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GLOBAL DYNAMICS OF HIV INFECTION WITH TWO DISEASE TRANSMISSION ROUTES - A MATHEMATICAL MODEL

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Abstract. In this paper, we have studied the global dynamics of HIV model with two transmission paths: direct transmission through cells-to-cells contact and indirect transmission through virus. We have derived a four dimensional mathematical model including uninfected $CD_4^{+}T$ cells, infected $CD4^{+}T$ cells, virus and the CTL immune response cells. The nonnegativity and boundedness property of the solutions the proposed mathematical system have been analysed, and the basic reproduction ratio R_0 has been derived with the help of next generation matrix method. We also discussed the local and global stability with respect to the basic reproduction ratio of both disease-free and interior equilibrium points under certain conditions. Through numerical simulations, we have validated the all analytical findings. We have established that the disease-free equilibrium is globally stable for $R_0 < 1$ and endemic equilibrium is globally stable for $R_0 > 1$ whenever exists. It is also observed that cells-to-cells transmission rate is more effective compare to virus-to-cells infection rate.

Keywords: HIV dynamics; mathematical model; basic reproduction ratio; Lyapunov function; global stability; numerical simulation.

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1. INTRODUCTION

Human Immunodeficiency Virus (HIV) is treated as the most serious infectious disease worldwide and Acquired Immunodeficiency Syndrome (AIDS) is the last stage of this deadly infection process. Till date, 35 million people (approx.) have died from AIDS related illness and 30-40 million individual are living with HIV [1, 2]. Mainly, HIV targets the human immune system and as a consequence immune system breaks down and can't work properly. As a result, HIV infected people can easily infected by the other infectious disease (influenza, pneumonia, tuberculosis etc.). When CD_4^+ T cells count is less than 200 mm^{-3}, then HIV infected patient is treated as an AIDS patient [3, 4].

CD_4^+ T cells plays various important role in human immune system.It also acts as the main defender against the deadly RNA-virus. Viruses can spread by infecting CD_4^+ T cells in two ways namely 'virus-to-cells' HIV infection as well as 'cells-to-cells' transmission. The pathway of Virus-to-cells HIV infection is considered as a multistage process [5, 6, 7, 8]. Firstly, the envelope protein (gp120) on the surface of HIV binds with CD_4^+ receptor and two co-receptors (CXCR4 and CCR5) of healthyCD_4^+ T cells. Then, virus injects the genetic material in to the healthy T cells by fusion process. This genetic material transforms viral RNA genome to DNA copy by reverse transcriptase enzyme. Then by another viral enzyme this DNA copy integrates into the viral DNA and at last by protease enzyme it transforms to infected provirus, thus the cells becomes infected. On the other hand, by the cells-to-cells transmission process virus is spread in our body through virological synapses which are a predominant mode of viral transmission [9, 10, 11]. These Virological synapses are formed for the interaction between CD_4^+ and HIV envelope glycoprotein. When the donor and target cells interact with each other, a large number of infectious particles are accumulated and released at the places of 'cells-to-cells' contacts [12]. It is well known that this cells-to-cells transmission process is significantly more efficient and faster viral replication mechanism. Also, during both process of infection due to huge replication of infected T cells and virus, immune system of our body produces an another type of T cells i.e. Cytotoxic T-lymphocyte cells (CTL). This immune cells has a significant role in suppressing HIV replication in acute infection [13, 14].

Since few years, several mathematical models have been proposed to capture the HIV viral dynamics in theoretical perceptive. In some of models, authors have considered that infection occurs only from free HIV virus to CD_4^+ T cells i.e. by "virus-to-cells transmission" [15, 16, 17, 27]. Recently, many eminent researchers have described that there is an another viral transmission mechanism for the case of HIV - the "cells-to-cells transmission" [20, 21]. Lai et al. have also proposed a mathematical model considering both mode of infection transmission viz. virus-to-cells and cells-to-cells [22]. Roy et al.[25] have described a mathematical model by considering the qualitative behavior of CTL response in a HIV model. Yet the global dynamics of a HIV model including both mode of infection transmission has not been explored.

In this paper, we develop a mathematical model by incorporating both mode of transmission with the immune response of CTL, which attacks infected cells and play a critical role for antiviral defense. We also consider that the virus can be proliferated by external viral sources other than infected T cells. Furthermore, we have analyzed the global stability of our formulated model by considering a suitable Lyapunov function. By using this global dynamical behavior, we also try to find out the answers of the following questions: (a) which transmission process is most effective? (b) how the CTLs response can prevent this effective transmission process?

This article is arranged as follows. Firstly, we formulate the model with initial condition in section 2. We have found the equilibrium points of the system and determine the basic reproductive ratio in Section 3. In Section 5 and Section 6, we discuss the local and global stability depending on the value of basic reproductive ratio respectively. Numerical simulations are presented in section 7 with discussion. Finally, section 8 concludes the paper with important findings.

2. Model Formulation

We construct a mathematical model of HIV disease dynamics considering both virus-to-cells infection and cells-to-cells transmission. Here $\mathrm{CD4}^+T$cells population is partitioned into uninfected $\mathrm{CD4}^+T$cells(x) and infected $\mathrm{CD4}^+T$cells(y), with $x(t)$ and $y(t)$ representing their concentration respectively at a time t. We also consider virus population (v) and CTL population (z), with $v(t)$, $z(t)$ representing their concentration at a time t respectively.

The uninfected CD4^+Tcells are produced from bone marrow and mature in thymus at a constant rate. Here λ be the constant production rate of this uninfected immune cells. We assume that the uninfected CD4^+T cells become infected by direct cells-to-cells transmission at a rate β_1 and by free virus at a rate β_2. Here d_1 and d_2 are the per capita mortality rate of uninfected CD4^+Tcells and infected CD4^+Tcells respectively. Infected T cells are assumed to produce on average N mature viruses during its lifetime i.e we assume that Nd_2 is the growth rate of virus by infected CD4^+Tcells. We also consider that $\frac{av}{b+v}$ is the proliferation rate of virus from other infected cells like macrophages. It should be noted here that the growth rate of external viral source other than T cells is a and half saturation constant of external viral source is b. Here d_3 represents the natural removing rate of virus.

$$\begin{aligned} \frac{dx}{dt} &= \lambda - d_1 x - \beta_1 xy - \beta_2 xv \\ \frac{dy}{dt} &= \beta_1 xy + \beta_2 xv - d_2 y \\ \frac{dv}{dt} &= Nd_2 y + \frac{av}{b+v} - d_3 v \end{aligned} \tag{1}$$

We also consider CTL immune response to defend the virus replication and α is the proliferation rate due to immense growth of infected CD4^+Tcells. Here we assume d_4 as removing rate of CTL response. The following equation demontrate the CTL population dynamics.

$$\frac{dz}{dt} = \alpha yz - d_4 z \tag{2}$$

Here we also consider that the CTL response has a negative impact on infected CD4^+Tcells and assume that β_3 is the apoptosis rate of infected cells due to CTL response. Based on the considerations, growth rate of the uninfected CD4^+Tcan rewrite as follows

$$\frac{dy}{dt} = \beta_1 xy + \beta_2 xv - d_2 y - \beta_3 yz \tag{3}$$

Assembling together the above three system of equation (1, 2, 3), we can rewrite the compact proposed mathematical model

$$\begin{aligned}
\frac{dx}{dt} &= \lambda - d_1 x - \beta_1 xy - \beta_2 xv \\
\frac{dy}{dt} &= \beta_1 xy + \beta_2 xv - d_2 y - \beta_3 yz \\
\frac{dv}{dt} &= Nd_2 y + \frac{av}{b+v} - d_3 v \\
\frac{dz}{dt} &= \alpha yz - d_4 z
\end{aligned} \tag{4}$$

where $x(0) > 0$, $y(0) > 0$, $v(0) > 0$, $z(0) > 0$ are the initial condition for above system and for this given initial condition, the solution $(x(t), y(t), v(t), z(t))$ of the system (4) is positively invariant and uniformly bounded in a region Π for $t > 0$ where

$$\begin{aligned}
\Pi = \Bigg\{ \Big(x(t), y(t), v(t), z(t)\Big) : 0 < x \leq \frac{\lambda}{d_1}, 0 \leq y(t) \leq \frac{\lambda}{D_1}, \\
0 \leq v(t) \leq \frac{1}{2}\left(a + \frac{Nd_2\lambda}{d'}\right), 0 \leq z(t) \leq \frac{M}{D_2} \Bigg\}.
\end{aligned} \tag{5}$$

where $M = \alpha \frac{\lambda}{d_1}\left[\beta_1 \frac{\lambda}{d'} + \frac{1}{2}\beta_2\left(a + Nd_2 \frac{\lambda}{D_1}\right)\right]$, $D_1 = min\{d_1, d_2\}$ and $D_1 = min\{d_2, d_4\}$.

3. Equilibria and Stability Analysis

We will analyse the existence and stability of equilibria of the system (4) using the basic reproductive ratio which is determined below.

3.1. Basic reproductive ratio, R_0. Here, in case of both mode of transmission the infectious compartments of the Jacobian matrix of the system at E_0 can be written as

$$J_0 = \begin{bmatrix} \beta_1 x_0 - d_2 & \beta_2 x_0 \\ Nd_2 & \frac{a}{b} - d_3 \end{bmatrix}.$$

Now we define two matrices F and V as

$$F = \begin{bmatrix} \beta_1 x_0 & \beta_2 x_0 \\ 0 & 0 \end{bmatrix} \text{ and } V = \begin{bmatrix} d_2 & 0 \\ -Nd_2 & \frac{a}{b} - d_3 \end{bmatrix}.$$

such that $J_0 = F - V$

Thus the basic reproduction number R_0 can be defined as the spectral radius of the next generation operator FV^{-1} i.e the largest eigen value of the matrix FV^{-1}, where

$$FV^{-1} = \frac{1}{d_2(d_3-\frac{a}{b})}\begin{bmatrix} \beta_1 x_0(d_3-\frac{a}{b})+\beta_2 x_0 N d_2 & \beta_2 x_0 d_2 \\ 0 & 0 \end{bmatrix}.$$

Therefore,

$$R_0 = \rho(FV^{-1}) = \frac{\beta_1 x_0(d_3-\frac{a}{b})+\beta_2 x_0 N d_2}{d_2(d_3-\frac{a}{b})} = R_0^1 + R_0^2, \tag{6}$$

where,

$$R_0^1 = \frac{\beta_1 \lambda(d_3-\frac{a}{b})}{d_1 d_2(d_3-\frac{a}{b})}, \quad R_0^2 = \frac{\beta_2 \lambda N d_2}{d_1 d_2(d_3-\frac{a}{b})}. \tag{7}$$

3.2. Existence of equilibria. The system has four equilibria namely the infection-free equilibrium point, $E_0(\frac{\lambda}{d_1},0,0,0)$ which is always feasible, the another steady state is the endemic equilibrium $E^*(x^*,y^*,v^*,z^*)$ satisfying

$$\begin{aligned} x^* &= \frac{\alpha\lambda}{\alpha d_1+\beta_1 d_4+\alpha\beta_2 v^*}, \quad y^* = \frac{d_4}{\alpha}, \\ z^* &= \frac{\alpha\lambda(\beta_1 d_4+\alpha\beta_2 v^*)-d_2\beta_3 d_4(\alpha d_1+\beta_1 d_4+\alpha\beta_2 v^*)}{\beta_3 d_4(\alpha d_1+\beta_1 d_4+\alpha\beta_2 v^*)}, \end{aligned}$$

where v^* is a solution of $\Theta_1 v^{*2}+\Theta_2 v^*+\Theta_3 = 0$ with the coefficient

$$\Theta_1 = \alpha d_3,\ \Theta_2 = \alpha b d_3 - N d_2 d_4 - a\alpha,\ \Theta_3 = -N d_2 d_4 b$$

Since $\Theta_1 > 0$ and $\Theta_3 < 0$ then the above equation has a unique positive root. From the above expression of x^*,y^*,z^*, it can be shown that the endemic equilibrium point $E^*(x^*,y^*,v^*,z^*)$ is feasible when $R_0 > 1$.

4. Local Stability Analysis

Now the Jacobian of the system at any point $E(x,y,v,z)$ is given by

$$J(E) = \begin{bmatrix} -d-\beta_1 y-\beta_2 v & -\beta_1 x & -\beta_2 x & 0 \\ \beta_1 y+\beta_2 v & \beta_1 x-d_2-\beta_3 z & \beta_2 x & -\beta_3 y \\ 0 & N d_2 & \frac{ab}{(b+v)^2}-d_3 & 0 \\ 0 & \alpha z & 0 & \alpha y-d_4 \end{bmatrix}.$$

Now at the infection-free equilibrium E_0, the characteristic equation becomes

$$(\lambda + d_1)(\lambda + d_4)(\lambda^2 + A_1\lambda + A_2) = 0 \tag{8}$$

where

$$A_1 = d_2 + d_3 - \frac{a}{b} - \frac{\lambda\beta_1}{d_1} \text{ and } A_2 = \beta_1 \frac{a}{b}\frac{\lambda}{d_1} - \frac{ad_2}{b} - \beta_1 d_3 \frac{\lambda}{d_1} + d_2 d_3 - N\beta_2 d_2 \frac{\lambda}{d_1}$$

If A_1 and A_2 both positive then by "Routh-Hurwitz Criterion", all the eigenvalues have negative real parts and consequently the infection-free equilibrium point E_0 is locally asymptotically stable. Now $A_1 > 0$ and $A_2 > 0$ implies $R_0 < 1$. This concludes that the infection-free equilibrium point is locally asymptotically stable if $R_0 < 1$.

Thus we have the following proposition,

Proposition 1. *The infection-free equilibrium point E_0 is locally asymptotically stable if $R_0 < 1$. Moreover, the system* (4) *has a unique endemic equilibria for $R_0 > 1$.*

At the endemic equilibrium E^*, the characteristic equation becomes

$$\lambda^4 + B_1\lambda^3 + B_2\lambda^2 + B_3\lambda + B_4 = 0 \tag{9}$$

where

$$\begin{aligned}
B_1 &= -b_{11} - b_{22} - b_{33} - b_{44} \\
B_2 &= b_{11}b_{21} + b_{11}b_{33} + b_{11}b_{44} + b_{22}b_{33} + b_{22}b_{44} + b_{33}b_{44} - b_{23}b_{32} - b_{24}b_{42} - b_{12}b_{21} \\
B_3 &= -b_{11}b_{22}b_{33} - b_{22}b_{33}b_{44} - b_{33}b_{44}b_{11} \\
&\quad -b_{44}b_{11}b_{22} + b_{11}b_{23}b_{32} + b_{44}b_{23}b_{32} + b_{11}b_{24}b_{42} + b_{33}b_{24}b_{44} \\
&\quad +b_{12}b_{21}b_{33} + b_{12}b_{21}b_{44} + b_{13}b_{32} \\
B_4 &= b_{11}b_{22}b_{33}b_{44} - b_{11}b_{44}b_{23}b_{32} - b_{24}b_{42}b_{11}b_{33} - b_{12}b_{21}b_{33}b_{44} + b_{13}b_{32}b_{44}
\end{aligned}$$

where

$$b_{11} = -d - \beta_1 y^* - \beta_2 v^*, b_{12} = -\beta_1 x^*, b_{13} = -\beta_2 x^*, b_{21} = \beta_1 y^* + \beta_2 v^*, b_{22} = \beta_1 x^*,$$

$$b_{23} = \beta_2 x^*, b_{24} = -\beta_3 y^*, b_{32} = Nd_2, b_{33} = \frac{ab}{(b+v^*)^2} - d_3, b_{42} = \alpha z^*, b_{44} = \alpha y^* - d_4$$

Now, $B_1, B_3, B_4 > 0$ and $B_1 B_2 B_3 > (B_3)^2 + (B_1)^2 B_4$ imply that $R_0 > 1$. Then by "Routh-Hurwitz Criterion" at the endemic equilibrium point the system is locally asymptotically stable for $R_0 > 1$..

From the above discussion, we have the following theorem.

Theorem 1. *The endemic equilibrium E^* is locally asymptotically stable if $R_0 > 1$.*

5. GLOAL STABILITY ANALYSIS

Theorem 2. *The infection-free equilibrium point E_0 is globally asymptotically stable if $R_0 < 1$.*

Proof. We define a Lyapunov function as

$$V(t) = x - x_0 - x_0 \ln(\frac{x}{x_0}) + y(t) + \big(\beta_1 x_0 (d_3 - \frac{a}{b}) + \beta_2 x_0 N d_2\big) v(t) + \frac{\beta_3}{\alpha} z(t). \tag{10}$$

Here $V(t) > 0$ for all positive values of x(t), y(t), v(t), z(t) and $V(t) = 0$ at infection-free equilibrium point E_0. Now calculating time derivative of $V(t)$, we get

$$\begin{aligned} \dot{V(t)} &= \big(1 - \frac{x_0}{x(t)}\big)\frac{x(t)}{dt} + \frac{y(t)}{dt} + (\beta_1 x_0 (d_3 - \frac{a}{b}) + \beta_2 x_0 N d_2)\frac{v(t)}{dt} + \frac{\beta_3}{\alpha}\frac{z(t)}{dt} \\ &= \big(1 - \frac{x_0}{x(t)}\big)[\lambda - d_1 x - \beta_1 xy - \beta_2 xv] + [\beta_1 xy + \beta_2 xv - d_2 y - \beta_3 yz] \\ &\quad + \big(\beta_1 x_0 (d_3 - \frac{a}{b}) + \beta_2 x_0 N d_2\big)[N d_2 y + \frac{av}{b+v} - d_3 v] + \frac{\beta_3}{\alpha}[\alpha yz - d_4 z] \\ &\leq d_1 x_0 \big(2 - \frac{x(t)}{x_0} - \frac{x_0}{x(t)}\big) + \frac{y}{(d_3 - \frac{a}{b})}(R_0 - 1) \end{aligned} \tag{11}$$

Therefore using the fact that Aritheoremetic Mean (A.M.) $\geq$ Geometric Mean (G.M), we have obtained $\dot{V} \leq 0$ if $R_0 < 1$. Moreover at E_0 , $\dot{V(t)} = 0$. Hence infection-free equilibrium point E_0 is globally asymptotically stable if $R_0 < 1$.

□

Theorem 3. *The endemic equilibrium point E^* is globally asymptotically stable if $R_0 > 1$.*

Proof. Let us consider a Lyapunov function as

$$W(t) = x - x^* - x^* \ln(\frac{x}{x^*}) + y - y^* - y^* \ln(\frac{y}{y^*}) + v - v^* - v^* \ln(\frac{v}{v^*}) + z - z^* - z^* \ln(\frac{z}{z^*})$$

(12)

Here $W(t) > 0$ for all positive values of x(t), y(t), v(t), z(t) and $W(t) = 0$ at endemic equilibrium point E^*. Now calculating time derivative of $W(t)$, we get

$$\begin{aligned}
\dot{W(t)} &= \big(1 - \frac{x^*}{x(t)}\big)\frac{x(t)}{dt} + \big(1 - \frac{y^*}{y(t)}\big)\frac{y(t)}{dt} + \big(1 - \frac{v^*}{v(t)}\big)\frac{v(t)}{dt} + \big(1 - \frac{z^*}{z(t)}\big)\frac{z(t)}{dt} \\
&= \big(1 - \frac{x^*}{x(t)}\big)[\lambda - d_1 x - \beta_1 xy - \beta_2 xv] + \big(1 - \frac{y^*}{y(t)}\big)[\beta_1 xy + \beta_2 xv - d_2 y - \beta_3 yz] \\
&\quad + \big(1 - \frac{v^*}{v(t)}\big)[Nd_2 y + \frac{av}{b+v} - d_3 v] + \big(1 - \frac{x^*}{x(t)}\big)[\alpha yz - d_4 z] \\
&= -d_1 \frac{(x-x^*)^2}{x} + \beta_1 x^* y^* (1 - \frac{x^*}{x} - \frac{x}{x^*}) + \beta_1 x^* v^* (1 - \frac{x^*}{x} - \frac{x}{x^*}) + \beta_2 xv^* + \beta_2 x^* v \\
&\quad + \beta_1 x^* y + d_2 y^* + \beta_3 y^* z + (\frac{v}{N} - \frac{v^*}{N})(\frac{a}{b+v} - d_3) - d_2 y \frac{v^*}{v} + \frac{\beta_3 d_4}{\alpha}(z^* - z) - \beta_3 yz^* \\
&= -d_1 \frac{(x-x^*)^2}{x} + \beta_1 x^* y^* (1 - \frac{x^*}{x} - \frac{x}{x^*}) + \beta_1 x^* v^* (1 - \frac{x^*}{x} - \frac{x}{x^*}) + \beta_2 xv^* \\
&\quad + \frac{\alpha\lambda d_4(\beta_1 y + \beta_2 v) + \lambda d_4(\beta_1 d_4 + \alpha\beta_2 v^*) - \alpha\lambda(\beta_1 d_4 + \alpha\beta_2 v^*)}{d_4(\alpha d_1 + \beta_1 d_4 + \alpha\beta_2 v^*)} \\
&\quad + (\frac{v}{N} - \frac{v^*}{N})(\frac{a}{b+v} - d_3) + d_2 y(1 - \frac{x^*}{x} - \frac{x}{x^*}) \\
&\leq -d_1 \frac{(x-x^*)^2}{x} + \beta_1 x^* y^* (1 - \frac{x^*}{x} - \frac{x}{x^*}) + \beta_1 x^* v^* (1 - \frac{x^*}{x} - \frac{x}{x^*}) \\
&\quad + d_2 y(1 - \frac{x^*}{x} - \frac{x}{x^*}) + \frac{1}{d_4(\alpha d_1 + \beta_1 d_4 + \alpha\beta_2 v^*)}(1 - R_0)
\end{aligned} \tag{13}$$

Therefore using A.M. $\geq$ G.M., we conclude that the 2nd, 3rd, 4th term of the last equation is less than zero. Hence $\dot{W} \leq 0$ if $R_0 > 1$. Moreover at E^* , $\dot{W} = 0$. Using the Lyapunov-LaSalle invariance principle, we conclude that E^* is global asymptotically stable for $R_0 > 1$.

6. NUMERICAL SIMULATIONS

In this section, on the basis of analytical findings, we carry out the numerical results of our system. We check the numerical results considering parameter values from different articles

given in Table 1. The dynamics of cells are plotted with respect to time to investigate the qualitative behavior of considered cells between 100 days. Numerical simulations are done using MATLAB. In this section, we have tried to focus numerical view on dynamical cells interaction globally of the system that is considered in our proposed model.

TABLE 1. Parameters value using for numerical simulation [18, 23, 19, 30, 31].

Parameter	Description	Assigned Value
λ	production rate of uninfected T cells	12 day^{-1}
β_1	cells-to-cells transmission rate	0.0001 day^{-1}
β_2	virus-to-cells transmission rate	0.00024 day^{-1}
β_3	apoptosis rate of infected cells due to CTL	0.02 day^{-1}
α	proliferation rate infected T cells due to CTL	0.15 day^{-1}
N	No of infected cells produce from viruses	2000 day^{-1}
a	growth rate of external viral source	2 day^{-1}
b	half saturation constant	14 mm^3
d_1	mortality rate of uninfected T cells	0.05-0.1 day^{-1}
d_2	mortality rate of infected T cells	0.2-0.3 day^{-1}
d_3	mortality rate of virus	0.34 day^{-1}
d_4	mortality rate of CTL	0.12 day^{-1}

Figure 1 shows the contour plot of the basic reproductive ration R_0 as a function of β_1 (the rate at which the uninfected $CD4^+T$cells become infected by cells-to-cells transmission) and d_2 (the mortality rate of infected $CD4^+T$cells). This figure reflects the changes of the threshold value of R_0 as β_1 and d_2 fluctuate. From this figure it is easy to explain that the infection-free equilibrium will be stable if $\beta_1 < 0.00036$ with $d_2 > 0$ as well as if β_1 increases and $d_2 > 0$ increases rapidly then also $R_0 < 1$ i.e infection-free equilibrium point is stable. Now if $d_2 > 0$ decreases as cells-to-cells transmission rate (β_1) increases then the equilibrium state loses its stability.

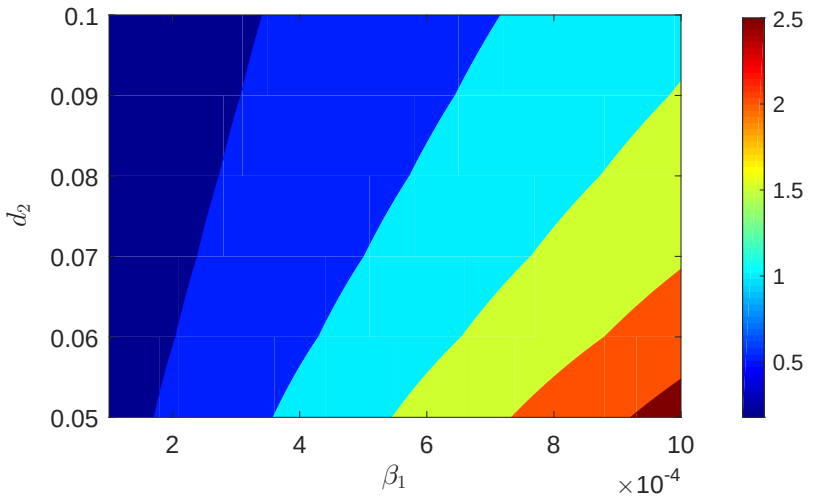

FIGURE 1. Contour plot for R_0 as a function of β_1 and d_2. Color bar denotes the value of R_0.

Figure 2 shows that when $R_0 < 1$ i.e. for infection-free steady state the model variables viz uninfected CD_4^+ T cells $(x(t))$, infected CD_4^+ T cells $(y(t))$, virus $(v(t))$, CTL $(z(t))$ moves to the stable disease-free condition E_0 after 100 days (approximately) as time increases. Due to the lower infection rates (both cells-to-cells and virus-to-cells) uninfected cells are present in the system where as the two infected class vanished. According to Theorem 2, the steady state E_0 is globally stable for the set of parameters used.

In Figure 3, we demonstrate the stability property of endemic steady state. When $R_0 > 1$, the model variables goes to a stable steady state E^* after approximately 100 days. Due to both type of transmissions, the infected CD_4^+ T cells increases rapidly for first 5-6 days approximately, but due to CTL immune response after 5-6 days infected cells can't proliferate swiftly. As a result, infected cells population decreases to a positive steady state after 30 days (approximately). Here, uninfected cells decreases and virus population increases as time increases. CTL population responses after 5-6 days due to rapid growth of infection and as a result CTL increases smoothly till infected cells goes to stable state. Then after 30 days, CTL immune responses decreases to a certain level as infected cells grows. According to Theorem 3, the steady state E^* is globally asymptotically stable for the set of parameters used for this figure.

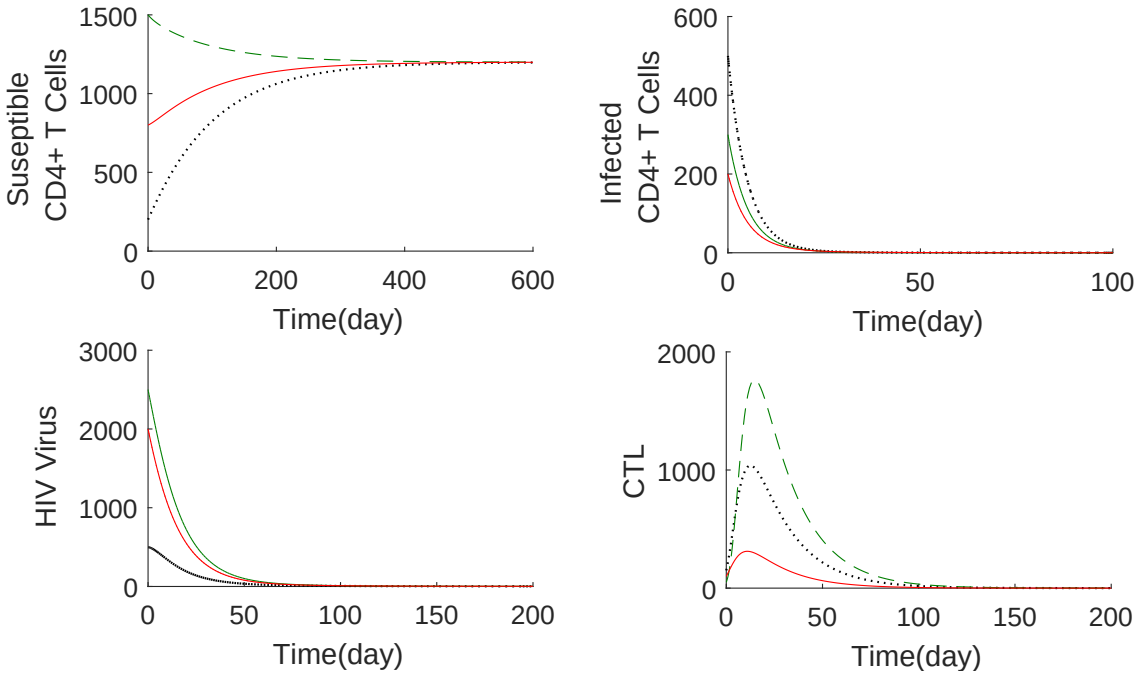

FIGURE 2. Trajectories showing the time dependent changes in concentration of the model variables when $R_0 < 1$ (Infection-free steady state).

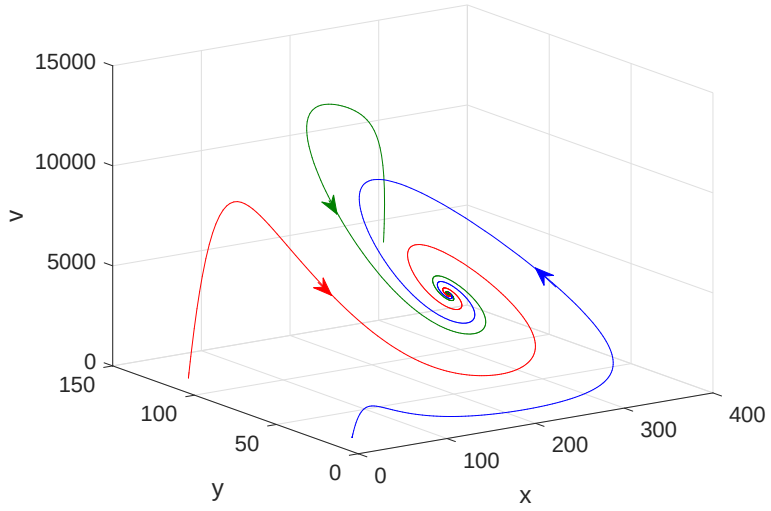

FIGURE 3. Trajectories showing the time dependent changes in concentration of the model variables when $R_0 > 1$ (Endemic steady state).

Figure 4 manifest the dynamical nature of infected $CD4^+T$ cells for different value of β_1 (cells-to-cells transmission rate) and β_2 (virus-to-cells transmission rate). In figure 4(A), we

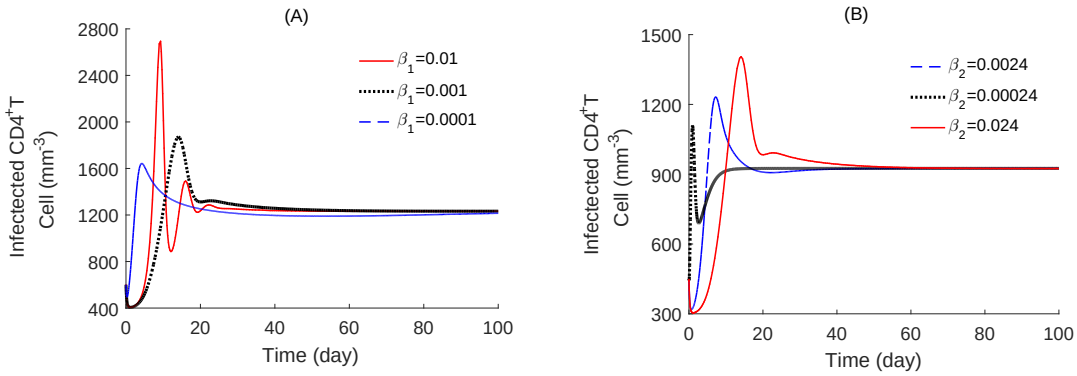

FIGURE 4. Trajectories showing the time dependent changes of infected cells with different β_1 and β_2 in (A) and (B) respectively.

plot different time dependent trajectories for variation of β_1 in range of 0.01-0.0001. Here we observe that for low value of β_1 (0.0001) the trajectories initially reaches at the level 1680 mm^{-3} and after 100 days it archives the stable condition at density level 1220 mm^{-3}. For the value of $\beta_1 = 0.01$ the trajectories initially increases rapidly at the level 2700 mm^{-3} within 10 days and then for 20 days it oscillates and finally after 100 days it goes to the stable state at 1250 mm^{-3}.

Considering the value of β_1 as 0.001, a dramatically behaviour is observed as the infected T cells increases not much rapidly and goes to stable condition at 1300 mm^{-3} after 100 days approximately. Figure 4(B) depict that for different values of β_2 the infected T cells shows different qualitative nature but after 100 days all trajectories converge to a single stable region at density level 1550 mm^{-3}.

Therefore Figure 4 reveals that for variation of β_2 the trajectories of infected T cells reaches to almost same density but for β_1 the trajectories goes to different density after 100 days. So finally from this figure we conclude that β_1 is more efficient compare to β_2 in disease progression.

7. DISCUSSION AND CONCLUSIONS

In this research, we have studied the global dynamics of HIV infection considering for both cells-to-cells and virus-to-cells infection. Accordingly, a mathematical model has been formulated and analyzed analytically and numerically. The local stability criterion for infection-free equilibrium and endemic equilibrium has also been studied depending on the basic reproductive

ratio, R_0. The global stability of the infection-free equilibrium and the endemic equilibrium of system has been established by considering a suitable Lyapunov function.

We have observed that cells-to-cells transmission rate (β_1) is more affective compare to virus-to-cells infection rate (β_2) i.e. cells-to-cells transmission have a great impact on spread of HIV infection. In presence of CTL, uninfected cells reaches to stable state at density level 375 mm^{-3} whereas without CTL it was 200 mm^{-3} after 100 days approximately. Therefore, the theoretical and the numerical results are in good agreement. Furthermore, our numerical studies also revel that when cells-to-cells transmission rate is high then CTL response is also quick and prominent. In a nutshell, our model based results suggest that the system immunity represented by CTL can control viral replication and reduce the infection under appropriate conditions.

The present study can be extended in many ways. Effect of time delay can be observed incorporating a time delay in immune response [27, 18]. Another important event is to see the effect of optimal therapy for controlling the disease in cost-effective and with minimum side effects[28, 29]. How we can enhance the CTL response when cells-to-cells transmission rate is high, that will be the great challenge of our future work.

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CONFLICT OF INTERESTS

The author(s) declare that there is no conflict of interests.

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