CONTINUOUS AND DISCRETE DYNAMICS OF A DETERMINISTIC MODEL OF HIV INFECTION

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ABSTRACT. We will study a mathematical model of the human immunodeficiency virus (HIV) infection in the presence of combination therapy that includes within-host infectious dynamics. The deterministic model requires us to analyze asymptotic stability of two distinct steady states, disease-free and endemic equilibria. Previous results have focused on investigating the global asymptotic stability of the trivial steady state using an implicit finite-difference method which generates a system of difference equations. We, instead, provide analytic solutions and long term attractive behavior for the endemic steady state using the theory of difference equations. The dynamics of estimated model is appropriately determined by a certain quantity threshold maintaining the immune response to a sufficient level. The result also indicates that a forward bifurcation in the model happens when the disease-free equilibrium loses its stability and a stable endemic equilibrium appears as the basic reproduction number exceeds unity. In this scenario, the classical requirement of the reproduction number being less than unity becomes a necessary and sufficient condition for disease mitigation. When the associated reproduction number is in excess of unity, a stable endemic equilibrium emerges with an unstable disease-free equilibrium (leading to the persistence and existence of HIV within the infected individuals). The attractivity of the model reveals that the disease-free equilibrium is globally asymptotically stable under certain assumptions. A comparison between the continuous and estimated discrete models is also provided to have a clear perception in understanding the behavioral dynamics of disease modelling. Finally, we show that the associated estimation method is very robust in the sense of numerical stability since the equilibria and the stability conditions are independent of the time step.

1. INTRODUCTION

Although rising number of anti-HIV (human immunodeficiency virus) preventive vaccines (also prophylactic vaccines) currently undergo clinical trials (see [1] and the references therein), there has been a surge of interest during the past decades with regards to mathematical model for HIV infection in order to determine the side effects and long term impacts of such vaccines to the community. Identifying an optimal treatment therapy to minimize the viral load still poses significant threats to the human beings and a dilemma for public health policy maker [27, 24, 19, 36]. In particular, since none of the current anti-HIV vaccines attains high enough efficacy to prevent HIV infection, such models may give insight into the optimal efficacy and treatment coverage levels needed to mitigate HIV infection in the community [1].

Although some published papers concerning the HIV infection models provides mostly slight details on the system of difference equations extracted from associated systems of differential equations, authors have thoroughly studied this subject [6, 9, 12, 18, 32, 39, 43]. Besides, there are outstanding published papers in the mathematical literature in the field of difference equations while a few of them discussed systems of difference equations with two equations or more than one equilibrium point [2, 33, 45, 48, 52]. Implementation of control
theory to infectious diseases is another challenge to alleviate infection widespread. For instance, Jaberi et al. [19] developed an optimal control theory to a population model for influenza infection with sensitive and resistant strains and solved the adjoin control components to find the optimal treatment profile that reduces the epidemic final size. In the current research work, however, we attempt to analyze and mitigate a HIV infection presented by a model of difference equations with three equations associated with two distinct equilibrium points.

Apart from impede and enhance performance in mathematical analysis, several challenges related to the characteristics of the pathogen, e.g. replication and evolution, have been encountered the nature of host immune responses at the individual level [1, 2, 11, 13, 14, 37]. The viral replication is essential for progression of HIV to AIDS and, as a result, requires better administration and intervention of antiretroviral drugs [29, 30, 31, 38]. The replication process of the HIV pathogen undergo a cycle of development within a human host. Several essential phases (enzymes) such as reverse transcriptase, protease, ribonuclease and integrase are required for successful development of infectious virus particle [1, 2, 11, 13, 14, 31, 38]. In most cases these replication process are taken into consideration and mathematically formulated by different types of population models using differential equations. Generally speaking, a handful of these models underwent analytic approaches to investigate the sensitivity and stability analysis. Other approaches, mostly computational, have been taken into account to determine the most efficient way of drug treatment at both the individual and population levels [14]. Not surprisingly, some mathematical models dealing with a nonlinear IVP (initial value problem) system do not have a closed form solution, nor can one, even locally, predict the long-term behavior of infection. As a result, a numerical method (e.g. see section 3.2) is widely applied to observe the characteristics of the system with various effects of time steps, especially for artificially large time steps. However, one may argue that if a numerical method is applied to a system of differential equations, the solution obtained through the numerical scheme may be inconsistent with the original system. An appropriate explanation to this argument will be provided in section 5.1.

The outline of current paper is organized as follows. Our main purpose in this work is to study the stability and bifurcation of the existing mathematical model for HIV infection

\[
T_4'(t) = (s + r T_4(t)) V_1(t) - k_v (1 - E_{RT}) (r + \alpha) T_4(t) V_1(t) - \gamma_1 T_4(t), \quad T_4(t_0) = T_4^0, \quad (1.1)
\]

\[
T_1'(t) = (k_v (1 - E_{RT}) (r + \alpha) T_4(t) V_1(t) - (\gamma_2 + k_c) T_1(t), \quad T_1(t_0) = T_1^0, \quad (1.2)
\]

\[
V_1'(t) = \gamma_2 (1 - E_{PI}) N (1 - L) T_1(t) - \sigma V_1(t), \quad V_1(t_0) = V_1^0, \quad (1.3)
\]

where the parameters are given in Table I. We will investigate the long-term behavior of solutions in two different scenarios, continuous and discrete forms. A system of difference equations will be obtained from discretization of the mathematical model. It will be shown that the estimation method used in [14] to discretize system (1.1)–(1.3) is significantly compatible with the continuous system and is a robust numerical method to investigate the nature of the IVP system (for instance, see [39]), that is, we can obtain similar properties (such as boundedness, asymptotic stability, oscillatory behavior) of the IVP system from the associated numerical scheme. It is worthwhile to point out that we demonstrate the condition for the endemic equilibrium point of the discrete model to be stable is given by \( e > (b - 1)(1 - d)(1 - f) \) which was conjectured in [44] as an Open Problem, i.e. the associated reproduction number is greater than unity for stable endemic state. Similarities and differences between two models are reported in the beginning of Section 4. This research ends with extensive simulations and a brief conclusion.

2. A SURVEY ON MATHEMATICAL MODEL AND DYNAMICS OF CONTINUOUS SYSTEM

The viral replication is essential for progression of HIV to AIDS and, as a result, requires better administration and intervention of antiretroviral drugs [29, 30, 31, 38]. The replication process of the HIV pathogen
undergo a cycle of development within a human host. Several essential phases (enzymes) such as reverse transcriptase, protease, ribonuclease and integrase are required for successful development of infectious virus particle [1, 2, 11, 13, 14, 31, 38]. Each step is therefore a potential target for identification of an optimal treatment therapy. In the first step, infectious virus particles locate appropriate host cells such as a CD4+ T cells to infect. The process of infection begins by entering HIV into the target cell by fusion after binding to the CD4 glycoprotein and then releasing three crucial replication enzymes: Reverse Transcriptase, Integrase and Protease. Prophylactic medications which interfere with the principal stages of viral replication can inhibit this mortal contamination. For instance, introduction of HIV into the recipient cell which involves in initial infection can be possibly impeded by implementation of fusion inhibitors. Mitigation of reverse transcriptase by application of nucleoside inhibitors or by non-nucleoside Reverse Transcriptase inhibitors is also part of standard therapeutic course of medical treatments. Besides, the fatal process of Retroviral Integrase which enables the genetic material of retrovirus enzyme to be integrated into the DNA of the infected cell can be blocked by HIV integrase inhibitors such as Raltegravir [53]. Perhaps the last key step in a standard antiretroviral therapy is to inhibit the retroviral aspartyl protease causing disease progression by intervention of protease inhibitors including Saquinavir, Ritonavir, Indinavir, Nelfinavir, Amprenavir [50].

The model simulates the interaction between CD4+ T-lymphocyte (these cells perform essential helper functions in the development of cellular and humoral immunity against pathogens including HIV, see [11, 13, 14]) and HIV in vivo when combination antiretroviral therapy is used. Namely, reverse transcriptase (RT) inhibitors and protease inhibitors (PIs) as antiviral drug intervention are exerted for the perturbation of HIV infection.

The existing mathematical model will be briefly described in the sequel, for further information and the terminology used here, we refer readers to [14, 43, 44, 46]. The experiment shows that the reciprocal interplay between infectious viral particles and CD4+ T cells produces three sizable quantities in vivo which are characterized by the mathematical notations: \( T_{4}, T_{I}, \) and \( V_{I} \), where the variable \( T_{4} \) is used to illustrate the amount of inactivated CD4+ T cells at each unit of time which is not accompanied by integrated HIV (or susceptible cells in patient), the second quantity \( T_{I} \) is taken into consideration to represent the amount of CD4+ T cells carrying integrated HIV (infected cells), and the third class \( V_{I} \) indicates infectious HIV load (infectious particles) released from infected cells. As depicted in Figure 1 a compartmental model is used to facilitate the flow in each category and the interaction between CD4+ T cells and viral particles with the intervention of combination antiretroviral therapy. Using the three compartments illustrated for the sizable amount of susceptibles, infected

| Parameter | Interpretation | Value |
|-----------|----------------|-------|
| \( s \)   | Source term for uninfected CD4+ T cells | \( 8.076 \, \text{d}^{-1} \text{mm}^{-3} \) |
| \( r \)   | Rate of proliferation of CD4+ T cells | \( 0.03 \, \text{d}^{-1} \) |
| \( k_{v} \) | Probability of infection of activated CD4+ T cells | 1 |
| \( \gamma_{1} \) | Natural death rate of uninfected CD4+ T cells | \( 0.5 \, \text{d}^{-1} \) |
| \( \gamma_{2} \) | Natural death rate of infected CD4+ T cells | \( 0.5 \, \text{d}^{-1} \) |
| \( k_{c} \) | Anti-HIV immune response | 0.5 |
| \( N \) | Number of free viruses produced per infected cell | 1000 |
| \( L \) | Proportion of latently infected T cells | 0.2 |
| \( E_{RT} \) | Effectiveness of RT inhibitors | \( 0 < E_{RT} < 1 \) |
| \( E_{PI} \) | Effectiveness of protease inhibitors | \( 0 < E_{PI} < 1 \) |
| \( \sigma \) | Rate of clearance of infectious virions | \( 10 \, \text{d}^{-1} \) |
| \( \alpha \) | Proportion of pre-existing activated CD4+ T cells | \( 0 < \alpha < 1 \) |

**TABLE 1.** Description of parameters in HIV model and their estimated values [8, 14, 44]
In fact, the system of differential equations (2.1) where the recruitment term is also examined by Petrov et al. [49], see also [42], with cubic and quadratic autocatalysis term). Note that the infection term is given by

\[ \lambda_1 = (r + \alpha)(1 - E_{RT})k_v \]

\[ \lambda_2 = \gamma_2(1 - E_{RT})N(1 - L) \]

and the parameters are given in Table 1 and defined by

\[ e_1 = r - k_v (1 - E_{RT}) (r + \alpha) \quad \text{and} \quad e_2 = k_v (1 - E_{RT}) (r + \alpha); \]

\[ e_3 = \gamma_2 + k_c \quad \text{and} \quad e_4 = \gamma_2 (1 - E_{RT}) N (1 - L). \]

where the recruitment term \((s + r T_4(t) V_I(t))\) represents the autocatalysis (autocatalytic reaction in a chemical reaction was also examined by Petrov et al. [49], see also [42], with cubic and quadratic autocatalysis term) and the parameters are given in Table 1 and defined by

\[ e_1 = r - k_v (1 - E_{RT}) (r + \alpha) \quad \text{and} \quad e_2 = k_v (1 - E_{RT}) (r + \alpha); \]

\[ e_3 = \gamma_2 + k_c \quad \text{and} \quad e_4 = \gamma_2 (1 - E_{RT}) N (1 - L). \]

Note that the infection term is given by \(\lambda_1\) in Figure 1 not by \(e_1\). As a result, the law of conservation of mass will remain constant over time, that is, the population mass leaving the susceptible (healthy) compartment is taken into account in the succeeding compartment regarded as infected cells carrying integrated virus particles. For the simplicity in analysis of system (2.1)–(2.3) and comparative presentation, we add together \(r\) and \(k_v (1 - E_{RT}) (r + \alpha)\) and use the notation \(e_1\).

The following change of variables simplifies the model (2.1)–(2.3), where \(e_1 \neq 0\):

\[ T_4 = \frac{s}{\gamma_1} x, \quad T_I = \frac{e_2 s}{|e_1| \gamma_1} y, \quad \text{and} \quad V_I = \frac{e_2 e_4 s}{|e_1| e_3 \gamma_1} z. \]

(2.5)

In fact, the system of differential equations (2.1)–(2.3) takes the following form:

\[ x' = F(x, z) = \text{sign}(e_1) \rho x z + \tau - \tau x, \quad x(0) = x_0, \]

\[ y' = G(x, y, z) = \rho x z - \zeta y, \quad y(0) = y_0, \]

\[ z' = H(y, z) = \zeta y - \eta z, \quad z(0) = z_0, \]

(2.6)

in which \(\tau = \gamma_1, \rho = \frac{e_2 e_4 s}{e_3 \gamma_1}, \zeta = e_3, \eta = \sigma, \text{ and sign}(\cdot)\) is the signum function of real numbers. It is worthwhile to mention that solutions of system (2.6) is positively invariant with respect to the first octant, i.e.
\( \mathbb{R}^3_+ = \{(x, y, z)|x \geq 0, y \geq 0, z \geq 0\} \). The equilibria of system (2.6),

\[
E_1 = (1, 0, 0) \quad \text{and} \quad E_2 = \left( \frac{\eta}{\rho}, \frac{\tau (\eta - \rho)}{\text{sign}(e_1) \rho \xi}, \frac{\tau (\eta - \rho)}{\text{sign}(e_1) \rho \eta} \right).
\]

(2.7)
can easily be evaluated by some algebraic calculation. Now set \( R_e = \rho/\eta \). The quantity \( R_e \) is the basic reproduction number for the continuous model (2.6). Note that if \( R_e = 1 \), then the system (2.6) has no equilibria other than \( E_1 \). To investigate the local asymptotic stability, we evaluate the characteristic polynomial by first differentiating the right-hand side of (2.6) and then calculating the Jacobian matrix at the equilibria \([17][40][47]\). The characteristic polynomial at the disease-free equilibrium, \( E_1 \), is given by \( -(\lambda + \tau) [\lambda^2 + (\zeta + \eta)\lambda + \zeta(\eta - \rho)] \), and the characteristic polynomial at the endemic state, \( E_2 \), is presented by

\[
-\lambda^3 - \left( \zeta + \eta + \frac{\tau \rho}{\eta} \right) \lambda^2 - \left( \tau \rho + \frac{\tau \rho \xi}{\eta} \right) \lambda - \tau \zeta (\rho - \eta).
\]

(2.8)

Using the Routh–Hurwitz criterion \([40]\) for the above characteristic polynomials, one can show \([8][14]\) that the disease-free state \( E_1 \) is locally asymptotically stable if \( R_e < 1 \) and is unstable if \( R_e > 1 \). Also for the latter case, the endemic state \( E_2 \) is locally asymptotically stable and is unstable if \( R_e < 1 \). In addition, the system has no equilibria other than \( E_1 \) when \( R_e = 1 \). The eigenvalues of the Jacobian matrix at the disease-free state are \( \{0, -\tau, -\zeta - \eta\} \). It was shown (see Theorem 3.4 in \([8]\)) that if \( e_1 > 0 \) and \( R_e > 1 \), it follows that \((x, y, z) \rightarrow (\infty, \infty, \infty)\) for \((x_0, y_0, z_0) \in \Delta = \{(x, y, z)|y \neq 0 \text{ or } z \neq 0\} \cap \mathbb{R}^3_+ \). It was also illustrated by some experiments in \([8]\) that system (2.6) has bounded and unbounded solutions depending on the domain of initial values when \( e_1 > 0 \) and \( R_e \geq 1 \), while the following result shows the stability of steady states when \( e_1 < 0 \) (see Theorems 4.1, 4.11 and Remark 4.2 in \([8]\)).

**Theorem 2.1.** Consider system (2.6) with \( e_1 < 0 \). Then the following statements are true.

(i) If the reproduction number \( R_e \) is less than or equal to unity, then the disease-free state is globally asymptotically stable in \( \mathbb{R}^3_+ \). In this case, HIV infection is eradicated from the infected host.

(ii) If the reproduction number \( R_e \) is greater than unity, then the endemic state is globally asymptotically stable in \( \Delta \). This case leads to the persistence and existence of HIV infection within the individual.

Considering system (2.1)–(2.3) with \( e_1 = 0 \), it follows that the equilibrium point \((s/\gamma_1, 0, 0)\) is unique when \( w = C e_3 \gamma_1 - s e_2 e_4 \neq 0 \). When \( w = 0 \), the model (2.1)–(2.3) also possesses the unique positive equilibrium \((s/\gamma_1, e_4 \theta/C, \theta)\), in which \( \theta \) depends critically on the coefficients of the system and the initial value \((x_0, y_0, z_0)\). The following theorem shows the qualitative behavior of system (2.1)–(2.3) when \( e_1 = 0 \).

**Theorem 2.2** (See \([8]\)). Consider system (2.7)–(2.9) with \( e_1 = 0 \). Then the following statements are true.

(i) If \( w > 0 \), then the disease-free state is globally asymptotically stable in \( \mathbb{R}^3_+ \).

(ii) If \( w = 0 \), then positive solutions converges eventually to \((s/\gamma_1, e_4 \theta/C, \theta)\) when \((T^0_4, T^0_1, V^0) \in \mathbb{R}^3_+ \).

The model (2.1)–(2.3) has unbounded solutions whenever \( e_1 = 0 \) and \( w < 0 \) (see Remark 5.4 and examples illustrated in \([8]\)).

### 3. Analysis of Discrete Model

#### 3.1. Preliminaries to difference equations.

In this part, we begin by presenting some basic definitions to study the qualitative behavior of a system of difference equations. Let \( I_1, I_2, \) and \( I_3 \) be some intervals of real numbers and let

\[ F_i : I_1 \times I_3 \times I_3 \rightarrow I_i, \quad \text{for } i \in \{1, 2, 3\} \]
be three continuously differentiable functions. Then for every initial condition \((x_0, y_0, z_0) \in I_1 \times I_2 \times I_3\), the system of difference equations
\[
x_{n+1} = F_1(x_n, z_n), \quad y_{n+1} = F_2(x_{n+1}, y_n, z_n), \quad z_{n+1} = F_3(y_{n+1}, z_n)
\]  
has a unique solution \(\{x_n, y_n, z_n\}_{n=0}^{\infty}\). A point \((\bar{x}, \bar{y}, \bar{z}) \in I_1 \times I_2 \times I_3\) is called an equilibrium point of system (3.1) if
\[
\bar{x} = F_1(\bar{x}, \bar{z}), \quad \bar{y} = F_2(\bar{x}, \bar{y}, \bar{z}), \quad \bar{z} = F_3(\bar{y}, \bar{z}).
\]

**Definition 3.1.** The equilibrium point \((\bar{x}, \bar{y}, \bar{z})\) of system (3.1) is called

1. stable (or locally stable) if for every \(\epsilon > 0\), there exists \(\delta > 0\) such that for all \((x_0, y_0, z_0) \in I_1 \times I_2 \times I_3\) with \(\|x_0, y_0, z_0\| - (\bar{x}, \bar{y}, \bar{z})\| < \delta\) implies \(\|(x_n, y_n, z_n) - (\bar{x}, \bar{y}, \bar{z})\| < \epsilon\) for all \(n \geq 0\). Otherwise the equilibrium point is called unstable.

2. asymptotically stable (or locally asymptotically stable) if it is stable and there exists \(\gamma > 0\) such that for all \((x_0, y_0, z_0) \in I_1 \times I_2 \times I_3\) with \(\|x_0, y_0, z_0\| - (\bar{x}, \bar{y}, \bar{z})\| < \gamma\) implies \(\lim_{n \to \infty} \|(x_n, y_n, z_n) - (\bar{x}, \bar{y}, \bar{z})\| = 0\).

3. globally asymptotically stable if it is locally stable and for every \((x_0, y_0, z_0) \in I_1 \times I_2 \times I_3\), we have \(\|(x_n, y_n, z_n) - (\bar{x}, \bar{y}, \bar{z})\| \to 0\), as \(n \to \infty\).

4. a repeller, if there exists \(r > 0\) such that for all \((x_0, y_0, z_0) \in I_1 \times I_2 \times I_3\) with \(0 < \|(x_0, y_0, z_0) - (\bar{x}, \bar{y}, \bar{z})\| < r\), there exists \(N \geq 1\) such that \(\|(x_N, y_N, z_N) - (\bar{x}, \bar{y}, \bar{z})\| \geq r\).

**3.2. Discretizing the model.** Here, we investigate the boundedness, the stability analysis, and the bifurcation phenomenon of a discrete system in general cases. The development of the numerical method will be based on the first-order approximation and using a numerical method of the form \([14, 39, 41, 54, 55, 56, 22, 23, 25, 26]\)
\[
W^{n+1} = W^n + l f(W^n, W^{n+1}), \quad n \geq 0
\]  
where \(W^n = [T^n_1, T^n_2, V^n_1]^\top\), \(\top\) denoting transpose. The robust numerical method can be obtained by approximating the time derivative with its first-order forward-difference approximation for each equation in the left side of system (2.1)–(2.3) and making appropriate estimations for the right side, as follows with the fixed time step size \(\ell > 0\).
\[
\begin{align*}
(T_4^{n+1} - T_4^n) / \ell &= s + e_1 T_4^{n+1} V^n_1 - \gamma_1 T_4^{n+1}, \\
(T_1^{n+1} - T_1^n) / \ell &= e_2 T_1^{n+1} V^n_1 - e_3 T_1^{n+1}, \\
(V_1^{n+1} - V_1^n) / \ell &= e_4 T_2^{n+1} - \sigma V_1^n.
\end{align*}
\]  
Note that the variables \(T^n_1, T^n_2,\) and \(V^n_1\) denote the estimation values of \(T_1(n\ell), T_2(n\ell),\) and \(V_1(n\ell)\) respectively. In addition, \(T_1^n, T_2^n,\) and \(V_1^n\) are taken into consideration as a set with three non-negative sequences consistent with the biological nature of the model in practice. In fact, the parameters of the model should be chosen such that \(T_1^n, T_2^n,\) and \(V_1^n\) are non-negative. In most cases, the non-negativity is a standard assumption in the literature of difference equations \([7, 18, 33, 34]\), besides the nature of the model (the IVP system) is another reason. Note also that it is a very difficult task to investigate \([9]\) the behavior of solutions of a difference equation which attains negative and positive values simultaneously. For instance, finding a forbidden set, the set of initial conditions through which the related difference equation is undefined, is a difficult task for this class of difference equations. To observe these types of complexities, readers are encouraged to study \([34, p.17]\). However, in this work we will obtain some results where \(\hat{c} > 0\) in Equation (3.4), that is, the solutions of system (3.4)–(3.6) deal with negative numbers, see Appendix A.

Using the following change of variables
\[
T_4^n = ls x_n, \quad T_1^n = (1 + l \sigma) y_n / l e_4, \quad V_1^n = z_n,
\]  
\[\text{(3.7)}\]
and re-arranging system (3.4)–(3.6), it follows that
\begin{align*}
x_{n+1} &= \frac{1 + x_n}{b + c z_n}, \quad (3.8) \\
y_{n+1} &= d y_n + e x_{n+1} z_n, \quad (3.9) \\
z_{n+1} &= f z_n + y_{n+1}, \quad (3.10)
\end{align*}
where \( b = 1 + l \gamma_1 > 1, c = -l e_1 \in \mathbb{R}, 0 < d = (1 + l e_3)^{-1} < 1, e = l^3 s e_4 e_2 ((1 + l e_3)(1 + l \sigma))^{-1} > 0, \) and \( 0 < f = (1 + l \sigma)^{-1} < 1. \)

Define \( \mathcal{R}_d = e/((b - 1)(1 - d)(1 - f)), \) the threshold \( \mathcal{R}_d \) is the basic reproduction number for discrete model (3.8)–(3.10). Suppose that \( c \neq 0 \) and \( \mathcal{R}_d \neq 1, \) then it is easy to show that system (3.8)–(3.10), independent of time step size, has the disease-free equilibrium point
\[ ((b - 1)^{-1}, 0, 0), \]
and the endemic equilibrium point
\[ \left( \frac{(1 - d)(1 - f)}{e}, \frac{e + (1 - b)(1 - d)(1 - f)}{c(1 - d)}, \frac{e + (1 - b)(1 - d)(1 - f)}{c(1 - d)(1 - f)} \right). \]
Note that system (3.8)–(3.10) has only one equilibrium point (3.11) where either \( c \neq 0 \) or \( \mathcal{R}_d \neq 1. \) We also observe that system (3.8)–(3.10) has the following equilibrium point \((1/(b - 1), (1 - f) \psi, \psi),\) where \( c = 0 \) and \( \mathcal{R}_d = 1, \) in which \( \psi \) depends on the coefficients of system (3.8)–(3.10) and the initial value \((x_0, y_0, z_0).\)

The following theorem provides us the boundedness of solutions which will be trapped into some intervals.

**Theorem 3.2** (See [44], Section 4.1). Let \( b > 1, c > 0, \) \( 0 < d < 1, \) \( e > 0 \) and \( 0 < f < 1. \) Then either \((x_n, y_n, z_n)\) converges to an equilibrium point or the following statements are true.
\begin{align*}
\Gamma &\leq \lim \inf x_n \leq \lim \sup x_n \leq (b - 1)^{-1}, \quad (3.13) \\
0 &\leq \lim \inf y_n \leq \lim \sup y_n \leq \frac{b e}{c(1 - d)} \left( \frac{1}{b - 1} - \Gamma \right), \quad (3.14) \\
0 &\leq \lim \inf z_n \leq \lim \sup z_n \leq \frac{b e}{c(1 - d)(1 - f)} \left( \frac{1}{b - 1} - \Gamma \right). \quad (3.15)
\end{align*}
where \( \Gamma = \min \left( \frac{(b - 1)(1 - d)(1 - f)}{b e}, \frac{1}{b - 1} \right). \)

### 3.3. Analysis of disease-free and endemic states.

We state some theorems that will be of help in the subsequent sections and are derived from the theoretical results of Dehghan et al [44] Section 4.2–4.3]. These results present the local stability of both equilibrium points and the global stability of (3.11).

**Theorem 3.3** (See [44], Theorem 4.4). Consider system (3.8)–(3.10) with \( b > 1, 0 < d < 1, e > 0, \) and \( 0 < f < 1. \) Then the following statements are true.

(i) If \( \mathcal{R}_d < 1 \) holds, then the equilibrium point (3.11) is asymptotic stable.

(ii) If \( \mathcal{R}_d > 1 \) holds, then the equilibrium point (3.11) is unstable.

(iii) If \( \mathcal{R}_d = 1 \) holds, then the roots of the characteristic polynomial at the equilibrium points \((1/b - 1, 0, 0)\) and \((1/b - 1, 1 - f) \psi, \psi)\) are \( \{1, \frac{1}{b - 1}, d f\} \).

(iv) The equilibrium point \((1/b - 1, 0, 0)\) is not a repeller.

**Theorem 3.4** (See [44], Theorem 4.7). Consider system (3.8)–(3.10) with \( b > 1, c > 0, 0 < d < 1, e > 0, \) and \( 0 < f < 1. \) If the reproduction number \( \mathcal{R}_d \) is less than unity, then the equilibrium point \((1/b - 1, 0, 0)\) is globally asymptotically stable. Therefore the disease can be eradicated from the host.
Theorem 3.5 (See [44], Theorem 4.5). Consider system \((3.8)-(3.10)\) with \(b > 1, 0 < d < 1, e > 0,\) and \(0 < f < 1.\) Then the following statements are true.

(i) If \(R_d > 1\) holds, then the equilibrium point \((3.12)\) is asymptotic stable. In addition, the system has no equilibrium point in \(\mathbb{R}^2 > 0 = \{(x, y, z)| x > 0, y > 0, z > 0\}\) when \(c \leq 0.\)

(ii) If \(R_d < 1\) holds, then the equilibrium point \((3.12)\) is unstable. In addition, the system has no equilibrium point in \(\mathbb{R}^2 > 0\) when \(c \geq 0.\)

(iii) The equilibrium point \((3.12)\) is not a repeller.

Theorems 3.3 and 3.5 show that a bifurcation occurs when \(R_d = 1\) (See [44, Corollary 4.6]). On the other hand, the disease will persist if \(R_d\) exceeds unity, where a stable endemic equilibrium exists. This phenomenon, where the disease-free equilibrium loses its stability and a stable endemic equilibrium appears as \(R_d\) increases through one, is known as forward bifurcation [3, 4, 5, 10]. This pattern was first noted by Kermack and McKendrick [28], and has been observed in the vast majority of disease transmission models in the literature ever since (see [10] 15 16 35 and the references therein). For models that exhibit forward bifurcation, the requirement \(R_d < 1\) is necessary and sufficient for disease elimination. Furthermore, these theorems express that the equilibria \((3.11)\) and \((3.12)\) are not asymptotically stable simultaneously.

Now we give the main question of this work which was given as an Open Problem in [44, Section 4.3]. Hopefully we then show that, based on the parameter set requirement, the conjecture is true.

Open Problem : Show that the positive equilibrium point \((3.12)\) is globally asymptotically stable if \(R_d > 1\) along with the following conditions imposed to the parameters:

\[
b > 1, \ c > 0, \ 0 < d < 1, \ e > 0, \text{ and } 0 < f < 1.\]

In the first place, we show that the this problem holds under the assumption when \(e > (b - 1)(1 - d).\) But before demonstrating this statement, we need to state the following theorem as things develop.

Theorem 3.6. Let \([a_1, b_1], [a_2, b_2],\) and \([a_3, b_3]\) be intervals of real numbers, and let

\[
f_i : [a_1, b_1] \times [a_2, b_2] \times [a_3, b_3] \to [a_i, b_i], \quad \text{for } i \in \{1, 2, 3\}
\]

be continuous functions. Consider the system of difference equations

\[
x_{n+1} = f_1(x_n, z_n), \quad y_{n+1} = f_2(x_{n+1}, y_n, z_n), \quad z_{n+1} = f_3(y_{n+1}, z_n), \quad n = 0, 1, 2, ...
\]

(3.16)

with initial conditions \((x_0, y_0, z_0) \in [a_1, b_1] \times [a_2, b_2] \times [a_3, b_3].\) Suppose that the following statements are true.

(1) \(f_1(x, z)\) is non-increasing in \(z\) and is non-decreasing in \(x.\)
(2) \(f_2(x, y, z)\) is non-decreasing in \(x, y,\) and \(z.\)
(3) \(f_3(y, z)\) is non-decreasing in \(y\) and \(z.\)
(4) If \((m_i, M_i) \in [a_i, b_i]^2,\) for \(i \in \{1, 2, 3\},\) is a solution of the system of equations

\[
m_i = f_i(m_1, m_2, m_3) \quad \text{and} \quad M_i = f_i(M_1, M_2, M_3) \quad \text{for } i \in \{1, 2, 3\}
\]

(3.17)

then \(m_1 = M_1, m_2 = M_2,\) and \(m_3 = M_3.\)

Then there exists exactly one equilibrium point \((\bar{x}, \bar{y}, \bar{z})\) of system \((3.16)\) and every solution of system \((3.16)\) converges to \((\bar{x}, \bar{y}, \bar{z}).\)
Proof. It is obtained in the same argument as [20, 21].

We showed that solutions of system (3.8 – 3.10) are bounded from above in (3.13 – 3.15) (see Theorem 3.2). We now demonstrate that solutions are bounded from below, namely \( (y_n, z_n) \) are away from \((0, 0)\) (this was already shown for \(x_n\)).

**Theorem 3.7.** Assume that \( e > (b - 1)(1 - d) \) and \( (y_0, z_0) \neq (0, 0) \) hold. Then every solution of system (3.8 – 3.10) is bounded from below, i.e. \( \lim \inf (x_n, y_n, z_n) > (0, 0, 0) \).

Proof. It was already shown in (3.13) that \( x_n > 0 \). One can use equations (3.8 – 3.10) to show simply that if \( \limsup_{n \to \infty} y_n \) or \( \liminf_{n \to \infty} z_n \) equals zero, then \( \{y_n\}_{n=0}^\infty \) and \( \{z_n\}_{n=0}^\infty \) converge to zero as well. Now assume on the contrary that one of the sequences \( y_n \) or \( z_n \) converges to zero, then the other one converges to zero as well. So \( (x_n, y_n, z_n) \to (\frac{1}{b-1}, 0, 0) \) with \( y_n > 0 \) and \( z_n > 0 \) for all \( n \in \mathbb{N} \). Let \( e > 0 \) satisfy

\[
(b - 1)(d - 1) + e - e(b - 1)e \geq 0,
\]

then there is \( N \) such that \( x_n \) is very close to \( \frac{1}{b-1} \) and for \( n \geq N \)

\[
\frac{1}{b-1} - \epsilon < x_n < \frac{1}{b-1} + \epsilon.
\]

As a result, for \( n \geq N \),

\[
y_{n+1} > dy_n + e \left( \frac{1}{b-1} - \epsilon \right) z_n.
\]

Using the fact that \( z_n \geq y_n \), we have

\[
y_{n+1} > dy_n + e \left( \frac{1}{b-1} - \epsilon \right) y_n = \left( d + e \left( \frac{1}{b-1} - \epsilon \right) \right) y_n.
\]

In view of (3.18), we have \( y_{n+1} > y_n > \ldots > y_N \), which is a contradiction. So the desired result follows.

Now we present one of the main theorems of this work which provide partially an answer to the Open Problem given in [44] when \( e > (b - 1)(1 - d) \).

**Theorem 3.8.** Assume that \( e > (b - 1)(1 - d) \) holds. Then the equilibrium point (3.12) of system (3.8 – 3.10) is globally asymptotically stable.

Proof. It was shown in Theorem 3.5 that the equilibrium point (3.12) of system (3.8 – 3.10) is locally asymptotically stable. It is just required to demonstrate that every solution of system (3.8 – 3.10) converges to the equilibrium point (3.12). We use the result of Theorems 3.6 and 3.7. It follows by Theorem 3.7 that there are \( (m_x, M_x) \), \( (m_y, M_y) \), and \( (m_z, M_z) \), a solution of (3.17), such that

\[
0 < m_x = \lim \inf x_n \leq x_n \leq \lim \sup x_n = M_x,
\]

\[
0 < m_y = \lim \inf y_n \leq y_n \leq \lim \sup y_n = M_y,
\]

\[
0 < m_z = \lim \inf z_n \leq z_n \leq \lim \sup z_n = M_z.
\]

Now if we show that \( m_x = M_x \), \( m_y = M_y \), and \( m_z = M_z \), then we prove the part (4) of Theorem 3.6 and other parts of this theorem are clearly true. To this end, we substitute \( (m_x, M_x) \), \( (m_y, M_y) \), and \( (m_z, M_z) \) in system (3.8 – 3.10), it then follows that

\[
m_x = \frac{1 + m_x}{b + c M_z} \quad \text{and} \quad M_x = \frac{1 + M_x}{b + c m_z},
\]

\[
m_y = d m_y + e m_x m_z \quad \text{and} \quad M_y = d M_y + e M_x M_z,
\]

\[
m_z = f m_z + m_y \quad \text{and} \quad M_z = f M_z + M_y.
\]
First isolating \( m_x \) and \( M_x \) in (3.22) give
\[
m_x = \frac{1}{b - 1 + cM_x} \quad \text{and} \quad M_x = \frac{1}{b - 1 + cM_z},
\]
we then replace \( m_x \) and \( M_x \) in (3.23). Likewise solving (3.23) for \( m_y \) and \( M_y \) gives
\[
m_y = \frac{eM_x}{(1 - d)(b - 1 + cM_z)} \quad \text{and} \quad M_y = \frac{eM_x}{(1 - d)(b - 1 + cM_z)},
\]
and we are now able to generate \( m_z \) and \( M_z \) in (3.24).
\[
m_z = \frac{eM_x}{(1 - f)(1 - d)(b - 1 + cM_z)} \quad \text{and} \quad M_z = \frac{eM_x}{(1 - f)(1 - d)(b - 1 + cM_z)},
\]
which is equivalent to
\[
1 = \frac{e}{(1 - f)(1 - d)(b - 1 + cM_z)} \quad \text{and} \quad 1 = \frac{e}{(1 - f)(1 - d)(b - 1 + cM_z)}.
\]
This shows that \( m_z = M_z \), so are \( m_x = M_x \) and \( m_y = M_y \). As a result the assumptions of Theorem 3.6 hold, then there exists exactly one equilibrium point (3.12) of system (3.8)-(3.10) and every solution of system (3.8)-(3.10) converges to (3.12). \( \square \)

**Theorem 3.9.** Consider system of difference equation (3.8)-(3.10) with \( b > 1 \), \( c > 0 \), \( 0 < d < 1 \), \( e > 0 \), and \( 0 < f < 1 \). Assume that \((x_0, y_0, z_0) \in \mathbb{R}^3_+\), then \( \{ (x_n, y_n, z_n) \}_{n=0}^{\infty} \) converges to (3.11) or (3.12).

**Proof.** Using Theorems 3.4 and 3.8 it is sufficient to show the argument hold only for
\[
(b - 1)(1 - d)(1 - f) < e < (b - 1)(1 - d).
\]
The same reasoning as in the proof of Theorem 3.8 produces system (3.22)-(3.24). If \( m_y \) or \( m_z \) is zero, say \( m_y \), then by (3.9) and the fact that \( m_x \) is bounded and greater than zero it follows that \( m_z \) is zero. As a result by (3.22), we deduce that \( m_x = M_x = 1/(b - 1) \), hence \( M_y = M_z = 0 \). So the solution converges to (3.11).

**Theorem 3.10.** Assume that \((b - 1)(1 - d)(1 - f) < e < (b - 1)(1 - d) \) and \((y_0, z_0) \neq (0, 0) \) hold. Then every solution of system (3.8)-(3.10) is bounded from below.

**Proof.** Assume on the contrary that one of \( y_n \) or \( z_n \) converges to zero, the other one converges to zero too, and then \( x_n \to \frac{1}{b - 1} \). Since \((b - 1)(1 - d)(1 - f) < e\), choose \( e > 0 \) and \( l > 0 \) such that
\[
(1 - b)(1 - d)(1 - f) + e(1 - d^{l+1}) - e(b - 1)e \geq 0,
\]
then there is \( N \) such that \( x_n \) is very close to \( \frac{1}{b - 1} \) and for \( n \geq N \)
\[
\frac{1}{b - 1} - e < x_n < \frac{1}{b - 1} + e.
\]
As a result, for \( n \geq N \)
\[
y_{n+1} > dy_n + eKz_n,
\]
where \( K = \left( \frac{1}{b - 1} - e \right) \). Let \( z_{i,l} = \min\{z_i, z_{i-1}, ..., z_{i-l}\} \), then by (3.25) it follows that
\[
z_{n+1} > f z_n + eKz_n + dy_n > f z_n + eKz_{n-l} + eKd z_{n-l} + ... + eKd^l z_{n-l} + d^l y_{n-l}
\]
\[
> (f + eK + eKd + ... + eKd^l)z_{n,l} + d^l y_{n-l}
\]
\[
> \left( f + eK \left( \frac{1 - d^{l+1}}{1 - d} \right) \right) z_{n,l}.
\]
Then by induction \( n \), it follows that
\[
z_{n+T} > ... > z_{n+2,l} > z_{n+1,l} > z_{n,l}
\]
which is a contradiction. So the desired result obtains.

The following theorem is the main result of this research which answers to the Open Problem given in [44].

**Theorem 3.11.** Assume that $e > (b - 1)(1 - d)(1 - f)$ holds. Then the equilibrium point (3.72) of system (3.8)—(3.10) is globally asymptotically stable.

**Proof.** It follows from Theorem 3.10 and the argument of Theorem 3.8.

4. **Inference in Continuous HIV Infection Model with Correlated Dynamic Discrete Model**

This section develops a reliable comparison for the original continuous HIV infection model, system (2.1)—(2.3), with estimation of correlated dynamic discrete model, system (3.8)—(3.10). Inference in dynamic discrete model involves computing the solutions to a high-dimensional system and analyzing theoretically the long-term behavior of solutions. The parameter values used for the numerical scheme, system (3.8)—(3.10), are derived technically by employing the change of variables in Section 5.2, given as follows,

$$b = 1 + l \gamma_1, \quad c = -le_1, \quad d = \frac{1}{1 + le_3}, \quad e = \frac{l^3 s e_2 e_4}{(1 + le_3)(1 + l \sigma)}, \quad \text{and} \quad f = \frac{1}{1 + l \sigma}$$

from which it follows that $b > 1$, $e \in \mathbb{R}$, $0 < d < 1$, $e > 0$, and $0 < f < 1$ when $l > 0$. The parameter values for the continuous HIV infection model, system (2.6), were correspondingly chosen by (2.4) in Section 2 and the change of variables (2.5) so that all the possible observed steady states $(x, y, z)$ were identified clearly by

$$\tau = \gamma_1, \quad \rho = \frac{e_2 e_4 s}{e_3 \gamma_1}, \quad \zeta = e_3, \quad \text{and} \quad \eta = \sigma.$$

The chain convergence is checked by comparing the estimation results for several different parameter values in Theorems 3.3 and 3.5 with the results of [8, Theorem 2.1] or [14, Section 4]. Surprisingly, we observe that the local behavior of solutions of the continuous HIV infection model is qualitatively similar to that of numerical scheme for discrete model corresponding to the same parameter set, since the conditions $\mathcal{R}_d = \frac{e}{(b - 1)(1 - d)(1 - f)} > 1$, $\mathcal{R}_d = 1$, or $\mathcal{R}_d < 1$ are equivalent to $\mathcal{R}_d = \frac{s e_2 e_4}{\sigma \gamma_1 e_3} > 1$, $\mathcal{R}_d = 1$, or $\mathcal{R}_d < 1$ respectively. In addition, the conditions $d < b$, $d = b$, and $d > b$ are equivalent to $\sigma \gamma_1 e_3 < se_2 e_4$, $\sigma \gamma_1 e_3 = se_2 e_4$, and $\sigma \gamma_1 e_3 > se_2 e_4$, respectively. Therefore, Theorems 2.1, 3.4, and 3.9 and Corollary 4.3 in [44] show that global dynamics of these models are considerably equivalent for $e_1 < 0$ which is related to $c > 0$. The estimation results for the correlated dynamic discrete model are only slightly affected by the fixed time step size $l$, see Subsection 5.1. Such a case scenario shows that the numerical scheme (3.3) is an efficient algorithm in conjunction with $e_1 < 0$ and suitable for use to solve the dynamic continuous HIV infection model.

The following results are motivated by the stage estimation procedure in which the key parameter $c$ is taken to be zero, that is, $c = 0$ corresponding to $e_1 = 0$ for the dynamic continuous model. In fact, these results are provided by Theorem 2.2 in [8] (proved for the continuous model) and Theorem 4.2 and Corollary 4.3 in [44] (proved for the discrete model). The paper studies theoretically the estimation method’s performance in the case when $e_1 = 0$ or $c = 0$. The findings demonstrate that the estimation accuracy of the proposed numerical method is excellent since similar results for both models are achieved.

However, the main difference appears in the qualitative behaviors of solutions of the models when $e_1 > 0$. Theoretical results and several experiments on artificial data and parameter values show that the dynamic discrete model conducted by the estimated method and the continuous model with HIV infection can behave quite differently when $e_1 > 0$. More generally, the experiments demonstrate that system (2.6) can attain bounded or unbounded solutions [8] while the qualitative behavior of system (3.8)—(3.10) with different initial values can lead to dispersion and serious misspecification errors referred to as forbidden sets, see Appendix A. The proposed theoretical framework for system (2.6) is flexible and leaves room for experimentation and abstract results. Experiments with the numerical estimation algorithm for solving system (3.8)—(3.10) requires
a discovery of modifications and development of the numerical method in our future work that will hopefully provide a very efficient alternative to iterating the approximation (3.3) for negative parameter $c$. The most important reason for this difference seems to be, a great deal, based on forward-difference approximation (3.3).

5. Numerical experiments

A verification of the algorithm implementation for the above scenario cases is provided in this section. For example, the effect of different parameter values for time-step and immune response to the proposed estimation algorithm (3.3) are studied to identify an effective treatment for the management of HIV infection administering multiple anti-HIV preventive drugs in vivo. Multiple parameter sets are used to check the convergence of the estimation procedure in which solving the exact solution of model (2.6) can be quickly computed. Also several examples show that with different initial values $(x_0, y_0, z_0) \in \mathbb{R}^3_+$, solutions of (3.8)–(3.10) attain negative values. However, theoretical results are provided to show that some solutions of system (2.6) remains in $\mathbb{R}^3_+$ whenever $(x_0, y_0, z_0) \in \mathbb{R}^3_+$ in Appendix A.

5.1. Effect of time-step, $l$. We will show that the associated numerical estimation method is very robust in terms of numerical stability since the equilibria and the stability conditions are independent of the time step by detailed comparisons. Several numerical simulations were carried out using the numerical method (3.3), regarded as Method A in Table 2, to identify the behavior of solutions of the model (3.8)–(3.10) with various time steps. An intuitive comparison of the results obtained from the application of the fourth-order Runge-Kutta method (RK4) and Method A is depicted in Table 2 from which it is obvious that numerical scheme (3.3) is more competitive in connection with numerical stability. Extensive numerical simulations performed by the numerical approximation (3.3) show that Method A did not provide solutions with chaotic behavior [14]. In fact, every solution of estimation method converges either to the disease-free state or endemic state. This scenario was given by some numerical examples in [14] without any theoretical proof.

Interestingly the equilibrium point of system (3.4)–(3.6), say $(\bar{T}_4, \bar{T}_I, \bar{V}_I) = (\bar{\tilde{a}}, \bar{\tilde{y}}/\hat{\tilde{g}}, \hat{\tilde{z}})$, is independent of the time step, that is, the solution approaches to the disease-free or endemic equilibrium point of the original model given by the system of ordinary differential equations (2.1)–(2.3) or system (2.6). As a result, regardless of the implementation of time step, a unique equilibrium point is eventually obtained. It is also shown in Theorems 3.4 and 3.11 that the solution obtained by the numerical scheme approaches to the disease-free or endemic equilibrium point, whether the reproduction number $R_d$ is less than or in excess of unity. The demonstrations are independent of variation of $l$ as long as $l > 0$. Using the previous discussion and dynamical comparison of Section 4, the solution likewise converges to the equilibrium point for sufficiently small values $l (0 < l << 1)$ and is, as a result, consistent with the compartmental model (2.1)–(2.3).

5.2. Effect of basic reproduction number, $R_d$. Here we attempt to determine appropriately the dynamics of discrete model by the sensitive quantity threshold, $R_d$, keeping the immune response to a sufficient level. A reliable comparison of the estimation results for the proposed numerical approximation (3.3) suggests that

| $l$    | RK4       | Method A          |
|--------|-----------|-------------------|
| 0.001  | Convergence | Convergence       |
| 0.01   | Divergence | Convergence       |
| 10     | Divergence | Convergence       |
| 200    | Divergence | Convergence       |
a qualitative behavioral change to the model appears through destabilizing the disease-free equilibrium and emergence of a stable endemic equilibrium. A stable endemic equilibrium branch appears with an unstable disease-free equilibrium (leading to the persistence and existence of HIV within the infected individual) when the related reproduction number is less than one. The attractivity of the model reveals that the disease-free equilibrium is globally asymptotically stable under certain assumptions. Nevertheless the unique endemic equilibrium is globally asymptotically stable in the presence of 60% effective combination therapy. In addition, a comparison between the discrete and continuous models is presented to have a better view in understanding the behavioral dynamics of HIV infection modelling.

The correlated dynamic discrete model may exhibit a threshold behavior of a possibility of sustained oscillations. Oscillations in the model mean fluctuations in the number of uninfected/infected/infectious cells to be expected and the HIV infection still persists but in an oscillatory manner for certain parameters values. The model (3.3)–(3.10) suggests that the presence of damped oscillations is inevitable to emerge if the threshold distinguished as the basic reproduction number is maintained above a certain quantity during therapy. This includes the possibility that the presence of certain parameter values can destabilize the endemic equilibrium point of the model with constant coefficients and lead to sustain damped oscillations for the reproduction number exceeding a threshold value. Such a change in behavioral dynamics of infection is considerably affected by the insufficient level of CTL response in the immediate surroundings of antiretroviral therapy with relapse. Clearly a higher magnitude of basic reproduction numbers inferred from both continuous HIV infection model and dynamic discrete model is related to a comparatively lower threshold level of immune response or ineffective combination of reverse transcriptase and protease inhibitors in vivo.

Numerical simulations, Figure 2, indicate that transitory oscillations are observed for about the first 100 units of time and no sustained oscillations are obtained when the endemic equilibrium point appears to be stable for lower values of $R_d$ close to unity, $R_d \geq 1$, but not for significantly large values. As the threshold level of basic reproduction number exceeds unity and is maintained above a certain threshold, the time periods of oscillations to the solutions of the model become shorter and rapid in conjunction with occurrence of higher amplitudes of oscillations.

Comparison of the two rows in Figure 2 for two different parameter values $c = 0.6, 0.006$ shows that the magnitude of maximal density for the activated CD4$^+$ T cells carrying integrated HIV (infected cells) and density of virus particles is overwhelmingly larger in the top array corresponding to smaller value, $c = 0.006$, while the estimation results for the density of uninfected cells are only slightly affected by the same parameter values. Surprisingly, the qualitative oscillatory behavior of the correlated dynamic discrete model is not substantially perturbed by the implementation of various parameter values for $c$. This result seems to have a simple explanation. The expected long-term solution of the model (3.8)–(3.10) associated with the equilibrium point (3.12) is intuitively sensitive to the implementation of the parameter $c$ and the basic reproduction number. The larger the parameter value $c$, the higher amplitude is observed for the density of infected cells and virus particles, Figure 2. However the parameter value $c$ produces directly no sizable effects or possible repercussions to the density of uninfected cells.

5.3. **Effect of immune response, $k_c$.** The effect of the CTL (cytotoxic T lymphocyte) response was investigated [14] by simulating Method A with various values of the CTL response parameter, $k_c$, in the absence of therapy (that is $E_{RT} = E_{PI} = 0$). The steady-state values of the corresponding viral loads are given in the following table. Another experiment was carried out to monitor $k_c$ when combination therapy is 60% effective ($E_{RT} = E_{PI} = 0.6$) and the results are tabulated in Table 3. It is worth mentioning that such limited efficiency of combination therapy (60%) may occur due to many reasons, including sub-optimal usage of the regimen, poor compliance, poor absorption of certain drugs, mutation, etc.
TABLE 3. Effect of CTL response, steady-state values of infectious viral load (density of HIV) [14]

| $k_c$ | Effect of CTL response in the absence of effective protease inhibitors where $E_{RT} = 0$ | Effect of CTL response in the presence of 60% combination therapy |
|-------|---------------------------------------------------------------------------------|---------------------------------------------------------------|
| 0.0   | 834.90                                                                          | 588.11                                                        |
| 0.6   | 376.77                                                                          | 254.93                                                        |
| 1.0   | 274.97                                                                          | 180.89                                                        |

5.4. Combination antiretroviral therapy versus monotherapy. In this experiment, we make use of the mathematical discrete model (3.8)–(3.10) to identify an effective treatment strategy for the management of HIV infection using multiple anti-HIV preventive drugs in vivo. Figure 3 describing the within-host infectious dynamics provide us an intuitive comparison for both combination antiretroviral therapy and monotherapy using the quantity threshold $R_d = \frac{\delta e_2 e_3}{\sigma \gamma_1 e_3}$ related to the set of parameter values $s = 8.076$, $r = 0.03$, $k_v = 1$, $\gamma_1 = 0.5$, $\gamma_2 = 0.5$, $N = 1000$, $L = 0.2$, $\sigma = 10$ and multiple sets of variables $(E_{RT}, E_{PI}, \alpha)$. For the monotherapy experiment, we assume that only protease inhibitors, e.g., nelfinavir, are administered to the HIV-infected patient [14, Section 6.3]; thus the horizontal axis as a variable is used for the effectiveness values.

![Figure 3](image_url)
$E = E_{PI}$ with $E_{RT} = 0$. Note that a similar experiment can be illustrated by assuming $E_{RT}$ as a variable with $E_{PI} = 0$. As the administration of a combination of two or more drugs to the HIV-infected patient is currently a treatment strategy [14, Section 6.3], another experiment with respect to the combination therapy is conducted with an equivalent administration of both reverse transcriptase and protease inhibitors, that is, we assume that the horizontal axis as a variable represents the effectiveness values $E = E_{PI} = E_{RT}$. In both experiments, vertical axes represent the effect of the CTL (cytotoxic T lymphocyte) response. The black/gray/white shaded areas are used for various values of pre-existing activated CD4$^+$ T cells, $0 \leq \alpha \leq 1$. The basic reproduction number is in excess of unity in each corresponding area with the stated value $\alpha$ and including the area(s) with lower values of $\alpha$. For instance, the basic reproduction number for $\alpha = 0.1$ not only represents the corresponding shaded area but also includes the areas with $\alpha = 0$, 0.01.

In both scenarios, further computational experiments of the model for an enhanced comparison are performed on the representation of 60% and 80% effectiveness of therapy with 50% and 75% immune response. In each set of these independent experiments, four distinguishable horizontal and vertical dashed lines are drawn on the shaded areas for this model, see Figure 3. These experimental results are intriguing. Using both experiment presented in Figure 3 clearly the chance to suppress the viral load is so narrow for monotherapy, in some cases less than one percent and it may be interpreted as impossible, while combination therapy provide better confidence in removal of integrated HIV cells. For instance, the experimental analysis on the model with administration of only protease inhibitors refereed as monotherapy indicates that the basic reproduction number is greater than one for the ordered pair $(0.6, 0.5)$ with a proportion $\alpha \geq 0.01$ of pre-existing activated CD4$^+$ T cells, that is, the virus load cannot be entirely inhibited in the presence of 60% effective monotherapy at 50% effective immune system or more. In contrast, the suppression of virus load in the patient is likely to occur for $\alpha \leq 0.1$ by implementing the same experiment using 60% effective combination therapy in the presence of more than 90% effective immune system.

Second analysis on the model may be performed in the immediate surroundings of 80% effective monotherapy and combination therapy to a HIV-infected patient. The findings, based on simulations for the correlated dynamic discrete model, suggest that the combination therapy is greatly efficient in mitigating the infectious viral load with a possibility of successful suppression for the proportion $\alpha \leq 0.5$, since in this case $R_d$ will be equal or inferior to one. On the contrary, by administrating only protease inhibitors in a similar experiment, the infectious virus is most likely to persist within an infected individual if $\alpha \geq 0.1$. The amount of viral load is not sufficiently reduced to a certain extent required for $R_d < 1$.

Alternatively, to further verify the possibility of successful persistence or inhibition of infectious viral load in a patient, we conduct this experiment with a proportion value of pre-existing activated CD4$^+$ T cells close to unity to perturb the dynamics of the HIV model, these experimental results are also intriguing. To control and bring down the volume of viral load for monotherapy scenario, it is required to monitor treatment not less than 99% effective, and in some cases it is impossible to mitigate HIV risk in vivo. However the consequence of administrating two drugs is a success for mitigation and prevention of infectious virus load using antiretroviral treatment that is 90% effective or more if $\alpha$ is close to one.

Besides, Table 4 depicts the steady-state values of the viral load with multiple parameter values for the effectiveness of the inhibitors (RT and PIs). In the numerical simulation, identical efficiency levels were conducted for the management of HIV infection in vivo using the mathematical model (3.8−3.10) [14]. It is clearly illustrated that as the efficiency level of the drugs is increased, the infectious virus density decreases. With the administration of 99% effective combination therapy (that is, $E_{RT} = E_{PI} = 0.99$), however, the two steady states exchange their stability, and the virus particle density converges to zero [14]. The endemic equilibrium loses its stability and a stable disease-free equilibrium appears as the basic reproduction number falls behind unity. In such a scenario, the associated reproduction number being inferior to unity becomes a necessary and
sufficient condition for disease elimination to the HIV-infected patient. This result is, of course, consistent with the theoretical analysis of previous sections.

| $E_{PI}$ | $E_{RT}$ | $V_I$ |
|----------|----------|------|
| 0.2      | 0.2      | 356.44 |
| 0.6      | 0.6      | 282.69 |
| 0.99     | 0.99     | 0     |

5.5. Identification of regions for incompatible estimated densities. Our objective here is to identify regions where solutions generated from the numerical estimation for the correlated with dynamic discrete model is inconsistent with the behavior of solutions of the continuous HIV infection model. Based on the description of parameters in HIV model and their estimated values presented in Table 4, incompatible iterative solutions is most likely to be generated in the regions when the key parameter $e_1$ is positive. As discussed previously, the estimated parameter $c$ can hold negative values conjunction with positive values for $e_1$.

In order to get more insight into the effects of the key parameter $c$ on the perturbation of the solution, we conducted another experiment using the function $E_{RT} = \frac{\alpha}{\alpha + \gamma}$ for the effectiveness of reverse transcriptase inhibitors proportional to the pre-existing activated CD4$^+$ T cells, $\alpha$. In Figure 4, we observe that the effectiveness of reverse transcriptase inhibitors decline as the magnitude of the rate of proliferation of CD4$^+$ T cells is increased from 0 to 1. Hence this can significantly reduce the area where $e_1$ can be positive shrinking the regions of incompatible iterative solutions for numerical estimations.

**FIGURE 3.** A comparison between effectiveness of antiretroviral monotherapy versus combination therapy using the quantity threshold $R_d = \frac{\tilde{e}_2 \tilde{e}_4}{\alpha_1^* e_3^*}$ is studied in this experiment related to the multiple sets of variables ($E_{RT}$, $E_{PI}$, $\alpha$). The horizontal and vertical axes are used for monotherapy or combination therapy, and the effect of CTL response respectively. Based on simulations and theoretical results, an effective treatment strategy for the removal of integrated HIV cells is identified by the administration of combination therapy. From both experiments, we observe that the possibility of survival of viral load using monotherapy is more than 99% for some HIV-infected patients while it can be broadly reduced to 80% by intervention of both $E_{RT}$ and $E_{PI}$.
6. Conclusion

This paper presents a method for analogy in continuous HIV infection model, system (2.1)–(2.3), with estimation of correlated dynamic discrete model, system (3.8)–(3.10). We primarily construct the compartmental model of HIV infection for three different cell types, i.e. susceptible, infected, and infectious categories. The model simulates the interaction between CD4$^+$ T cells and HIV in vivo when combination antiretroviral therapy is used for the management of infection. Basically, reverse transcriptase inhibitors and protease inhibitors are exerted for the perturbation of HIV. Developing the robust numerical method [3,3] we can successfully identify dynamics of behavioral changes in solutions of non-denationalized system (3.8)–(3.10) by the quantity threshold $R_d$. A complete proof for the convergence of the proposed estimation solutions to the endemic equilibrium point is obtained for the Open problem given in [44, Section 4.3] with the assumptions imposed to the set of parameter values. The findings show that the burden of characterizing dynamics of the continuous HIV infection model (2.1)–(2.3) can be reduced to the computational discrete model at each iteration by efficient use of the estimation algorithm [3,3] and the information obtained on previous stages.

Next a reliable comparison for the original deterministic HIV infection model with correlated dynamic discrete model is studies to analyze theoretically the long-term and oscillatory behavior of solutions. The results demonstrate that the estimation accuracy of the proposed numerical method is an efficient algorithm for solving the dynamic continuous model in conjunction with $e_1 \leq 0$, since similar results for both models are achieved. The main difference turns out to be in the qualitative behaviors of solutions of the models when $e_1 > 0$. Theoretical results and extensive experiments on artificial data with multiple sets of parameter values show that the discrete model conducted by the computational method conducted can behave quite different with the continuous deterministic model with HIV infection when $e_1 > 0$. Roughly speaking, the experiments demonstrate that system (2.6) can attain bounded or unbounded solutions [3] while the qualitative behavior of system (3.8)–(3.10) with different initial values can lead to serious misspecification errors referred to as forbidden sets, see Appendix A. In analysis of system (3.8)–(3.10), the paper establishes the complete convergence of the solutions to the nonnegative equilibrium points depending on the quantity threshold $R_d$; it then follows that no bistability occurs to the solutions and a forward bifurcation is observed when the equality $e = (b - 1)(1 - d)(1 - f)$ hold.

![Figure 4](image-url)  
**Figure 4.** A comparison analysis for different values of the rate of proliferation of CD4$^+$ T cells. The parameter $e_1$ ($e$, respectively) can be positive (negative) in the area delimited by each curve, $E_{RT}$ axis and the constant value $E_{RT} = 1$. Different curves are generated by the function $E_{RT} = \frac{\alpha}{\alpha + r}$ with respect to the proportion of pre-existing activated CD4$^+$ T cells, $\alpha$, for $r = 0, 0.03, 0.2, 0.8$, respectively.
The theoretical results follow by implementation of several experiments with respect to numerical algorithm to verify, among other things, the effect of multiple parameter values for time-step and immune response. For instance, we show that the numerical method was a very robust and efficient technique in terms of stability to solve the continuous HIV infection system for large/small time steps since the equilibria and the stability conditions are independent of the time step. This was claimed without theoretical results by Gumel et al. \[14\].

Numerical simulations also indicate that transitory oscillations are observed for about the first 100 time units and no sustained oscillations are observed when the endemic equilibrium point appears to be stable for lower values of $R_d$ close to unity but not for significantly large values. However, the time periods of oscillations to the solutions of the model become shorter and rapid in conjunction with occurrence of higher amplitudes of oscillations when the threshold level of basic reproduction number exceeds unity and is maintained above a certain threshold sufficiently large. Besides, we observe that the qualitative oscillatory behavior of the correlated dynamic discrete model is not substantially perturbed by the implementation of various parameter values for $c$.

Further computational experiments are performed for the within-host infectious model in order to identify an effective treatment strategy for the control of HIV infection by application of single/multiple anti-HIV prophylactic medications within a patient. An intuitive comparison for both combination antiretroviral therapy and monotherapy is described for several case studies using multiple sets of variables $(E_{RT}, E_{PI}, \alpha)$. We subsequently study the possibility of successful persistence or inhibition of infectious viral load. In fact, we conduct these experiments to investigate the qualitative effect of various proportion values of pre-existing activated CD4$^+$ T cells through perturbation of dynamics of the HIV model. To control and bring down the volume of viral load for monotherapy scenarios, the findings suggest that, in some cases, it is impossible to mitigate HIV risk in vivo, or it is required to monitor antiretroviral treatment that is 99% effective or more. However the consequence of administrating two drugs is a success for mitigation and prevention of infectious virus load. Especially, if $\alpha$ is close to one, the virus particles can be significantly inhibited in the presence of only 90% effective combination therapy.

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APPENDIX A. DYNAMICS OF SOLUTIONS WITH NEGATIVE PARAMETER $c$

In this section, $c$ is considered a negative number. As we will see in the next section, this situation is equivalent to $e_1 > 0$ in the continuous model.

In this case we have again two equilibrium points (3.11) and (3.12). But the equilibrium point (3.12) has negative components, i.e. $\tilde{y}$ and $\tilde{z}$, while (3.12) is locally asymptotically stable (Theorem 3.5). However, if we can show that the solution eventually enters a negative area of $\mathbb{R}^3$, then viral load can be suppressed from the host.

Theorem A.1. The following statements are true:

(i) Assume that $x_0 \geq -1$, $y_0 = 0$, and $z_0 = 0$, then $x_n > 0$, $y_n = 0$, and $z_n = 0$.

(ii) Assume that $x_0 \geq -1$, $y_0 < 0$, and $z_0 < -\frac{b}{c}$, then $x_n \geq 0$, $y_n < 0$, and $z_n < 0$.

Proof. The proof is an obvious result of system (3.8)–(3.10). \hfill $\square$

Now if we multiply the second and third equations of system (3.8)–(3.10) by $-1$, the change of variables $X_n = x_n$, $Y_n = (-y_n)$, $Z_n = (-z_n)$ gives system (3.8)–(3.10) with $c$ substituted by $(-c)$ which is positive in the first equation, and then we have $\{(X_n, Y_n, Z_n)\}_{n=1}^\infty \subset \mathbb{R}_+^3$. As a result, the dynamic of the solution when $c$ is negative with $x_0 \geq -1$, $y_0 < 0$, and $z_0 < -\frac{b}{c}$ is exactly the same as the positive case.

For other situations, it is not possible to verify the dynamics of solutions, since it is difficult to find the forbidden set $F$, the set of initial conditions $(x_0, y_0, z_0) \in \mathbb{R}^3$ through which the denominator $(b + cz_n)$ in equation (3.8) will become zero for some value of $n \geq 0$. Note that the situation $c < 0$, $x_0 \geq -1$, $y_0 < 0$, and $z_0 < -\frac{b}{c}$ in (3.8)–(3.10) corresponds to $e_1 > 0$, $x_0 \geq 0$, $y_0 < 0$, and $z < 0$ in the continuous model (2.6).

However we can leave a conjecture here that with an initial solution in this form $(x_0, y_0, z_0) \in \mathbb{R}^3 \setminus F$, the solution will become eventually as follows:

$$x_n \geq 0, \quad y_n \leq 0, \quad \text{and} \quad z_n \leq 0.$$  

A.1. Sensitivity analysis for negative parameter experiments.

Example A.2. In order to test the stability and convergence properties of the scheme constructed in Sections 5.4, 5.5, and 5.6, we use the method to simulate the model (3.8)–(3.10) with the initial values and parameter $(x_0, y_0, z_0) = (1, 0, 10^{-10})$, $b = 2$, $c = -1$, $d = 0.5$, $e = 1$, and $f = 0.5$.

We have clearly that $e > (b - 1)(1 - d)(1 - f)$, therefore, the equilibrium point, $(0.25, -1.5, -3)$, is locally asymptotically stable. Table 5 illustrates the global asymptotical stability of the equilibrium point $(0.25, -1.5, -3)$. 

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Example A.3. In this example, we assume $b = 5$, $c = -1$, $d = 0.2$, $e = 1$, and $f = 0.5$. We consider two solutions of (3.8)–(3.10) with respect to two initial values $(0.4, 0.75, 1.5 + 10^{-5})$ and $(0.4, 0.75, 1.5 - 10^{-5})$.

We observe that $e < (b - 1)(1 - d)(1 - f)$, therefore, the equilibrium point, $(0.25, 0, 0)$, is locally asymptotically stable. Table 6 and 7 illustrate the global asymptotical stability of the equilibrium point $(0.25, 0, 0)$. With the initial value $(0.4, 0.75, 1.5 + 10^{-5})$, $y_n$ and $z_n$ are negative after finite iterations. While for the initial value $(0.4, 0.75, 1.5 - 10^{-5})$, each component of $(x_n, y_n, z_n)$ is positive.

Table 5. Negative parameter together with positive initial values leads to negative solutions, that is, a small portion of viral load can be suppressed immediately.

| $n$ | Density of $x_n$ | Density of $y_n$ | Density of $z_n$ |
|-----|------------------|------------------|------------------|
| 0   | 1                | 0                | $10^{-10}$       |
| 10  | $1.000000015$    | $0.2955390683 \times 10^{-7}$ | $0.4037138739 \times 10^{-7}$ |
| 50  | $0.2502325578$   | $-1.499534885$   | $-2.997032087$   |
| 100 | $0.2500000000$  | $-1.500000000$  |                  |

Table 6. Positive initial values and negative parameter converges eventually to zero but not inside the first octant.

| $n$ | Density of $x_n$ | Density of $y_n$ | Density of $z_n$ |
|-----|------------------|------------------|------------------|
| 0   | 0.4              | 0.75             | $1.5 + 10^{-9}$  |
| 20  | 0.4000775562     | 0.7503877812     | 1.500649000      |
| 100 | 0.2499950251     | $-0.2487438382 \times 10^{-4}$ | $-0.6262803901 \times 10^{-4}$ |
| 200 | 0.2500000000     | $-0.187945081 \times 10^{-12}$ | $-0.4732063579 \times 10^{-12}$ |

Table 7. Negative parameter and positive initial values leads to positive solutions, that is, the viral load can still persist. One may compare this result with Table 6.

| $n$ | Density of $x_n$ | Density of $y_n$ | Density of $z_n$ |
|-----|------------------|------------------|------------------|
| 0   | 0.4              | 0.75             | $1.5 - 10^{-5}$  |
| 20  | 0.3999225278     | 0.7496126391     | 1.499351619      |
| 100 | 0.2500297591     | $0.1487952268 \times 10^{-3}$ | $0.3746036600 \times 10^{-3}$ |
| 200 | 0.2500000000     | $0.1124473755 \times 10^{-11}$ | $0.2831137823 \times 10^{-11}$ |