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Modeling and Analysis of Population Dynamics of Human Cells Pertaining to HIV/AIDS with Treatment

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Abstract: In this paper, a mathematical model has been formulated to describe the population dynamics of human cells pertaining to the HIV/AIDS disease with ART as treatment and is analyzed. The human cells have been divided into four compartments Susceptible – Asymptomatic – Symptomatic – AIDS (SAIV). The well posedness of the four dimensional dynamical system is proved and the steady states of the model are identified. Additionally, parametric expression for the basic reproduction number is constructed following next generation matrix method and analyzed its stability using Routh Hurwitz criterion. From the analytical and numerical simulation studies it is observed that if the basic reproduction is less than one unit then the solution converges to the disease free steady state i.e., disease will wipe out and thus the treatment is said to be successful. On the other hand, if the basic reproduction number is greater than one then the solution converges to endemic equilibrium point and thus the infectious cells continue to replicate i.e., disease will persist and thus the treatment is said to be unsuccessful. Sensitivity analysis of the model parameters is conducted and their impact on the reproduction number is analyzed. Finally, the model of the present study simulated using MATLAB. The results and observations have been included in the text of this paper lucidly.

Keywords: HIV, ART, Basic Reproduction Number, Stability Analysis, Routh Hurwitz Criterion

1. Introduction

The Human Immunodeficiency Virus HIV infects cells of the immune system as well as that of the central nervous system inhuman body. The T-helper lymphocytes are the main type of cells that will be infected by HIV disease. It is well known that the role of these T-helper lymphocytes cells in the immune system is to coordinate with the actions of other immune system cells. A large reduction in the number of these cells results in weakening the immune system [1, 2].

HIV infects the T-helper cells because it has the protein called CD4+ on its surface, which HIV uses to attach itself to cells before entering to them. That is why the T-helper cell is referred to as a CD4+T lymphocyte. Once it attaches itself into a cell, HIV produces new copies which are capable of infecting other cells.

According to WHO clinical staging of HIV/AIDS, HIV infection has four distinct stages viz., acute stage, Asymptomatic stage, Asymptomatic stage and Advanced AIDS stage [3]. These four stages of the disease have been introduced in what follows.

Stage 1 (Primary HIV infection): First stage of HIV infection is called primary infection stage. Primary infection begins shortly after an individual becomes infected with HIV for the first time. This stage lasts for a few weeks. During this period, individuals experience Flu like symptoms. Very few individuals seek treatment during this stage and those are usually misdiagnosed as if they are suffering from general viral infection. It is common that whenever an HIV test is performed in a medical lab then the result may come out to be negative. The reason for such negative results is antibodies which are yet not produced by the individual's immune system. Since antibodies have not yet been developed, HIV continues to replicate, resulting in a very high level of the virus [4]. Few weeks after getting the infection, the infected individuals become highly infectious. At this stage there would be a large amount of HIV in the peripheral blood amounting around 106 copies of virus per micro-litter µl of blood. Peripheral blood is the blood which is in the circulating system but not in the lymphatic system,

bone marrow, liver. Antibodies and cytotoxic lymphocyte start getting produced in response to the virus which is known as sero-conversion. At this stage about 20 percent of people who are HIV positive show symptoms which are not mild. However, any diagnosis for detecting HIV infection at this stage will go wrong as already mentioned. Those who believe that they were exposed to HIV should repeat the medical test after six months.

Stage 2 (Asymptomatic HIV): In the second stage, individuals become free from all types of symptoms of HIV although there will be some swollen glands. The HIV appears in blood in a very low Level, but is detectable. If an HIV test is performed, the result will come out to be positive. While the individuals remain asymptomatic, the HIV in their blood continues to reproduce constantly. This stage lasts for about ten years. However, the period of second stage can be much longer or shorter depending on the individual and is also characterized by a CD4+count whose normal count is around 500 cells per µl.

Stage 3 Symptomatic HIV: In the third stage, symptoms start appearing and the immune system becomes so damaged by HIV. Further, it leads to greater destruction ofCD4+ cell and the immune system will not able to replace them. By now the immune system fails and as a result the symptoms start developing [3]. Symptoms are typically mild initially and they gradually become more severe. Opportunistic infections, infections that take advantage of the vulnerable immune system, begin to occur. These infections affect almost all the systems of the body and include both infections and cancers. Some common opportunistic infections include tuberculosis, cytomegalovirus, and shingles. In this stage HIV infection is often characterized by multi-system diseases and infections in body. Treatment for a particular infection or cancer is often carried out. However, the main cause is the action of HIV as it attacks the immune system. Unless HIV is reduced the immune suppression will continue to be weaker.

Stage 4 (Acquired Immune Deficiency Syndrome AIDS): In fourth and last stage, a person can be medically tested positive as having AIDS. The progression to AIDS can be characterized by CD4+ count which is 200 per ml or below in a patient, while it is around 1000 per ml in a normal person. At this stage, the infected individual is likely to develop opportunistic infections in their respiratory system, gastro-intestinal system, central nervous system and on the skin as well. Once a person is diagnosed with AIDS, the AIDS status is permanent. A blood test can determine if a person is infected with HIV, but if a person tests positive for HIV, it does not necessarily mean that the person has AIDS. A diagnosis of AIDS is made by a physician according to the CDC AIDS Case definition.

Organization of the paper: In Section 2, assumptions of the model are stated and based on which a mathematical model for describing the population dynamics of human body cells pertaining to the HIV/AIDS disease is formulated.

In section 3, well possedness of the model formulation, stability analysis of the equilibrium points and reproduction number are included.

In Section 4, numerical simulation studies of the model equations are performed by assigning various sets of numerical values to the model parameters.

In Section 5 sensitivity analysis of model parameters towards the reproduction number is carried out.

In section 6 Result and Discussion are presented. Finally in Section 7, conclusions are stated.

2. Model Formulation

In the present model describing Human Immunodeficiency virus (HIV) with treatment the total human body cells are divided into four classes: (i) Susceptible cells class. It is denoted by $S(t)$. These susceptible cells are capable of becoming infected cells in future. These include new cells that not infected yet. (ii) Asymptomatic cells class. It is denoted by $A(t)$. This class consists of cells which are infected with virus but shows no signs of infections. These cells are active to transmit infections to other cells but they still continue as normal. (iii) Symptomatic cells class. It is denoted by $I(t)$. This class consists of infectious cells and they show signs of infections. Such cells manifest their weakness as they harmed by virus. (iv) AIDS cells class. It is denoted by $V(t)$. They are cells that highly contains virus that weakens T-helper cells. This categorical cell requires high medications and cares.

Here, a mathematical model of the Human Immunodeficiency virus (HIV) is constructed based on the following assumptions made on the human body cells:

i. The total population size of human body cells is assumed to be constant.
ii. Both the numbers of births and deaths of cells are equal.
iii. Human Immunodeficiency virus (HIV) model classifies the cell population into four compartments SAIV at any time.
iv. Susceptible cells are recruited into the compartment $S(t)$ at a constant rate τ.
v. Susceptible cells are infected when they come into effective contact with asymptomatic cells and join asymptomatic cells class at a rate β.
vi. Asymptomatic cells join symptomatic cells at a rate α and AIDS cells at arate δ.
vii. The symptomatic cells join AIDS cells class at a rate ω.
viii. All types of cells suffer natural mortality with a rate μ.
ix. AIDS cells die of infection at a rate γ.
x. Symptomatic cells die due at the rate ofρ due to disease.
xi. Asymptomatic cells die due to disease at the rate of ρ.
xii. Asymptomatic and Symptomatic cells are treated

All parameters used in the model are positive.

Table 1. *Notations and description of model variables.*

Variable	Description
S(t)	Population size of susceptible cells
A(t)	Population size of asymptomatic cells
I(t)	Population size of symptomatic cells
V(t)	Population size of AIDS cells

Table 2. *Notations and description of model parameters.*

Parameter	Description
τ	Recruitment rate of susceptible cells. With this rate new cells will born and they will enter into susceptible class.
β	Transmission rate of infection cells. With this rate cells transfer from compartment S to A.
α	Rate of cells transferring from compartment A to I.
ω	Rate of cells transferring from compartment I to V.
ϕ	Treatment rate of I.
γ	Death rate of cells due to infection. With this rate cells of V compartment die of the disease.
μ	Natural death rate. With this rate cells of all compartments die naturally.
η	Treatment rate of asymptomatic cells I.
ρ	Death rate of symptomatic cells I due to disease.

Based on the basic assumptions together with the description of both model variables and parameters the schematic diagram of the model compartments and the cell flow directions can be given as in Figure 1.

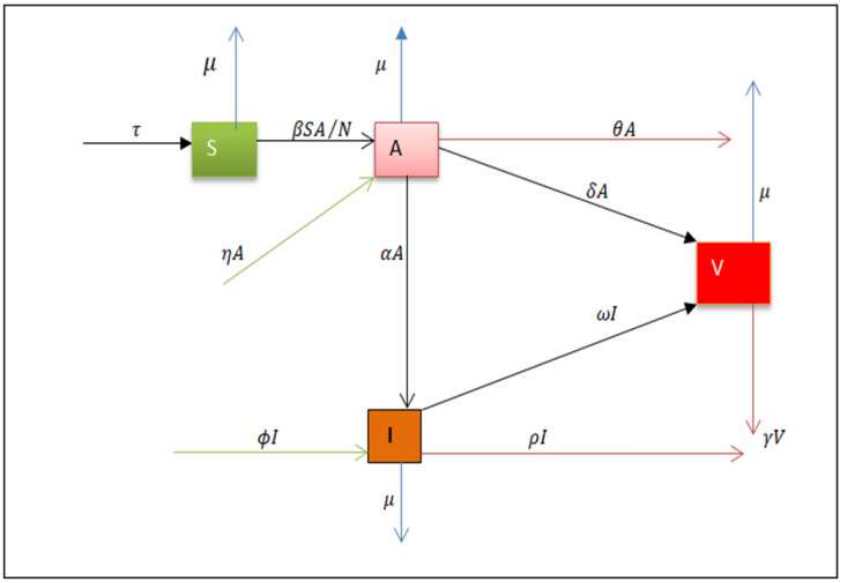

Figure 1. *Schematic diagram of compartmental structure of the model.*

Based on the model assumptions, the notations of variables and parameters and the schematic diagram, the model equations are formulated and are given as follows:

$$dS/dt = \tau - (\beta AS/N) - \mu S \quad (1)$$

$$dA/dt = (\beta AS/N) - (\alpha + \mu + \theta + \delta - \eta)A \quad (2)$$

$$dI/dt = \alpha A - (\omega + \mu + \rho - \emptyset)I \quad (3)$$

$$dV/dt = \delta A + \omega I - (\mu + \gamma)V \quad (4)$$

The non-negative initial conditions of the model equations (1) – (4) are denoted by $S(0) > 0, A(0) \geq 0, I(0) \geq 0, V(0) \geq 0$. This system consists of four first order non-linear ordinary differential equations.

3. Mathematical Analysis of the Model

In this section mathematical analysis of the present improved and modified model is conducted. The analysis consists of the features including (i) existence, positivity and boundedness of solutions (ii) steady states (iii) disease free equilibrium points (iv) endemic equilibrium points (v) basic reproduction number (vi) stability analysis of the disease free equilibrium points (vii) local stability of disease free equilibrium point (viii) global stability of disease free equilibrium point (ix) stability analysis of endemic equilibrium point and (x) local stability of endemic equilibrium point. These mathematical aspects of the model are presented and discussed in the following sub-sections respectively.

3.1. Existence, Positivity and Boundedness of Solution

In order to show that the model is biologically valid, it is required to prove that the solutions of the system of differential equations (1) – (4) exist and are both positive and bounded for all time. It is done starting with proving Lemma 1.

Lemma 1 (Positivity) Solutions of the model equations (1) – (4) together with the initial conditions $S(0) \geq 0, A(0) \geq 0, I(0) \geq 0, V(0) \geq 0$ are always positive (OR) the model variables $S(t), A(t), I(t)$, and $V(t)$ are positive for all t and will remain in $\mathbb{R}^4_+$.

Proof Positivity of the solutions of model equations is shown separately for each of the model variables

$S(t), A(t), I(t)$, and $V(t)$.

Positivity of $S(t)$ *:* The model equation (1) given by $dS/dt = \tau - (\beta AS/N) - \mu S$ can be expressed without loss of generality, after eliminating the positive termτ appearing on the right hand side, as an inequality as $dS/dt \geq -[\mu + (\beta A/N)]S$. Using variables separable method and on applying integration, the solution of the foregoing differentially inequality can be obtained as $S(t) \geq S(0)e^{-\mu t - \beta \int A(t)dt}$. Recall that an exponential function is always non–negative irrespective of the sign of the exponent i.e. the exponential function $e^{-\mu t - \beta \int A(t)dt}$ is a non-negative quantity. Hence, it can be concluded that $S(t) \geq 0$.

Positivity of $A(t)$ *:* The model equation (2) given by $dA/dt = (\beta AS/N) - (\alpha + \mu + \theta + \delta - \eta)A$ can be expressed without loss of generality, after eliminating positive term $(\beta AS/N)$ and ηA which are appearing on the right hand side, as an inequality as $dA/dt \geq -(\alpha + \mu + \theta + \delta)A$. Using variables separable method and on applying integration, the solution of the foregoing differentially inequality can be obtained as $A(t) \geq A(0)e^{-(\alpha+\mu+\theta+\delta)t}$. Recall that an exponential function is always non–negative irrespective of the sign of the exponent i.e. the exponential function $e^{-(\alpha+\mu+\theta+\delta)t}$ is a non-negative quantity. Hence, it can be concluded that $A(t) \geq 0$.

Positivity of $I(t)$ *:* The model equation (3) given by $dI/dt = \alpha A - (\omega + \mu + \rho - \emptyset)I$ can be expressed without loss of generality, after eliminating the positive terms (αA) and (ϕI) which are appearing on the right hand side, as an inequality as $dI/dt \geq -(\omega + \mu + \rho)I$. Using variables separable method and on applying integration, the solution of the foregoing differentially inequality can be obtained as $I(t) \geq I(0)e^{-(\omega+\mu+\rho)t}$. Recall that an exponential function is always non–negative irrespective of the sign of the exponent i.e. the exponential function $e^{-(\omega+\mu+\rho)t}$ is a non-negative quantity. Hence, it can be concluded that $I(t) \geq 0$.

Positivity of $V(t)$ *:* The model equation (4) given by $dV/dt = \delta V + \omega I - (\mu + \gamma)V$ can be expressed without loss of generality, after eliminating the positive terms $\delta V, \omega I$, and γV which are appearing on the right hand side, as an inequality as $dV/dt \geq -(\mu + \gamma)V$. Using variables separable method and on applying integration, the solution of the foregoing differentially inequality can be obtained as $V(t) \geq V(0)e^{-(\mu+\gamma)t}$. Recall that an exponential function is always non–negative irrespective of the sign of the exponent i.e. the exponential function $e^{-(\mu+\gamma)t}$ is a non-negative quantity. Hence, it can be concluded that $V(t) \geq 0$.

Thus, the model variables $S(t), A(t), I(t)$, and $V(t)$ representing population sizes of various types of human body cells are positive quantities and will remain in $\mathbb{R}_+^4$ for all$t$.

Lemma 2 (Boundedness) The positive solutions of the system of model equations (1) – (4) are bounded. That is the model variables $S(t), A(t), I(t)$ and $V(t)$ are all bounded for all t.

Proof: Recall that each population size is bounded if and only if the total population size is bounded. Hence, in the present case it is sufficient to prove that the total population size $N = S(t) + A(t) + I(t) + V(t)$ is bounded for all t. It can be begun by showing that all feasible solutions are uniformly bounded in a proper subset $\Omega \in \mathbb{R}_+^4$ where the feasible region Ω is given by $\Omega = \{(S, A, I, V) \in \mathbb{R}_+^4;\ \mathrm{N} \leq [\tau/(\mu - \eta - \phi)]\}$.

Now, summation of all the four equations (1) – (4) of the model gives $\mathrm{dN(t)/dt} = \tau + \eta\mathrm{A} + \phi\mathrm{I} - \mu\mathrm{N(t)} - \theta\mathrm{A} - \rho\mathrm{I} - \gamma\mathrm{V}$. It can be expressed without loss of generality, after eliminating the negative terms $(-\theta\mathrm{A} - \rho\mathrm{I} - \gamma\mathrm{V})$ which are appearing on the right hand side, as an inequality as $\mathrm{dN(t)/dt} \leq [\pi + (\eta + \phi - \mu)\,\mathrm{N(t)}]$. Equivalently this inequality can be expressed as a linear ordinary differential inequality as $[\mathrm{dN(t)/dt}] + [(\eta + \phi - \mu)\mathrm{N(t)}] \leq \tau$ giving general solution upon solving as $\mathrm{N(t)} \leq [\tau/(\mu - \eta - \phi)] + ce^{-(\mu-\eta-\phi)t}$. But, the term $N(0)$ denotes the initial values of the respective variable i.e. $\mathrm{N(t)} = \mathrm{N(0)}$ at $\mathrm{t} = 0$. Thus, in terms of a new parameter $\mu_d = (\mu - \eta - \phi) > 0$, the particular solution can be expressed as $\mathrm{N(t)} \leq (\tau/\mu_d) + [\mathrm{N(0)} - (\tau/\mu_d)]e^{-(\tau/\mu_d)t}$. Further, it can be observed that $N(t) \to (\tau/\mu_d)$ as $t \to \infty$. That is, total population size $N(t)$ takes off from a value $\mathrm{N(0)}$ at the initial time $\mathrm{t} = 0$ and ends up with a bounded value (τ/μ_d) as the time t progresses to infinity. Thus, it can be concluded that $N(t)$ is bounded as $0 \leq N(t) \leq (\tau/\mu_d)$.

Therefore, (π/μ_d) where $\mu_d = (\mu - \eta - \phi)$ is an upper bound of $N(t)$. Hence, feasible solution of the system of model equations (1) – (4) remains in the region Ω which is positively invariant set. Thus, the system is biologically meaningful and mathematically well posed in the domainΩ. Further, it is sufficient to consider the dynamics of the populations represented by the model system (1) – (4) in that domain.

Therefore, it can be summarized the result of Lemma 2 as "the model variables $S(t), A(t), I(t)$, and $V(t)$ are bounded for all t". Also, here Lemma 2 sets a restriction on the model parameters as $(\mu - \eta - \phi) > 0$ or equivalently $\mu > (\eta + \phi)$.

Lemma 3 (Existence) Solutions of the model equations (1) – (4) together with the initial conditions $S(0) > 0, A(0) \geq 0, I(0) \geq 0, V(0) \geq 0$ exist in $\mathbb{R}_+^4$ i.e. the model variables $S(t), A(t), I(t)$, and $V(t)$ exist for all t and will remain in$\mathbb{R}_+^4$.

Proof: Let the right hand sides of the system of equations (1) – (4) are expressed as follows:

$$dS/dt = \tau - (\beta AS/N) - \mu S \equiv g_1$$

$$dA/dt = (\beta AS/N) - (\alpha + \mu + \theta + \delta - \eta)A \equiv g_2$$

$$dI/dt = \alpha A - (\omega + \mu + \rho - \emptyset)I \equiv g_3$$

$$dV/dt = \delta A + \omega I - (\mu + \gamma)V \equiv g_4$$

According to Derrick and Groosman theorem, let Ω denote the region $\Omega = \{(S, A, I, V) \in \mathbb{R}_+^4;\ \mathrm{N} \leq (\pi/\mu_d)\}$. Then equations (1) – (4) have a unique solution if $(\partial f_i)/(\partial x_j) : i, j = 1, 2, 3, 4$ are continuous and bounded inΩ. Here, $x_1 = S, x_2 = A, x_3 = I, x_4 = V$.

The continuity and the boundedness of g_1, g_2, g_3, g_4 are verified as here under:

For g_1:

$$|(\partial g_1)/(\partial S)| = |-[\mu + \beta A/N]| < \infty$$

$$|(\partial g_1)/(\partial A)| = |-\beta S/N| < \infty$$

$$|(\partial g_1)/(\partial I)| = 0 < \infty$$

$$|(\partial g_1)/(\partial V)| = 0 < \infty$$

For g_2:

$$|(\partial g_2)/(\partial S)| = |\beta A/N| < \infty$$

$$|(\partial g_2)/(\partial A)| = |\beta S/N - (\alpha + \theta + \mu + \delta - \eta)| < \infty$$

$$|(\partial g_2)/(\partial I)| = 0 < \infty$$

$$|(\partial g_2)/(\partial V)| = 0 < \infty$$

For g_3:

$$|(\partial g_3)/(\partial S)| = 0 < \infty$$

$$|(\partial g_3)/(\partial A)| = |\alpha| < \infty$$

$$|(\partial g_3)/(\partial I)| = |-(\omega + \rho + \mu - \phi)| < \infty$$

$$|(\partial g_3)/(\partial V)| = 0 < \infty$$

For g_4:

$$|(\partial g_4)/(\partial S)| = 0 < \infty$$

$$|(\partial g_4)/(\partial A)| = |\delta| < \infty$$

$$|(\partial g_4)/(\partial I)| = |\omega| < \infty$$

$$|(\partial g_4)/(\partial V)| = |-(\mu + \gamma)| < \infty$$

Thus, all the partial derivatives $(\partial f_i)/(\partial x_j) : i, j = 1, 2, 3, 4$ exist, continuous and bounded in Ω. Hence, by Derrick and Groosman theorem, a solution for the model (1) – (4) exists and is unique.

3.2. Steady State Solutions

In order to understand the dynamics of the model, it is necessary to determine equilibrium points of the solution region. An equilibrium solution is a steady state solution of the model equations (1) – (4) in the sense that if the system begins at such a state, it will remain there for all times. In other words, the population sizes remain unchanged and thus the rate of change for each population vanishes. Equilibrium points of the model are found, categorized, stability analysis is conducted and the results have been presented in the following sub-sections:

3.2.1. Disease Free Equilibrium Point

Disease free equilibrium point is a steady state solution where there is no disease in the population. Now, absence of disease implies that $A(t) = I(t) = V(t) = 0$ and also setting the right hand sides of the model equations equal to zero results in giving

$$\tau - \mu S = 0$$

Solutions of which is the population size of the susceptible humans at the disease free equilibrium and is given by

$$S^0 = (\tau/\mu)$$

Thus, the disease free equilibrium point of the model equations (1) – (4) is given by

$$E_0 = \{S^0, \quad I^0, \quad A^0, \quad V^0\} = \{\tau/\mu, \quad 0, \quad 0, \quad 0\}$$

3.2.2. Endemic Equilibrium Point

The endemic equilibrium point $E_1 = \{S^1, \quad I^1, \quad A^1, \quad V^1\}$ is a steady state solution when the disease persists in the population. The endemic equilibrium point is obtained by setting rates of changes of variables with respect to time of model equations (1) – (4) to zero. That is, setting $dS/dt = dA/dt = dI/dt = dV/dt = 0$ the model equations take the form as

$$\tau - (\beta AS/N) - \mu S = 0 \tag{5}$$

$$(\beta AS/N) - aA = 0 \tag{6}$$

$$\alpha A - bI = 0 \tag{7}$$

$$\delta A + \omega I - cV = 0 \tag{8}$$

Here in (5) – (8), the quantities a, b, c represent the parametric expressions as $a = \alpha + \mu + \theta + \delta - \eta, b = \omega + \mu + \rho - \emptyset, c = \mu + \gamma$. Clearly, solutions of (5) – (8) will provide endemic equilibrium of the model equations and that is obtained as follows:

Now, (6) can be rearranged as $[(\beta S/N) - a]A = 0$ leading to the solutions $(\beta S/N) - a = 0$ or $A = 0$ or both. However, A does not vanish since the disease is assumed to persist. Thus, it leads to the only meaningful solution $(\beta S/N) - a = 0$ or equivalently $S = (aN/\beta)$. That is, the S^1 component of E_1 is given by

$$S^1 = (aN/\beta) = (a\tau/\beta u_d) = (\tau/\mu R_0) \tag{9}$$

Similarly, solving (7) and (8) gives expression for I and V as

$$I = (\alpha A/b) \tag{10}$$

$$V = (\delta A/c) + (\omega I/c) \tag{11}$$

Further, substitution of equation (9) into (5) gives $[\tau - \beta(a/\beta)(A) - \mu(a/\beta)] = 0$. But since $N = (\pi/\mu_d)$ and after some algebraic simplifications, an expression for A can be obtained as

$$A^1 = (\mu\tau/\beta\mu_d)(R_0 - 1) \tag{12}$$

Finally, substitution of A^1 into (10) and (11) respectively gives the expressions for I and V in terms of parameters as

$$I^1 = (\alpha\mu\tau/b\beta\mu_d)(R_0 - 1) \tag{13}$$

$$V^1 = (\mu\tau/\beta\mu_d)[(\delta/c) + (\omega\alpha/cb)](R_0 - 1) \tag{14}$$

Therefore, the endemic equilibrium point is given by $E_1 = \{S^1, \quad I^1, \quad A^1, \quad V^1\}$ where

$$S^1 = (a\tau/\beta u_d) = (\tau/\mu R_0)$$

$$A^1 = (\mu\tau/\beta\mu_d)(R_0 - 1)$$

$$I^1 = (\alpha\mu\tau/b\beta\mu_d)(R_0 - 1)$$

$$V^1 = (\mu\tau/\beta\mu_d)[(\delta/c) + (\omega\alpha/cb)](R_0 - 1)$$

3.3. Basic Reproduction Number

The basic reproduction number is denoted by R_0 and is defined as the expected number of people getting secondary infection among the whole susceptible population [13]. This number determines the potential for the spread of disease within a population. When $R_0 < 1$ each infected individual produces on average less than one new infected individual so that the disease is expected to die out. On the other hand if $R_0 > 1$ then each individual produces more than one new infected individual so that the disease is expected to continue spreading in the population. This means that the threshold quantity for eradicating the disease is to reduce the value of R_0 to less than one.

The basic reproductive number R_0 can be determined using the next generation matrix. In this method $R_0$is defined as the largest eigenvalue of the next generation matrix. The formulation of this matrix involves classification of all compartments of the model in to two classes: infected and non-infected. That is, the basic reproduction number cannot be determined from the structure of the mathematical model alone but depends on the definition of infected and uninfected compartments.

Assume that there are n compartments in the model and of which the first m compartments are with infected individuals [3]. From the system (1) – (4) the first three equations are considered and decomposed into two groups: F contains newly infected cases and V contains the remaining terms. Let $X = [S,\ A,\ I,\ V]^t$ be a column vector and the differential equations of the first three compartments are rewritten as $F(X) - V(X)$.

Now, let $F(X) = [F_1,\ F_2,\ F_3]^t$. Here (i) $F_1 = (\beta SA\ /\ N)$ denotes newly infected cases which arrive into the asymptomatic compartment, (ii) $F_2 = 0$ denotes newly infected cases arrived into the infectious compartment, and (iii) $F_3 = 0$ denotes newly infected case from susceptible compartment. Further, let $V(X) = [V_1,\ V_2,\ V_3]^t$. Here $V_1 = aA, V_2 = -\alpha A + bI$ and $V_3 = -\delta A - \omega I + \mu V$. Here, as it is already mentioned, the parameters a, b, c denote $a = \alpha + \mu + \theta + \delta - \eta, b = \omega + \mu + \rho - \emptyset, c = \mu + \gamma$.

The next step is the computation of square matrices F and V of order $m \times m$, where m is the number of infected classes, defined by $F = [\partial F_i(E_0)/\partial x_j]$ and $V = [\partial V_i(E_0)/\partial x_j]$ with $1 \le i, j \le m$, such that F is non-negative, V is a non-singular matrices and E_0 is the disease free equilibrium point DFE.

If F and V are non-negative and V is non-singular then V^{-1} is non-negative and thus FV^{-1} is also non-negative. Also, the matrix FV^{-1} is called the next generation matrix for the model. Finally, the basic reproduction number R_0 is given by $R_0 = \rho(\mathrm{F}V^{-1})$. In general, $\rho(A)$ denotes the spectral radius of matrix A and the spectral radius is the biggest non-negative eigenvalue of the next generation matrix.

The Jacobian matrices for $F(X)$ and $V(X)$ with respect to $(A,\ \ I,\ \ V)$ can be constructed as

$$J_F(X) = \begin{bmatrix} \frac{\beta S}{N} & 0 & 0 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{bmatrix} \quad J_V(X) = \begin{bmatrix} a & 0 & 0 \\ -\alpha & b & 0 \\ -\delta & -\omega & c \end{bmatrix}$$

The Jacobian of F and V at the disease free equilibrium point E_0 takes the form respectively as

$$J_F(E_0) = \begin{bmatrix} \beta\mu_d/\mu & 0 & 0 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{bmatrix} \quad J_V(E_0) = \begin{bmatrix} a & 0 & 0 \\ -\alpha & b & 0 \\ -\delta & -\omega & c \end{bmatrix}$$

It can be verified that the matrix $J_V(E_0)$ is non-singular as its determinant $det[J_F(E_0)] = abc$ is non-zero and after some algebraic computations its inverse matrix is constructed as

$$[J_V(E_0)]^{-1} = \begin{bmatrix} 1/a & 0 & 0 \\ \alpha/ab & 1/b & 0 \\ (\alpha\omega + b\delta)/(abc) & \omega/bc & 1/c \end{bmatrix}$$

The product of the matrices $J_F(E_0)$ and $[J_V(E_0)]^{-1}$ can be computed as

$$[J_F(E_0)][J_V(E_0)]^{-1}$$

$$= \begin{bmatrix} \beta\mu_d/\mu & 0 & 0 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{bmatrix} \begin{bmatrix} (1/a) & 0 & 0 \\ (\alpha/ab) & (1/b) & 0 \\ (\alpha\omega + b\delta)/(abc) & \omega/bc & (1/c) \end{bmatrix}$$

$$= \begin{bmatrix} \beta\mu_d/a\,\mu & 0 & 0 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{bmatrix}$$

Now, it is possible to calculate the eigenvalues of the matrix $[J_F(E_0)][J_V(E_0)]^{-1}$ to determine the basic reproduction number R_0 which is the spectral radius or the largest eigenvalue. Thus, the eigenvalues are computed by evaluating the characteristic equation $det\big[[J_F(E_0)][J_V(E_0)]^{-1} - \lambda I\big] = 0$ or equivalently solving

$$\begin{vmatrix} (\beta\mu_d/a\,\mu) - \lambda & 0 & 0 \\ 0 & -\lambda & 0 \\ 0 & 0 & -\lambda \end{vmatrix} = 0$$

It reduces to the cubic equation for λas $\lambda^2[(\beta\mu_d/a\,\mu) - \lambda] = 0$ giving the three eigenvalues as

$$\lambda_1 = (\beta\mu_d/a\,\mu), \lambda_2 = 0, \lambda_3 = 0$$

However, the largest eigenvalue here is $\lambda_1 = (\beta\mu_d/a\,\mu)$

and is the spectral radius or the threshold value or the basic reproductive number. Thus, it can be concluded that the reproduction number of the model is given by $R_0 = [(\beta\mu_d)/(\mu a)]$.

3.4. Stability Analysis of the Disease Free Equilibrium

In absence of the infectious disease, the model populations have a unique disease free steady state E_0. To find the local stability of E_0, the Jacobian method of the model equations evaluated at DEF E_0 is used. Also, to determine the global stability at E_0 M-matrix method given in [10] is used. It is already shown that the DFE of model (1) – (4) is given b$E_0 = \{\tau/\mu, \quad 0, \quad 0, \quad 0\}$. Now, following [5-8] the stability analysis of DFE is conducted and the results are presented in the form of theorems and proofs in the following.

3.4.1. Local Stability of Disease Free Equilibrium Point

Theorem 1: The DFE E_0 of the system (1) – (4) is locally asymptotically stable if $R_0 < 1$ and unstable if $R_0 > 1$.

Proof: Consider the right hand side expressions of the equations (1) – (4) as functions so as to find the Jacobian matrix as follows:

$$dS/dt = \tau - (\beta AS/N) - \mu S \equiv g_1(S, \quad A, \quad I, \quad V)$$

$$dA/dt = (\beta AS/N) - (\alpha + \mu + \theta + \delta - \eta)A \equiv g_2(S, \quad A, \quad I, \quad V)$$

$$dI/dt = \alpha A - (\omega + \mu + \rho - \emptyset)I \equiv g_3(S, \quad A, \quad I, \quad V)$$

$$dV/dt = \delta A + \omega I - (\mu + \gamma)V \equiv g_4(S, \quad A, \quad I, \quad V)$$

Now, the Jacobian matrix of $(g_1, \quad g_2, \quad g_3, \quad g_4)$ with respect to $(S, \quad A, \quad I, \quad V)$ is given by

$$J = \begin{bmatrix} -\mu - (\beta A/N) & -(\beta S/N) & 0 & 0 \\ (\beta A/N) & (\beta S/N) - a & 0 & 0 \\ 0 & \alpha & -b & 0 \\ 0 & \delta & \omega & -c \end{bmatrix} \quad (15)$$

Furthermore, the Jacobian matrix J of model at the disease free equilibrium E_0 reduces to

$$J(E_0) = \begin{bmatrix} -\mu & -(\beta\mu_d/\mu) & 0 & 0 \\ 0 & \left((\beta\mu_d/\mu) - a\right) & 0 & 0 \\ 0 & \alpha & -b & 0 \\ 0 & \delta & \omega & -c \end{bmatrix}$$

Now, the eigenvalues of $J(E_0)$ are required to be found. The corresponding characteristic equation $det[J(E_0) - \lambda I] = 0$ is expanded and simplified as follows:

$$\begin{vmatrix} -\mu - \lambda & -(\beta\mu_d/\mu) & 0 & 0 \\ 0 & \left((\beta\mu_d/\mu) - a\right) - \lambda & 0 & 0 \\ 0 & \alpha & -b - \lambda & 0 \\ 0 & \delta & \omega & -c - \lambda \end{vmatrix} = 0$$

$$-(\mu + \lambda)\begin{vmatrix} \left((\beta\mu_d/\mu) - a\right) - \lambda & 0 & 0 \\ \alpha & -b - \lambda & 0 \\ \delta & \omega & -c - \lambda \end{vmatrix} = 0$$

$$(\mu + \lambda)(c + \lambda)(b + \lambda)[\lambda - (1 - R_0)a] = 0$$

$$(\mu + \lambda)(c + \lambda)(b + \lambda))[(1 - R_0)a - \lambda] = 0$$

Thus, the four eigenvalues of the matrix $J(E_0)$ are determined as

$$\lambda_1 = -\mu$$

$$\lambda_2 = -c$$

$$\lambda_3 = -b$$

$$\lambda_4 = (R_0 - 1)a$$

It can be observed that the first two eigenvalues λ_1 and λ_2 are absolutely negative quantities. However, the remaining two λ_3 and λ_4 are also negatives so long as the following restrictions on the parameters are valid: a, b, c are positive and $R_0 < 1$.

Therefore, using [1, 10] it can be concluded that the DFE E_0 of the system of differential equations (1) – (4) is locally asymptotically stable if $R_0 < 1$ and unstable if $R_0 > 1$.

3.4.2. Global Stability of Disease Free Equilibrium Point

Theorem 2: The disease free equilibrium point E_0 of the model is globally asymptotically stable if $R_0 < 1$ and unstable if $R_0 > 1$.

Proof Using the comparison theorem the rate of change of the variables representing the disease classes of the model can be rewritten as

$$\begin{bmatrix} A^0 \\ I^0 \\ V^0 \end{bmatrix} = (F - V)\begin{bmatrix} A \\ I \\ V \end{bmatrix} - M\theta\begin{bmatrix} A \\ I \\ V \end{bmatrix} \quad (16)$$

Here in (16), F and V represent matrices at the disease free equilibrium point E_0 as

$$F = J_F(E_0) = \begin{bmatrix} \beta\mu_d/\mu & 0 & 0 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{bmatrix} \quad V = J_V(E_0) = \begin{bmatrix} a & 0 & 0 \\ -\alpha & b & 0 \\ -\delta & -\omega & c \end{bmatrix}$$

Also θ is a non – negative matrix. However, $M = [1 - (S^0/N^0)] = 0$ since $S^0 = (\tau/\mu)$ and $N^0 = (\tau/\mu)$. Therefore, the equation (16) reduces to the simplified form as

$$\begin{bmatrix} A^0 \\ I^0 \\ V^0 \end{bmatrix} \leq (F - V)\begin{bmatrix} A \\ I \\ V \end{bmatrix}$$

Now, $(F - V)$ can be computed as

$$F - V = \begin{bmatrix} \beta\mu_d/\mu & 0 & 0 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{bmatrix} - \begin{bmatrix} a & 0 & 0 \\ -\alpha & b & 0 \\ -\delta & -\omega & -c \end{bmatrix} = \begin{bmatrix} \beta\mu_d/\mu - a & 0 & 0 \\ \alpha & -b & 0 \\ \delta & \omega & -c \end{bmatrix} \quad (17)$$

The eigenvalues of the matrix (17) are found by evaluating the characteristic equation $\det[(F - V) - \lambda I] = 0$ as follows:

$$\begin{vmatrix} (\beta\mu_d/\mu - a) - \lambda & 0 & 0 \\ \alpha & -b - \lambda & 0 \\ \delta & \omega & -c - \lambda \end{vmatrix} = 0$$

$$(\beta - a - \lambda)(-b - \lambda)(-c - \lambda) = 0$$

$$[(\beta\mu_d/\mu) - a] - \lambda = 0, (-b - \lambda) = 0, (-c - \lambda) = 0$$

$$\lambda_1 = (\beta\mu_d/\mu) - a = (R_0 - 1)a, \lambda_2 = -b, \lambda_3 = -c$$

Parametric expressions for the notations a, b have been defined earlier. Here it can be observed that all the three eigenvalues $\lambda_1, \lambda_2, \lambda_3$ have negative real parts and hence the matrix is stable for $R_0 < 1$.

Therefore by the comparison theorem, it follows that $\{A,\ I,\ V\} \to \{0,\ 0,\ 0\}$ and the remaining equations of model (1) – (4) give the solution$E_0 = \{\tau/\mu,\ 0,\ 0,\ 0\}$. Thus, the system approaches to the DFE as time progresses i.e. $\{S,\ A,\ I, V\} \to E_0$ as $t \to \infty$. Hence, the disease free equilibrium point E_0 is globally asymptotically stable if $R_0 < 1$ and unstable if $R_0 > 1$.

3.5. Stability Analysis of Endemic Equilibrium Point

By definition it is true that at the endemic equilibrium point $E_1 = \{S^1,\ A^1,\ I^1,\ V^1\}$ is the point where the disease persists or exists. To analyze the local stability ofE_1, Jacobian of the model evaluated at that equilibrium point is used. Further, recall that the endemic equilibrium point $E_1 = \{S^1,\ A^1,\ I^1,\ V^1\}$ of the given model (1) – (4) is already computed. The local stability of endemic equilibrium point is stated and proved in Theorem 3.

Theorem 3: The endemic equilibrium point is locally asymptotically stable if $R_0 > 1$.

Proof: The stability analysis of E_1 is conducted by following the similar procedure adopted as in the case of E_0. Thus, the procedure starts with the construction of Jacobian matrix at E_1. Now, the Jacobian matrix of the model given in (15) at endemic equilibrium point E_1 takes the form as

$$S^1 = (a\tau/\beta u_d) = (\tau/\mu R_0)$$

$$A^1 = (\mu\tau/\beta\mu_d)(R_0 - 1)$$

$$I^1 = (\alpha\mu\tau/b\beta\mu_d)(R_0 - 1)$$

$$V^1 = (\mu\tau/\beta\mu_d)[(\delta/c) + (\omega\alpha/cb)](R_0 - 1)$$

$$J = \begin{bmatrix} -\mu - (\beta A^1/N) & -(\beta S^1/N) & 0 & 0 \\ (\beta A^1/N) & (\beta S^1/N) - a & 0 & 0 \\ 0 & \alpha & -b & 0 \\ 0 & \delta & \omega & -c \end{bmatrix}$$

$$J(E_1) = \begin{bmatrix} -R_0\mu & -a & 0 & 0 \\ \mu(R_0 - 1) & 0 & 0 & 0 \\ 0 & \alpha & -b & 0 \\ 0 & \delta & \omega & -c \end{bmatrix}$$

Now the trace of $J(E_1) = -R_0\mu - b - c$ is a negative quantity while $detJ(E_1) = (R_0 - 1)(abc\mu)$ is a positive quantity provided that $a, b, c, \mu, (R_0 - 1)$ are positive quantities. Hence, using [1, 10] it can be concluded that the endemic equilibrium point E_1 is locally asymptotically stable if $R_0 > 1$.

4. Numerical Simulation

In this section, numerical simulation study of model equations (1) – (4) is carried out using the software MATLAB. To conduct the study, a set of physically meaningful values are assigned to the model parameters. These values are either taken from literature or assumed on the basis of reality. These sets of parametric values are given under figures.

The following have been observed in Figure 2: (i) initially the population size of susceptible compartment S decreases. These cells get infected and migrate to asymptomatic compartment. At a later stage these susceptible cells increase because the production of new cells continues and the conversion of susceptible cells into asymptotic cells reduce due to treatment. (ii) Initially the population size of asymptomatic compartment A increases because body immune system has not yet started fighting against the HIV virus and as a result the susceptible cells get infected and become asymptomatic and joins this compartment. (iii) As human immune system start fighting the asymptomatic cells began decreasing (iv) Initially the population size of asymptomatic compartment A is increasing because body immune system has not yet started fighting the HIV virus.

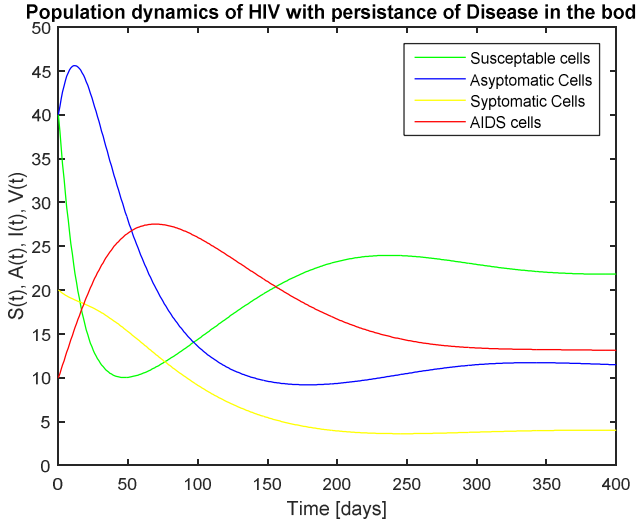

Figure 2. *Population dynamics of SAIV compartments with the parametric values* $\tau = 20, \mu = 0.005, \beta = 0.076, \alpha = 0.008, \theta = 0.01, \delta = 0.01, \eta = 0.002, \omega = 0.01, \rho = 0.01, \phi = 0.002$.

In figure 3, it can be observed that the extinction of the virus for many days but finally the virus persists in human cells without showing any signs of infections. This happens because of treatment properly taken by the patients. The patient lives as normal as asymptomatic stage for long period of time.

The differences and similarities between the existing and modified model are given respectively in the tables 3 and 4.

Table 3. *Differences of existing and modified model.*

Differences		
SN	**Existing model [11]**	**Modified (Present) model**
1	Has Three compartments	Has four compartments
2	Has health cells, infected cells, and virus cells	Has susceptible cells, asymptomatic cells, symptomatic cells, AIDS cells
3	Assumed only natural mortality	Assumed both death due to sickness and natural mortality
4	Treatments not assumed	Assumed ART Treatment
5	There is no treatment representation as parameter or variable	Treatment is taken as parameter

Table 4. *Similarities of existing and modified model.*

Similarities
Both existing [11] and modified (Present) model have the following similarities
Transmission rate
Natural mortality
Infected cell

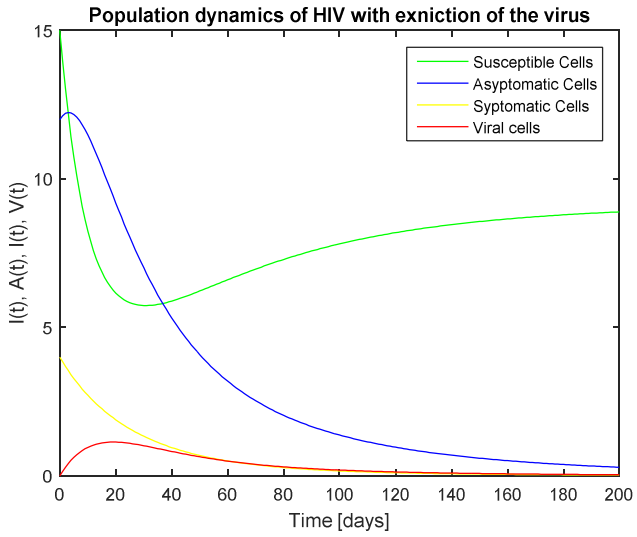

Figure 3. *Population dynamics of SAIV compartments with the parametric values* $\tau = 0.46, \mu = 0.05, \beta = 0.2, \alpha = 0.008, \theta = 0.01, \delta = 0.01, \eta = 0.02, \omega = 0.01, \rho = 0.01, \phi = 0.02$ *F.*

5. Sensitivity Analysis

Sensitivity analysis is used to determine the sensitivity of the model with respect to the parameters involved in it. That is, how changes in the value of the parameters of the model result in changing the dynamics of the infection. It is used to discover parameters that have a high impact on R_0 and should be targeted by intervention strategies. More precisely, sensitivity indices allow measuring the relative change in a variable when parameter changes [9]. If the result is negative, then the relationship between the parameters and R_0 is inversely proportional. In this case, the modulus of the sensitivity index will be taken so that the size of the effect of changing that parameter can be deduced.

On the other hand, a positive sensitivity index means that both the function and the parameter are proportional to each other i.e. both of them grow or decay together.

It is already shown that the explicit expression of R_0 is given by $R_0 = [(\beta\mu_d)/(a\mu)]$. Since,$R_0$depends only on four parameters, an analytical expression will be derived for its sensitivity to each of the parameters using the normalized forward sensitivity index as given by Chitnis [16].

$$\Upsilon_{\beta}^{R_0} = [\partial R_0/\partial\beta] \times [\beta/R_0]$$

$$\Upsilon_{\mu}^{R_0} = [\partial R_0/\partial\mu] \times [\mu/R_0]$$

$$\Upsilon_{\eta}^{R_0} = [\partial R_0/\partial\gamma] \times [\gamma/R_0]$$

$$\Upsilon_{\alpha}^{R_0} = [\partial R_0/\partial\gamma] \times [\gamma/R_0]$$

$$\Upsilon_{\phi}^{R_0} = [\partial R_0/\partial\gamma] \times [\gamma/R_0]$$

$$\Upsilon_{\theta}^{R_0} = [\partial R_0/\partial\gamma] \times [\gamma/R_0]$$

$$\Upsilon_{\delta}^{R_0} = [\partial R_0/\partial\gamma] \times [\gamma/R_0]$$

Table 5. *Sensitivity of* R_0 *evaluated for the parametric values.*

Parameter	Sensitivity index
μ	+3.9409
η	-1.6553
β	+1
α	-0.1379
ϕ	-2
θ	-0.1724
δ	-0.1724

From Table 5, it can be observed that the values of two parameters μ, β are positive sensitivity indices and values of the remaining five parameters $\eta, \alpha, \phi, \theta, \delta$ get negative sensitivity indices.

As it is observed from the table the parameter with large magnitude is μ. Hence, it can be conclude that μ is the most sensitive parameter in the model equations. On the other hand an increase in these positive parameter values will cause an increasing R_0 this implies that disease persist in human cells. Similarly, a decrease in negative parameter values will cause a decrease in R_0 which means the disease die out from human cells.

6. Result and Discussion

In this study, a mathematical model describing the dynamics of Human Immunodeficiency Virus (HIV) with treatment by ART is formulated and analyzed. The model is

developed based on biologically reasonable assumptions made about Human Immunodeficiency Virus (HIV) and its treatment. The mathematical analysis has shown that if the reproduction number $R_0 < 1$ then the disease free equilibrium point is locally and globally asymptotically stable implying that the disease wipes out and the treatment is successful which is supported by the simulation results given in Figure 2. Also, if $R_0 > 1$ then the disease free equilibrium point is unstable implying that the treatment is not successful. These theoretical results have been supported by the simulation study as it is shown in Figure 1. Furthermore, the endemic equilibrium point is stable if $R_0 > 1$ resulting that the infectious cells continue to replicate. This fact has also been supported by Figure 1.

7. Conclusion

In this study, a mathematical model of Human Immunodeficiency Virus HIV using ART as treatment has been formulated. Moreover, existence, positivity and boundedness of the formulated model are verified to illustrate that the model is biologically meaningful and mathematically well posed. In particular, the stability analyses of the model were investigated using the basic reproduction number and Routh Hurwitz criterion. Also, the solution of the model equations is numerically simulated and sensitivity analysis of the model is conducted. Furthermore, results of the research work presented in this paper reveal that the model formulated here effectively supports treatment for HIV disease.

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