threat [1]. Nearly 79.3 million people worldwide have been infected with HIV with around 36.3 million people worldwide have already lost their lives [1]. According to World Health Organization (WHO), there are still around 37.7 million people in the world living with HIV, 1.5 million people were newly infected with HIV, and 680 thousand people died of HIV-related causes in 2020 [1]. After being infected with HIV for a long time, humans will suffer from AIDS. The disease can be transmitted quickly in several ways including through sexual intercourse, children born to mothers with AIDS or drinking breast milk from mother with AIDS, and the use of syringes that have been used by people with AIDS or people living with HIV/AIDS [2].

HIV infection is primarily through direct infection of $CD4^+$ T-cells by the HIV through exploitation of the CCR5 and CXCR4 co-receptors expressed on their surfaces. The major hallmarks of HIV infection include the destruction of helper $CD4^+$ T lymphocytes and subsequent loss of immune competence [3],[4]. HIV infection impairs cell function by destroying cells required to build a robust immune response [4]. Depletion of the $CD4^+$ T-cells results in a weakened immune system. Then the infection progresses slowly to cause the condition AIDS in which the immune system is vulnerable to opportunistic infections. The rate of infection progression depends on the robustness of human immune mechanisms that are mounted. The depletion of $CD4^+$ T cells and the rate of viral mutation determine the extent of the immune compromise caused by HIV infection [5]. HIV causes a decrease in the number of functional CD4+

T cells, thereby reducing the competence of the body's defense mechanisms to fight cell infection [6].

Not only prevention but also treatment is the best way to reduce the risk of HIV infection. Currently, the most efficacious method for inducing a decline in the number of HIV virus and effecting immune system reconstitution is by using Highly Active Antiretroviral Therapy (HAART) [7],[8]. A typical HAART treatment protocol consists of combinations of protease inhibitors (Pis) and types of reverse transcriptase inhibitors (RTIs) which are fabricated as a compact matrix tablet [7], [9], [10]. Nowadays HAART treatment generates several significant advantages, but it has certain drawbacks too. In short term, the beneficial effect of HAART on the survival and development of an AIDS-defining illness is well established [11], [12], [13], [14]. Not only has the life expectancy of HIV-infected patients increased but also their quality of life has improved [15], [16]. In addition, the spectrum of causes of mortality is changing as the number of deaths related to opportunistic infections has diminished [16], [17]. However, it was clinically observed that the HAART treatment regimen had associated side effects such as gastro-intestinal toxicity, lipodystrophy, anemia, thrombocytopenia, and renal failure [7], [18], [19].

Several mathematical models have been developed to describe the effect of therapy on HIV infection. Deterministic model is mainly used to study the problem theoretically. For instance, Ye et al. [8] constructed and elaborated mathematical model which described the reconstitution of thymic function in HIV-I patients during HAART therapy. Deterministic models also proposed by [20]-[30] typically consider the dynamic of the $CD4^+$ T-cell and virus populations as well as the effects of drug therapy. Kirschner and Webb [20], [31] constructed models that described viral dynamics and drug resistance during monotherapy of HIV infection. Perelson et al. [23] explored the decay characteristics of HIV infected compartments during combination therapy. Abdel-Aty et al. [29] investigated the exact traveling wave solutions of the fractional model of the human immun-odeficiency virus (HIV-1) infection for $CD4^+$ T-cells and treats the effect of antiviral drug therapy. In 2020, Ali et al. [28] analyzed the benefit of antiviral drug theraphy of HIV-1 infection of CD4+ T-cell through analytical and numerical study. A large number of other analytical and

numerical schemes was employed in order to find out the approximate solution of the effect of HAART on HIV-1 infection (see for instance [9], [11], [32]-[40] for details). Although the proposed models are mainly deterministic models, it cannot be denied that in reality most of the biological phenomena are more stochastic rather than deterministic. This is due to different infectious cells and viruses reacting in the same environment can produce different results. Therefore, the stochastic model will be more precise. The stochastic model can build a distribution of the results that allows to identify the number of infected at a given time, whereas for the deterministic model it will get a single result. The stochastic model has a more flexible distribution of results so that it can examine the variance of the number of infectious virus particles at a certain time that cannot be checked using a deterministic model [10]. In this study, an elaborate clinically plausible mathematical model is constructed to describe the effects of HAART therapy in controlling the infection rate of the HIV virus. Stochastic model is also formulated by considering the randomness coming from the uncertainty of the death rate of cells and the viruses. The generated model is in term of three-dimensional nonlinear stochastic differential equation. Non-negative solution is analysed for the stochastic model by referring the method explained in [45] and some numerical solutions are given using the Euler Maruyama method (see [46] for detail about the method).

2. METHODS

2.1 Deterministic Model

In this section, a simple HIV model with HAART on the dynamics of HIV virus and CD4+ T-cell is introduced. This model is divided into three compartments, namely, x_1 represents the number of suspectible cells, x_2 represents the number of cells infected with HIV virus, and x_3 represents the total of HIV virus in human body. The specific interaction between the cells and HIV viruses is depicted in Figure 1. We assume that all parameters in the model are positive. According to Fig. 1, we define λ as the number of healthy cells produced by the body per day, α_1 is the number of healthy cells that will decrease due to natural damage or death per day. Initially, when the body is

not infected by the HIV virus, all cells in the human body are in a good condition. When a small amount of HIV viruses enters the body, several healthy cells are successfully infected by the HIV virus where β expresses the success of the virus in infecting healthy cells per day. We assume that apart from the HIV virus, there are no other dangerous foreign pathogens that enter the body. The success of viruses in infecting healthy cells per day increases the number of infected cells. On the other hand, the infected cells will decrease due to self-damage or die naturally per day by α_2.

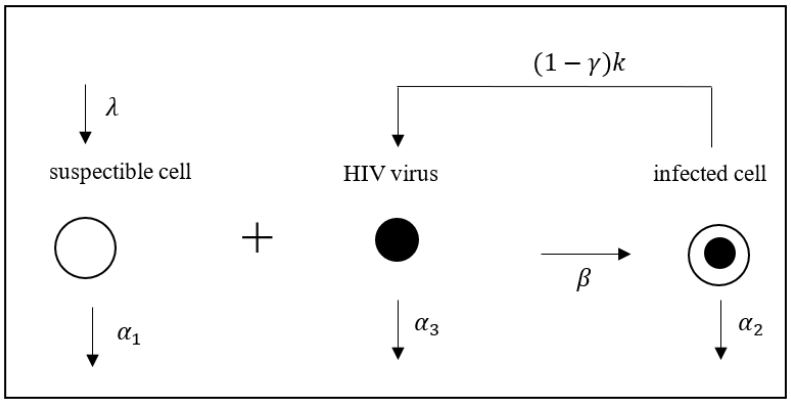

Figure 1. Interaction diagram of the model (2.1).

It is known that each virus has an equal chance of infecting cells and a small number of infected cells will produce the number of viruses in the body. Infected cells that produce virus per day are expressed as k. Furthermore, HAART, as treatment protocol that consists of combinations of protease inhibitors (Pis) and types of reverse transcriptase inhibitors (RTIs), is modeled as a constant function that will inhibit infected cells from producing virus by γ. Virus will decrease due to natural damage or death per day by α_3 and due to viral invasion of healthy cells per day which is stated to be β. Based on these assumptions and interaction diagram in Fig 1, we have following deterministic model:

$$\begin{aligned}
\frac{dx_1(t)}{dt} &= \lambda - \beta x_1(t)x_3(t) - \alpha_1 x_1(t), \\
\frac{dx_2(t)}{dt} &= \beta x_1(t)x_3(t) - \alpha_2 x_2(t), \\
\frac{dx_3(t)}{dt} &= (1-\gamma)k x_2(t) - \alpha_3 x_3(t) - \beta x_1(t)x_3(t),
\end{aligned} \tag{2.1}$$

with initial conditions: $x_1(0) = x_a,\ x_2(0) = x_b,\ x_3(0) = x_c, x_a, x_b, x_c > 0$. Definition of each parameter in equation (2.1) is summarized in Table 2.1.

Table 2.1. Definition of Model Parameters in Equations (2.1).

Variable/ Parameter	Definition	Term	Unit
x_1	Concentration of uninfected or healthy cells	$x_1 \geq 0$	dm^{-3}
x_2	Concentration of infected cells	$x_2 \geq 0$	dm^{-3}
x_3	Concentration of HIV viruses	$x_3 \geq 0$	dm^{-3}
λ	Number of healthy cells produced by the body per unit of time	$\lambda > 0$	$\mathrm{day}^{-1}\mathrm{dm}^{-3}$
β	The rate of success of the virus infecting cells or transmission between uninfected cells and infectious HIV virus	$\beta > 0$	$\mathrm{day}^{-1}\mathrm{dm}^{-3}$
k	Number of viruses produced by infected cells	$k > 0$	day^{-1}
α_1	Natural death rate of healthy cells	$\alpha_1 > 0$	day^{-1}
α_2	Natural death rate of infected cells	$\alpha_2 > 0$	day^{-1}
α_3	Natural death rate of HIV viruses	$\alpha_3 > 0$	day^{-1}
γ	The effect of HAART	$0 \leq \gamma < 1$	

2.1.1. Stability Analysis of Deterministic Model

Consider the HAART model in equation (2.1). The equilibrium point can be obtained by taking the first derivative equals to zero, i.e., $\frac{dx_1(t)}{dt} = 0, \frac{dx_2(t)}{dt} = 0$, and $\frac{dx_3(t)}{dt} = 0$. Obviously, the system (2.1) has two equilibria. The first equilibrium namely E_1 with $E_1 = \left(\frac{\lambda}{\alpha_1}, 0, 0\right)$ is called the virus-free equilibrium point because in this condition the virus and infected cells do not exist in the human body. The second solution is $E_2 = (x_1^*, x_2^*, x_3^*)$ with

$$x_1^* = \frac{\alpha_2\alpha_3}{(1-\gamma)k\beta-\alpha_2\beta}, \; x_2^* = \frac{(1-\gamma)k\lambda\beta-\alpha_1\alpha_2\alpha_3-\alpha_2\beta\lambda}{\alpha_2\beta((1-\gamma)k-\alpha_2)}, \; x_3^* = \frac{(1-\gamma)k\lambda\beta-\alpha_1\alpha_2\alpha_3-\alpha_2\beta\lambda}{\alpha_2\alpha_3\beta}.$$

The equilibrium point E_2 is called the virus-infected equilibrium point because in this condition

there are a number of viruses and infected cells in the human body meaning that virus and infected cells always remain in the human body. In other word, the first equilibrium point is a non-endemic equilibrium point and the second equilibrium point is an endemic equilibrium point. Furthermore, the basic reproduction number (R_0) of the model is determined using the Next Generation Matrix (NGM) method. By definition R_0 is the spectral radius of eigenvalues of the NGM. The calculation of the basic reproduction number R_0 is based on the linearization of the system of differential equations near the virus-free equilibrium point $E_1 = \left(\frac{\lambda}{\alpha_1}, 0,0\right)$. Since R_0 is a spectral radius, then we get $R_0 = \frac{(1-\gamma)k\beta\lambda}{\alpha_2\beta\lambda+\alpha_1\alpha_2\alpha_3}$.

The stability of system (2.1) will be carried out by investigating the stability of equilibrium point E_i. The Jacobian matrix, which is the result of the linearization of the system (2.1) around the equilibrium point E_i, is given by,

$$J = \begin{bmatrix} -\alpha_1 - \beta x_3 & 0 & -\beta x_1 \\ \beta x_3 & -\alpha_2 & \beta x_1 \\ -\beta x_3 & (1-\gamma)k & -\alpha_3 - \beta x_1 \end{bmatrix}.$$

For $E_1 = \left(\frac{\lambda}{\alpha_1}, 0,0\right)$, we get the eigenvalues of matrix $J(E_1)$ which are the solutions of the characteristic equation $\det\left(zI - J(E_1)\right) = 0$, i.e.

$z_{11} = -\alpha_1$,

$$z_{12,13} = -\frac{1}{2}\left(\alpha_3 + \frac{\beta\lambda}{\alpha_1} + \alpha_2\right) \pm \frac{1}{2}\sqrt{\left(\alpha_3 + \frac{\beta\lambda}{\alpha_1} + \alpha_2\right)^2 - 4\left(\alpha_2\alpha_3 + \frac{\alpha_2\beta\lambda}{\alpha_1} - \left(\frac{(1-\gamma)k\beta\lambda}{\alpha_1}\right)\right)}.$$

Since the value of model parameter is positive then $z_{11} < 0$. So, the equilibrium point E_1 will be stable if $Re\left(z_{12,13}\right) < 0$. Based on $z_{12,13}$, it is found that the non-endemic point E_1 will be asymptotically stable when $R_0 < 1$. For E_2, we have the Jacobian matrix $J(E_2)$ as follows,

$$J(E_2) = \begin{bmatrix} \frac{-(1-\gamma)k\lambda\beta + \alpha_2\beta\lambda}{\alpha_2\alpha_3} & 0 & -\frac{\alpha_2\alpha_3}{(1-\gamma)k - \alpha_2} \\ \frac{(1-\gamma)k\lambda\beta - \alpha_1\alpha_2\alpha_3 - \alpha_2\beta\lambda}{\alpha_2\alpha_3} & -\alpha_2 & \frac{\alpha_2\alpha_3}{(1-\gamma)k - \alpha_2} \\ \frac{-(1-\gamma)k\lambda\beta + \alpha_1\alpha_2\alpha_3 + \alpha_2\beta\lambda}{\alpha_2\alpha_3} & (1-\gamma)k & \frac{-(1-\gamma)k\alpha_3}{(1-\gamma)k - \alpha_2} \end{bmatrix}.$$

The eigenvalues of $J(E_2)$ are the solutions of the characteristic equation $\det(zI - J_{E_2}) = 0$, namely

$$z_{21} = -\alpha_1,$$
$$z_{22} = -\frac{(1-\gamma)k\lambda\beta - \alpha_2\beta\lambda}{\alpha_1\alpha_3},$$
$$z_{23} = -\alpha_3\left(\frac{(1-\gamma)k\lambda\beta - (\alpha_2\beta\lambda + \alpha_1\alpha_2\alpha_3)}{(1-\gamma)k\lambda\beta - \alpha_2\beta\lambda}\right) = -\frac{\alpha_3(R_0 - 1)}{(1-\gamma)k\lambda\beta - \alpha_2\beta\lambda}.$$

Since the model parameter are assumed positive then the endemic equilibrium point E_2 will be asymptotically stable when $R_0 > 1$.

2.2. Stochastic Model

The death of CD4 T lymphocyte cell or CD4+ T-Cell is caused by various things. Firstly, CD4 T lymphocyte cell death which is influenced by the formation of *syncytium* tissue. In addition, the death of CD4+ T-Cell occurs because the mature of age of the cells (the end of its lifetime). Moreover, the death of CD4+ T-Cell occurs when the cells no longer work or no needed by the body. As well as CD4+ T-Cell, the death rate of the HIV virus can be caused by several factors, including when the virus infects healthy cells, it is eliminated by the body's defense cells. Because the death rate of cells and HIV viruses is influenced by many factors then these biological phenomena can be considered as a randomness that occurs in the death rate of cells and the HIV virus in the human body. Biological phenomena factors that have a random effect on cell and virus death in the human body are involved in the model by adding randomness to the cell and virus death parameters. In equation (2.1), there is a parameter of number of healthy cells that will decrease due to damage or die naturally per day with a rate constant of α_1. If the intensity of randomness in healthy cells is added with a Brownian motion per day of $\sigma_1\dot{B}_1(t)$ then α_1 becomes $\alpha_1 + \sigma_1\dot{B}_1(t)$. Then a stochastic model can be formulated by considering $\dot{B}_1(t)$ which is a free Brownian motion with $\dot{B}_1(t) = \frac{dB_1(t)}{dt}$. Similarly for the parameter of the number of infected cells that will decrease due to natural damage or death per day with a rate constant of α_2. If the intensity of randomness in the infected cells is added with Brownian motion per day of $\sigma_1\dot{B}_1(t)$ then α_2 becomes $\alpha_2 + \sigma_1\dot{B}_1(t)$. If we assume that the biological factors of healthy cells and infected cells are the same, then the intensity of randomness in healthy cells and infected cells

is the same.

Whereas for the parameters of the number of viruses that will decrease due to damage or naturally die per day with a rate constant of α_3, if the intensity of randomness in the virus with Brownian motion per day is added as $\sigma_2\dot{B}_2(t)$, then α_3 becomes $\alpha_3 + \sigma_2\dot{B}_2(t)$. If it is estimated that the biological factors of the HIV virus are different from cells in the human body, the intensity of randomness in the virus is different from that of healthy cells and infected cells. By considering $\dot{B}_2(t)$ which is a free Brownian motion with $\dot{B}_2(t) = \frac{dB_2(t)}{dt}$, equation (2.1) can be written as a stochastic differential equation as follows:

$$\begin{aligned} dx_1(t) &= \big(\lambda - \beta x_1(t)x_3(t) - \alpha_1 x_1(t)\big)dt - \sigma_1 x_1(t)dB_1(t), \\ dx_2(t) &= \big(\beta x_1(t)x_3(t) - \alpha_2 x_2(t)\big)dt - \sigma_1 x_2(t)dB_1(t), \\ dx_3(t) &= \big((1-\gamma)kx_2(t) - \beta x_1(t)x_3(t) - \alpha_3 x_3(t)\big)dt - \sigma_2 x_3(t)dB_2(t). \end{aligned} \tag{2.2}$$

2.2.1. Non-negative Analysis of Stochastic model

For the stochastic differential equation model, it is necessary to show that the solution is a non-negative solution. Suppose that $(\Omega, \mathcal{F}, P)$ is a complete probability space with filtration $\{\mathcal{F}_t\}_{t\geq 0}$ which has fulfilled conditions such as the probability space $(\Omega, \mathcal{F}, P)$ will be monotonically ascending and continuous to the right while $\mathcal{F}_0$ contains all the empty sets of P. Also, let $B(t)$ be a one-dimensional Brownian motion defined in the probability space $(\Omega, \mathcal{F}, P)$. Let $R^3_{++} = \{\boldsymbol{x} \in R^3 : x_i > 0, \text{for } 1 \leq i \leq 3\}$ and $\boldsymbol{x}(t) = \big(x_1(t), x_2(t), x_3(t)\big)$. The proof of a non-negative solution of the stochastic model (2.2) is given in Theorem 1. However, previously we defined a lemma that will be used in the process of proving Theorem 1.

Lemma 1 [10]

$u \leq 2(u + 1 - log(u)) - (4 - 2\,log\,2) \quad \forall u > 0.$

Proof.

Suppose for every $u > 0$ a function is defined as follows:

$$f(u) = u + 2 - 2\log(u).$$

To determine the minimum value of the function $f(u)$, we will use a stationary condition, namely $f'(u) = 0$ such that $f(u)$ has a minimum value when $u = 2$ or

$$f(2) \leq f(u), \qquad \forall u > 0$$
$$4 - 2\log(2) \leq u + 2 - 2\log(u),$$
$$u + 4 - 2\log(2) \leq 2(u + 1 - \log(u)),$$
$$u \leq 2(u + 1 - \log(u)) - (4 - 2\log(2)).$$

Therefore, the inequality in Lemma 1 holds.

Furthermore, we analyse the positivity of the solution of model (2.2).

Theorem 1. *Assume* $0 < \gamma < 1$ *and the parameters* $\lambda, \alpha_1, \alpha_2, \alpha_3, k$ *and* β *are positive real numbers. For any initial value of* $\boldsymbol{x_0} \in R_+^3$*, there is a single* $\boldsymbol{x}(t)$ *solution of equation (2.2) for* $t \geq 0$*, and that solution will remain at* R_+^3 *with a probability of* 1*, such that* $\boldsymbol{x}(t) \in R_+^3$ *is guaranteed for all* $t \geq 0$*.*

Proof.

Based on equation (2.2) it can be written as follows:

$$\begin{aligned} dx_1(t) &= f_1(x)dt - g_1(x)dB_1(t), \\ dx_2(t) &= f_2(x)dt - g_2(x)dB_1(t), \\ dx_3(t) &= f_3(x)dt - g_3(x)dB_2(t). \end{aligned} \tag{2.3}$$

Since $f_i(x), i = 1,2,3$ and $g_i(x), i = 1,2,3$ are locally continuous Lipschitz functions then for any initial value given at $\boldsymbol{x_0} \in R_{++}^3$ there is a local solution $\boldsymbol{x}(t)$ where $t \in [0, \tau_e)$ with τ_e is called the explosion time. To prove that the local solution obtained is valid for the global solution, it is necessary to show $\tau_e = \infty$.

Suppose that $K_0 > 0$ is a large enough number such that each initial value of $\boldsymbol{x_0}$ is in the interval $[1/K_0, K_0]$ for each integer $K > 0$, i.e

$$\frac{1}{K_0} < \min(\boldsymbol{x_0}) < \max(\boldsymbol{x_0}) < K_0.$$

Consequently, for each integer $K \geq K_0$ the stopping time can be defined as follows:

$$\tau_K = \inf\{ t \in [0, \tau_e) | x_i(t) \notin [1/K, K] \text{ with } 1 \leq i \leq 3\}.$$

It is known that for $\inf \emptyset = \infty$ where $\emptyset$ is an empty set and τ_K monotonically increases with $K \to \infty$. Let $\tau_\infty = \lim_{K \to \infty} \tau_K$, where $\tau_\infty \leq \tau_e$. It will be shown that $\tau_\infty = \infty$, obtained $\tau_e = \infty$ and $\boldsymbol{x}(t) \in R_+^3$ for each $t \geq 0$. If $\tau_\infty = \infty$ is false, then there is a pair of constants $T > 0$ and

$\epsilon \in (0,1)$ such that the value of $P\{\tau_\infty \leq T\} > \epsilon$. If there is an integer $K_1 \geq K_0$ such that it can be defined

$$P\{\tau_K \leq T\} \geq \epsilon \text{ for all } K \geq K_1. \tag{2.4}$$

Given a function $C^2V: R_+^3 \to R_+$ with

$$V(\boldsymbol{x}) = \sum_{i=1}^{3}(x_i + 1 - \log(x_i)). \tag{2.5}$$

If the function $V(\boldsymbol{x})$ can be written as $u + 1 - \log(u)$ then the non-negative value of the function $V(\boldsymbol{x})$ can be viewed as $u + 1 - \log(u) \geq 0$, $\forall u > 0$. Hence, to solve the $V(\boldsymbol{x})$ function which has three variables, the Ito's multidimensional formula is used. Based on equation (2.2) and equation (2.5), three equations are obtained in the form $d\boldsymbol{x}(t) = \boldsymbol{f}(t)dt + \boldsymbol{g}(t)d\boldsymbol{B}_t$ with

$$\boldsymbol{f}(t) = \begin{pmatrix} \big(\lambda - \beta x_1(t)x_3(t) - \alpha_1 x_1(t)\big) \\ \big(\beta x_1(t)x_3(t) - \alpha_2 x_2(t)\big) \\ \big((1-\gamma)kx_2(t) - \beta x_1(t)x_3(t) - \alpha_3 x_3(t)\big) \end{pmatrix} = \begin{pmatrix} u_1 \\ u_2 \\ u_3 \end{pmatrix}, \tag{2.6}$$

$$\boldsymbol{g}(t) = \begin{pmatrix} -\sigma_1 x_1 & 0 \\ -\sigma_1 x_2 & 0 \\ 0 & -\sigma_2 x_3 \end{pmatrix} \text{ and } d\boldsymbol{B}_t = \begin{pmatrix} dB_1 \\ dB_2 \end{pmatrix}.$$

By using the Ito's multidimensional formula, we get

$$\begin{aligned} dV(\boldsymbol{x}(t), t) = \Bigg[& \lambda - \beta x_1(t)x_3(t) - \alpha_1 x_1(t) - \left(\frac{\lambda - \beta x_1(t)x_3(t) - \alpha_1 x_1(t)}{x_1}\right) + \beta x_1(t)x_3(t) - \alpha_2 x_2(t) \\ & - \left(\frac{\beta x_1(t)x_3(t) - \alpha_2 x_2(t)}{x_2}\right) + (1-\gamma)kx_2(t) - \beta x_1(t)x_3(t) \quad - \alpha_3 x_3(t) \\ & - \left(\frac{(1-\gamma)kx_2(t) - \beta x_1(t)x_3(t) - \alpha_3 x_3(t)}{x_3}\right) + {\sigma_1}^2 + \frac{1}{2}{\sigma_2}^2 \Bigg] dt \\ & + \sigma_1\big(2 - (x_1 + x_2)\big)dB_1 + \sigma_2(1 + x_3)dB_2, \end{aligned} \tag{2.7}$$

$$\begin{aligned} = \Bigg[& \lambda + \beta x_3(t) + \alpha_1 + \alpha_2 + (1-\gamma)kx_2(t) + \beta x_1(t) + \alpha_3 + {\sigma_1}^2 + \frac{1}{2}{\sigma_2}^2 \\ & - \alpha_1 x_1(t) - \frac{\lambda}{x_1} - \alpha_2 x_2(t) - \frac{\beta x_1(t)x_3(t)}{x_2} - \beta x_1(t)x_3(t) - \alpha_3 x_3(t) \\ & - \frac{(1-\gamma)kx_2(t)}{x_3} \Bigg] dt + \sigma_1\big(2 - (x_1 + x_2)\big)dB_1 + \sigma_2(1 - x_3)dB_2. \end{aligned} \tag{2.8}$$

From equation (2.8), we obtain

$$dV(\boldsymbol{x}(t),t) \le [\lambda + \beta x_3(t) + \alpha_1 + \alpha_2 + (1-\gamma)kx_2(t) + \beta x_1(t) + \alpha_3 + {\sigma_1}^2 + \frac{1}{2}{\sigma_2}^2\Big]dt + \sigma_1\big(2-(x_1+x_2)\big)dB_1 + \sigma_2(1-x_3)dB_2. \tag{2.9}$$

The right-hand side of (2.9) will be simplified by defining the variables $c_1 = \lambda + \alpha_1 + \alpha_2 + +\alpha_3 + {\sigma_1}^2 + \frac{1}{2}{\sigma_2}^2$ and $c_2 = 2(1-\gamma)k + 2\beta$. Based on Lemma 1, if $x_i \le 2(x_i + 1 - \log(x_i))$ then

$$(1-\gamma)kx_2(t) + \beta x_1(t) + \beta x_3(t) \le (2(1-\gamma)k + 2\beta)\left(\sum_{i=1}^{3}(x_i + 1 - \log(x_i))\right),$$

$$(1-\gamma)kx_2(t) + \beta x_1(t) + \beta x_3(t) \le (2(1-\gamma)k + 2\beta)V(\boldsymbol{x}),$$

$$(1-\gamma)kx_2(t) + \beta x_1(t) + \beta x_3(t) \le c_2 V(\boldsymbol{x}).$$

Therefore, we have

$$dV(\boldsymbol{x}(t),t) \le \big(c_1 + c_2 V(\boldsymbol{x})\big)dt + \sigma_1\big(2-(x_1+x_2)\big)dB_1 + \sigma_2(1-x_3)dB_2. \tag{2.10}$$

If $c_3 = \max\{c_1, c_2\}$ is defined, then equation (2.10) can be written as follows:

$$dV(\boldsymbol{x}(t),t) \le \big(c_3 + c_3 V(\boldsymbol{x})\big)dt + \sigma_1\big(2-(x_1+x_2)\big)dB_1 + \sigma_2(1-x_3)dB_2,$$

$$dV(\boldsymbol{x}(t),t) \le c_3\big(1 + V(\boldsymbol{x})\big)dt + \sigma_1\big(2-(x_1+x_2)\big)dB_1 + \sigma_2(1-x_3)dB_2. \tag{2.11}$$

Furthermore, if $t_1 \le T$ and both sides of equation (2.11) are integrated, we obtain the following expression,

$$\int_0^{\tau_K \wedge t_1} dV\big(\boldsymbol{x}(t)\big) \le \int_0^{\tau_K \wedge t_1} c_3\big(1 + V(\boldsymbol{x})\big)dt + \int_0^{\tau_K \wedge t_1} \sigma_1\big(2 - x_1(t) - x_2(t)\big)dB_1(t) + \int_0^{\tau_K \wedge t_1} \sigma_2\big(1 - x_3(t)\big)dB_2(t), \tag{2.12}$$

$$V\big(\boldsymbol{x}(\tau_K \wedge t_1)\big) - V(\boldsymbol{x}_0) \le \int_0^{\tau_K \wedge t_1} c_3\big(1 + V(\boldsymbol{x})\big)dt + \int_0^{\tau_K \wedge t_1} \sigma_1\big(2 - x_1(t) - x_2(t)\big)dB_1(t) + \int_0^{\tau_K \wedge t_1} \sigma_2(1 - x_3(t))dB_2(t), \tag{2.13}$$

$$V\big(\boldsymbol{x}(\tau_K \wedge t_1)\big) \le V(\boldsymbol{x}_0) + \int_0^{\tau_K \wedge t_1} c_3\big(1 + V(\boldsymbol{x})\big)dt + \int_0^{\tau_K \wedge t_1} \sigma_1\big(2 - x_1(t) - x_2(t)\big)dB_1(t) + \int_0^{\tau_K \wedge t_1} \sigma_2(1 - x_3(t))dB_2(t). \tag{2.14}$$

If we evaluate the expected of the both sides of integration (2.14), we have

$$E(V(\boldsymbol{x}(\tau_K \wedge t_1)\,)) \le E(V(\boldsymbol{x}_0)) + E\left(\int_0^{\tau_K \wedge t_1} c_3\big(1 + V(\boldsymbol{x})\big)dt\right) \tag{2.15}$$

$$+E\left(\int_0^{\tau_K \wedge t_1} \sigma_1\big(2 - x_1(t) - x_2(t)\big)dB_1(t)\right) + E\left(\int_0^{\tau_K \wedge t_1} \sigma_2(1 - x_3(t))dB_2(t)\right).$$

It is known that if $V(\boldsymbol{x}_0)$ is a constant then $E(V(\boldsymbol{x}_0)) = V(\boldsymbol{x}_0)$. It is also known from the definition of Brownian motion that Brownian motion has a normal distribution with zero mean. This property causes the expectation of Brownian motion is also to be zero. So, we have $E\left(\int_0^{\tau_K \wedge t_1} \sigma_1\big(2 - x_1(t) - x_2(t)\big)dB_1(t)\right) = 0$ and $E\left(\int_0^{\tau_K \wedge t_1} \sigma_2\big(1 - x_3(t)\big)dB_2(t)\right) = 0.$ Hence, equation (2.15) can be written as follows:

$$E\left(V\big(\boldsymbol{x}(\tau_K \wedge t_1)\big)\right) \le V(\boldsymbol{x}_0) + E\left(\int_0^{\tau_K \wedge t_1} c_3\big(1 + V(\boldsymbol{x})\big)dt\right) \tag{2.16}$$

$$\le V(\boldsymbol{x}_0) + E\left(\int_0^{\tau_K \wedge t_1} c_3 dt\right) + E\left(\int_0^{\tau_K \wedge t_1} c_3 V(\boldsymbol{x})dt\right)$$

$$\le V(\boldsymbol{x}_0) + E[c_3(\tau_K \wedge t_1) - c_3(0)] + E\left(\int_0^{\tau_K \wedge t_1} c_3 V(\boldsymbol{x})dt\right)$$

$$\le V(\boldsymbol{x}_0) + E[c_3(\tau_K \wedge t_1)] + E\left(\int_0^{\tau_K \wedge t_1} c_3 V(\boldsymbol{x})dt\right).$$

Since c_3 is a constant then $E[c_3(\tau_K \wedge t_1)] = c_3 t_1$ and $E\left(\int_0^{\tau_K \wedge t_1} c_3 V(\boldsymbol{x})dt\right) = c_3 E\left(\int_0^{\tau_K \wedge t_1} V(\boldsymbol{x})dt\right)$. Hence, equation (2.16) can be written as follows:

$$E\left(V\left(\boldsymbol{x}(\tau_K \wedge t_1)\right)\right) \leq V(\boldsymbol{x}_0) + c_3 t_1 + c_3 \left(E \int_0^{\tau_K \wedge t_1} V(\boldsymbol{x})dt \right). \tag{2.17}$$

Since τ_K is the infimum of $t \in [0, \tau_e)$ for each integer $K > 0$, then $t_1 \leq T$ such that the results of $\tau_K \wedge t_1$ is t_1 and equation (2.17) can be written as

$E\left(V\left(\boldsymbol{x}(\tau_K \wedge t_1)\right)\right) \leq V(\boldsymbol{x}_0) + c_3 t_1 + c_3 \left(E\left(\int_0^{t_1} V(\boldsymbol{x}(\tau_K \wedge t))dt\right)\right) \leq V(\boldsymbol{x}_0) + c_3 T +$

$c_3 E\left(\int_0^{t_1} V\left(\boldsymbol{x}(\tau_K \wedge t)\right)dt\right)$,

or

$$E\left(V\left(\boldsymbol{x}(\tau_K \wedge t_1)\right)\right) \leq V(\boldsymbol{x}_0) + c_3 T + c_3 \int_0^{t_1} E(V\left(\boldsymbol{x}(\tau_K \wedge t)\right))dt. \tag{2.18}$$

Furthermore, the Gronwall inequality will be applied in equation (2.18) by assuming several variables. Let $u(t) = E\left(V\left(\boldsymbol{x}(\tau_K \wedge t_1)\right)\right), c = V(\boldsymbol{x}_0) + c_3 T, v(s) = c_3$ and $\int_0^t u(s)ds = \int_0^{t_1} E(V(\boldsymbol{x}(\tau_K \wedge t)))dt$. The Gronwall inequality expresses, if $u(t) \leq c + \int_0^t v(s)u(s)ds$ then $u(t) \leq c \exp(\int_0^t v(s)ds)$. Then by applying that inequality into equation (2.18), we have the following results.

If

$$E\left(V\left(\boldsymbol{x}(\tau_K \wedge t_1)\right)\right) \leq V(\boldsymbol{x}_0) + c_3 T + c_3 \int_0^{t_1} E\left(V\left(\boldsymbol{x}(\tau_K \wedge t)\right)\right) dt,$$

then

$$EV\left(\boldsymbol{x}(\tau_K \wedge t_1)\right) \leq \left((V(\boldsymbol{x}_0) + c_3 T)\right) \exp \int_0^{t_1} c_3 dt. \tag{2.19}$$

Previously it was known that if $t_1 \leq T$ and assuming $c_4 = (V(\boldsymbol{x}_0) + c_3 T) \exp c_3 T$, then the solution of equation (2.19) follows this expression:

$$EV\big(\boldsymbol{x}(\tau_K \wedge t_1)\big) \leq (V(\boldsymbol{x}_0) + c_3 T)\exp[c_3(t_1) - c_3(0)] \tag{2.20}$$
$$\leq (V(\boldsymbol{x}_0) + c_3 T)\exp[c_3(t_1)]$$
$$\leq (V(\boldsymbol{x}_0) + c_3 T)\exp c_3 T$$
$$\leq c_4.$$

Suppose $\Omega_K = \{\tau_K \leq T\}$ for $K \geq K_1$ and there exists $P\{\tau_K \leq T\} \geq \epsilon$ for all $K \geq K_1$ then $P(\Omega_K) \geq \epsilon$. Notice that for each $\omega \in \Omega_K$, there is an i with $1 \leq i \leq 3$ so that $x_i(\tau_K, \omega)$ is equal to K or $1/K$. So, $V\big(\boldsymbol{x}(\tau_K, \omega)\big)$ is not less than the smallest $[K + 1 - \log(K)]$ and $[(1/K) + 1 - \log(1/K)]$, which can be written as follows:

$$V\big(\boldsymbol{x}(\tau_K, \omega)\big) \geq [K + 1 - \log(K)] \wedge \left[\left(\tfrac{1}{K}\right) + 1 + \log(K)\right]. \tag{2.21}$$

Therefore (2.20) has the following solution:

$$c_4 \geq E\big[V\big(\boldsymbol{x}(\tau_K \wedge T)\big)\big],$$
$$c_4 \geq E\big[1_{\Omega_K}(\omega) V\big(\boldsymbol{x}(\tau_K, \omega)\big)\big],$$
$$c_4 \geq \int_{\tau_K}^{\infty} V\big(\boldsymbol{x}(\tau_K, \omega)\big) f(t) dt. \tag{2.22}$$

It is known that 1_{Ω_K} is an indicator function of Ω_K. If $P\{\tau_K \leq T\} = \int_{\tau_K}^{\infty} f(t)dt$ and $P\{\tau_K \leq T\} \geq \epsilon$ then equation (2.22) can be written as follows:

$$c_4 \geq V\big(\boldsymbol{x}(\tau_K, \omega)\big) \int_{\tau_K}^{\infty} f(t) dt,$$
$$c_4 \geq \epsilon \left(V\big(\boldsymbol{x}(\tau_K, \omega)\big)\right),$$
$$c_4 \geq \epsilon \left([K + 1 - \log(K)] \wedge \left[\left(\frac{1}{K}\right) + 1 + \log(K)\right]\right). \tag{2.23}$$

For example, if K increases and goes to infinity then it produces a value of c_4 which is an infinite value as well. This leads us to have $\tau_\infty = \infty$. However, c_4 is a finite value, thus the statement produces a contradiction statement. Therefore, Theorem 1 is satisfied and the stochastic differential equation (2.2) has a non-negative solution.

3. NUMERICAL SIMULATION AND DISCUSSION

In this section, numerical simulations are carried out to determine the behaviour of system solutions and the effects of HAART parameters to inhibit the number of replicating viruses and infected cells in the patient's body such that patients can live longer. Numerical simulation was carried out by controlling the value of the HAART parameter (γ) while the value of other parameters is measured daily. The set of parameter values from [10] are employed to illustrate the numerical simulation. The data is presented in Table 2.2.

Table 2.2. Parameters of the model.

Variable/Parameter	Description	Estimated Value	Ref.
$x_1(0)$	Initial value of uninfected or healthy cells	$10^7 \mathrm{dm}^{-3}$	Estimated
$x_2(0)$	Initial value of infected cells	$2\,x\,10^5 \mathrm{dm}^{-3}$	Estimated
$x_3(0)$	Initial value of HIV virus	$10^5 \mathrm{dm}^{-3}$	Estimated
λ	The number of healthy cells produced by the body per unit time	$10^6 \mathrm{d}ay^{-1}\mathrm{dm}^{-3}$	[10]
β	The success rate of the virus infecting cells or transmission between uninfected cells and infectious HIV virus	$10^{-8}\mathrm{d}ay^{-1}\mathrm{dm}^{-3}$	[10]
k	The number of viruses produced by infected cells	$50\ \mathrm{d}ay^{-1}$	[10]
α_1	Natural death rate of healthy cells	$0.1\ \mathrm{d}ay^{-1}$	[10]
α_2	Natural death rate of infected cells	$0.5\ \mathrm{d}ay^{-1}$	[10]
α_3	Natural death rate of HIV viruses	$5\ \mathrm{d}ay^{-1}$	[10]

Numerical simulation of all related populations is observed both before and after HAART, in order to gain an insight into all the processes of what actually is occurring. We use 250 days as initial observation. Firstly, assuming there is no HAART in these patients, $\gamma = 0$. Here we show the solution both deterministic and stochastic model with $\gamma = 0$ depicted in Figures 1-3. Figures 1-3 show the condition without HAART where blue line represents the solution of the deterministic model of equation (2.1) and the red line represents the solution of the stochastic model of equation (2.2). Fig. 1 shows that healthy cells in the patient's body have decreased from the initial state in both the deterministic model and the stochastic model solutions. Fig. 2 shows the condition of the

number of infected cells in the patient's body coming from the deterministic and stochastic solutions showing that infected cells are still exist in the patient's body without HAART by looking at equilibrium conditions at the 250-day review time. Fig. 3 also shows the number of viruses in the patient's body that still exists by looking at the equilibrium state at the 250-day review time. This is because the virus continues to grow and there is no treatment that prevents the virus from reproducing or spreading to other healthy cells.

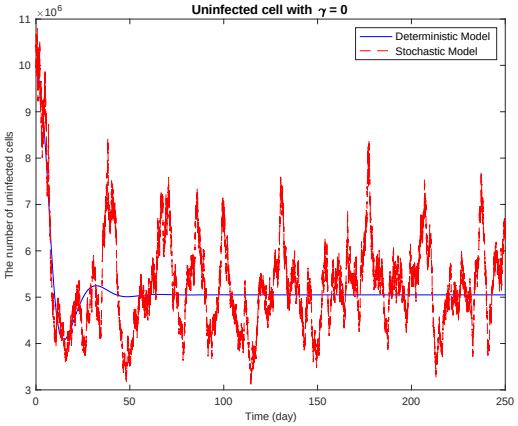

Figure 1. Solutions of deterministic and stochastic models with values of $\gamma = 0$ and $x_1(0) = 10^7$ for uninfected cells with observation time 250 days

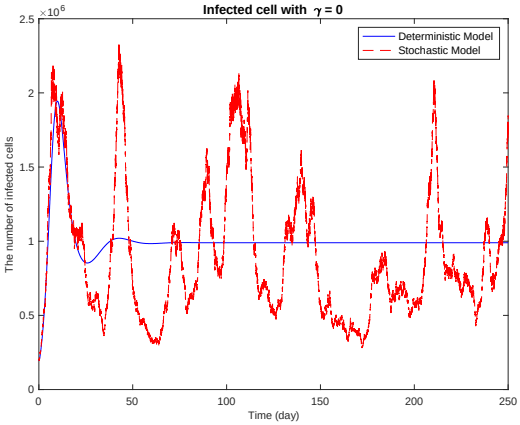

Figure 2. Solutions of deterministic and stochastic models with values of $\gamma = 0$ and $x_2(0) = 2 \times 10^5$ for infected cells with observation time 250 days

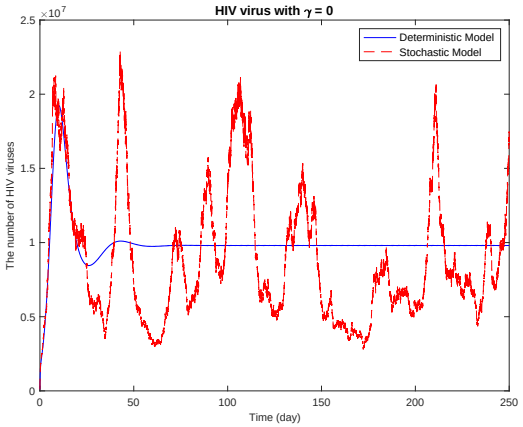

Figure 3. Solutions of deterministic and stochastic models with values of $\gamma = 0$ and $x_3(0) = 10^5$ for HIV viruses with observation time 250 days

The solution of the deterministic model of equation (2.1) with value of $\gamma = 0$ has basic reproduction number $R_0 = 1.96 > 1$ indicating a stability of the endemic equilibrium point. The solution of the deterministic model not only shows the state of the endemic equilibrium point but also illustrates those infected cells and virus will continue to exist in the patient's body without HAART.

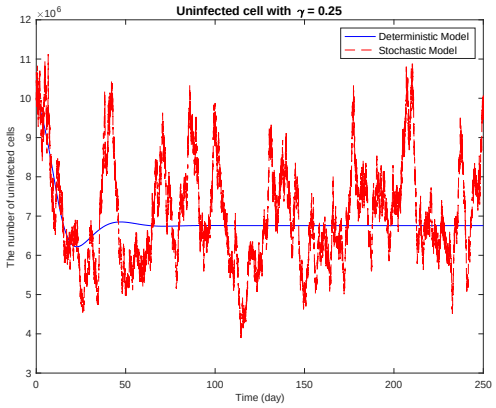

Figure 4. Solutions of deterministic and stochastic models with values of $\gamma = 0.25$ and $x_1(0) = 10^7$ for uninfected cells with observation time 250 days

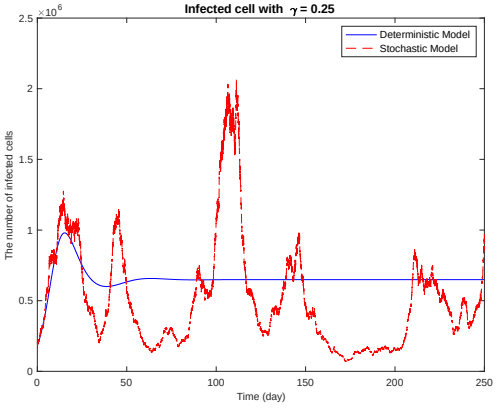

Figure 5. Solutions of deterministic and stochastic models with values of $\gamma = 0.25$ and $x_2(0) = 2 \times 10^5$ for infected cells with observation time 250 days

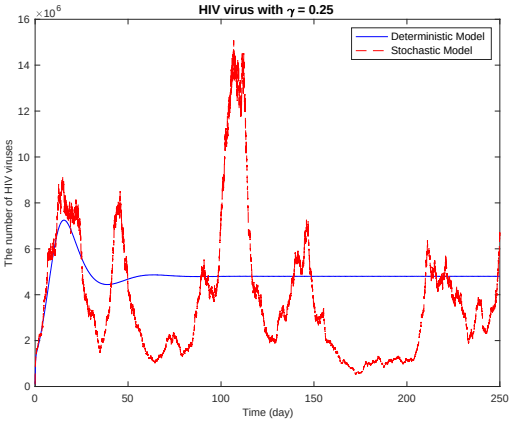

Figure 6. Solutions of deterministic and stochastic models with values of $\gamma = 0.25$ and $x_3(0) = 10^5$ for HIV viruses with observation time 250 days

The second case, we assume that there is HAART in the patient's body, but the treatment is not carried out routinely. Suppose $\gamma = 0.25$ and other parameters are still the same. Figures 4-6 show the dynamic of cells with small treatment effects. Fig. 4 shows a decrease in the number of healthy cells as in the first case, but the effect of HAART gives a difference in the number of healthy cells per day as well as the time of increasing and decreasing in the number of cells per day. Fig. 5 and Fig. 6 respectively illustrate infected cells and HIV viruses in human body with the effects of non-routine treatment. The two pictures show the difference in the number of infected cells and HIV viruses that decrease per day. The solutions of both deterministic and stochastic models show that the infected cells and viruses are still exist in the bodies by looking at its number at 250 days. The solution of the deterministic model of equation (2.1) with a value of $\gamma = 0.25$ has a basic reproduction number $R_0 = 1.47 > 1$ indicating that an endemic equilibrium point exists and asymptotically stable. The solution of the deterministic model that not only shows the state of the endemic equilibrium point but also illustrates those infected cells and viruses will continue to exist in the body of patients who are taking HAART irregularly. Irregular HAART treatment is described by stopping treatment which makes the virus resistant to the effects of HAART treatment, thus the virus continues to reproduce in the patient's body. The difference between taking HAART irregularly and without HAART is in the number of healthy cells that has increased, the number of infected cells or HIV viruses has decreased.

The third case assumes that there is regular HAART treatment for patient's body with $\gamma = 0.5$. The solution for this case is depicted in Figures 7-9. Fig. 7 illustrates that regular HAART treatment causes the number of healthy cells to be more constant. Fig. 8 shows that the number of infected cells decreased daily starting from the time of the first review. The solutions of both deterministic and stochastic models show that infected cells continued to decline in the bodies of patients taking HAART regularly. Fig. 9 also interprets the amount of HIV virus in the patient's body has decreased per day starting from the time of the first review. The impact of regular HAART treatment results in a reduction of the number of HIV viruses. Compared with Fig. 3 and Fig. 4 which show the HIV virus continues to reproduce in the patient's body, Fig. 9 shows that the virus can be inhibited from reproducing by taking HAART regularly. The solution of the deterministic model (2.1) with $\gamma = 0.5$ has a basic reproduction number, $R_0 = 0.98 < 1$ indicating a stability

for the non-endemic equilibrium point. The solution of a deterministic model that not only shows a non-endemic equilibrium point but also illustrates those infected cells and viruses are no longer replicating in the patient's body. This result differs from the scenario without HAART and irregular HAART that has $R_0 > 1$ meaning that those solutions towards endemic equilibrium point. This difference is in view of the fact that regular HAART will inhibit viral growth and decrease the number of infected cells. Reduction of HIV virus causes the number of healthy cells that is infected with the virus decreases as well. Therefore, the healthy cells continue to grow in the patient's body. This condition makes PLWHA get over and can live longer.

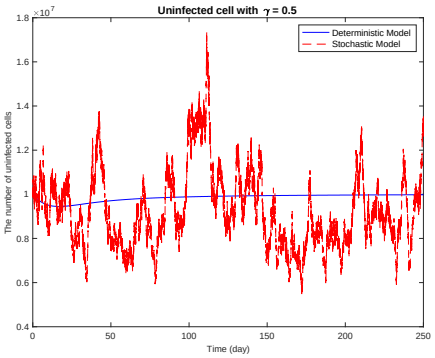

Figure 7. Solutions of deterministic and stochastic models with values of $\gamma = 0.5$ and $x_1(0) = 10^7$ for uninfected cells at 250 days

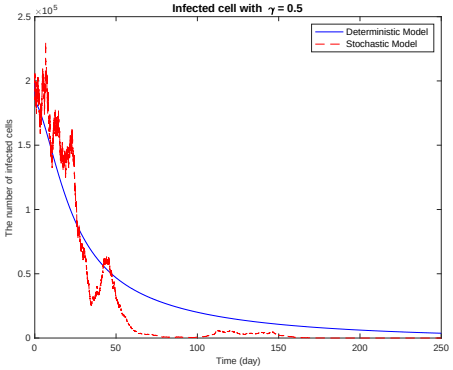

Figure 8. Solutions of deterministic and stochastic models with values of $\gamma = 0.25$ and $x_2(0) = 2 \times 10^5$ for infected cells at 250 days

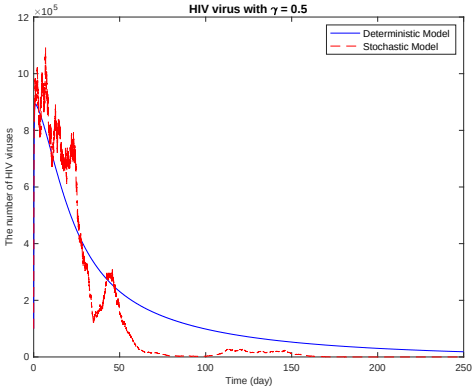

Figure 9. Solutions of deterministic and stochastic models with values of $\gamma = 0.5$ and $x_3(0) = 10^5$ for HIV viruses at 250 days

4. CONCLUSION

In this paper, we have constructed and derived an epidemic model HIV/AIDS using deterministic and stochastic modeling approaches. In deterministic model, we considered the existence and stability of equilibrium points. With the help of *Next Generation Matrix* (NGM) method, we obtained the basic reproduction number R_0, and derived the dynamical stability of the model. When the basic reproduction number R_0 is less than one, the non-endemic equilibrium is asymptotically stable meaning that the disease will be extinct. When the basic reproduction number R_0 is greater than one, the endemic equilibrium is locally asymptotically stable meaning that the disease will be permanent in the system. For the stochastic model, we presented an analysis for the non-negative solution. Numerical simulations show that the HAART parameters have significant effects on the dynamics of deterministic and stochastic solutions. The HAART parameter indicated that when the value of treatment parameter is small enough, the infected cells and virus will continue to replicate in the patient's body, which is also indicated by $R_0 > 1$. While if the value of the treatment parameter is high enough then the number of infected cells and viruses will continue to decrease until they no longer replicate in the patient's body, which are also indicated by $R_0 < 1$. In the stochastic solution, there is continuous randomness caused by the average parameter of death of healthy cells, infected cells, and viruses. The randomness will have a pattern at a certain time interval. In conclusion, HAART has considerable benefit as treatment. Our model predicted, both deterministic model and stochastic model that using HAART continuously is the best scenario for reducing the replication of the viruses in the system.

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CONFLICT OF INTERESTS

The authors declare that there is no conflict of interests.

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