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ON DYNAMICS OF A MATHEMATICAL MODEL FOR HIV INFECTION WITH FUSION EFFECT AND CURE RATE

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Abstract. In this manuscript, we have proposed and analyzed a differential equation model for HIV infection to study the dynamics of three different populations: HIV-free $CD4^+$ T cells, HIV-infected $CD4^+$ T cells and free virus of the model. In the model, we have incorporated fusion effect for HIV-free $CD4^+$ T cell and free virus, proliferation of HIV-free $CD4^+$ T cells which follows a full logistic growth term and cure rate for HIV-infected $CD4^+$ T cells. Our main objective is to investigate the effects of fusion and cure rate on the dynamics of the model. We have used next generation matrix method to calculate the basic reproduction number (R_0) for this proposed model. Local stability of the existing equilibrium points is discussed using Routh-Hurwitz theorem. Also, in order to establish the global stability criteria Lyapunov functional and geometric approach are used. From the analysis it is found that if the basic reproduction number $R_0 \leq 1$, HIV will be removed from the population of $CD4^+$ T cells and if $R_0 > 1$, there exists chronic infection. Also, we have carried out numerical simulations in order to verify the analytic results.

Keywords: HIV/AIDS; $CD4^+$ T cells; fusion effect; basic reproduction number; cure rate.

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1. INTRODUCTION

During the last decades, the mathematical theories have been used extensively to investigate different viral infections like HIV, HBV, HCV, HTLV-1 and so on. Among these, human

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immunodeficiency virus (HIV) is one of the most studied viruses in the field of mathematical theory of viral infections and researchers have developed a lots of mathematical models to investigate the in-host dynamics of HIV. Some of the main issues studied in the previous studies are: the dynamics of the $CD4^+$ T-cells [1, 2, 3], a type of lymphocytes that is mainly targeted by HIV [4]; the dynamics of $CD4^+$ T-cells and free virus with the effects of different inter-cellular delays [5, 6]; different infection mechanisms and their consequences [7, 8]; different treatment strategies to control infection with the effects of immune responses to the infection [9, 10].

In the year 2016, a generalized virus dynamics model was proposed by Hattaf and Yousfi [11] in which they incorporated both virus-to-cell and cell-to-cell transmission processes along with the cure rate. Mathematical analysis of the model was done and conditions for stability of all existing equilibrium points of the model were carried out. Xua *et al.* [12] proposed a model incorporating time delays and humoral immunity. From the analysis of the model, they found that the global behaviour depends on the basic reproduction ratio of virus and immune response. They also found that when basic reproduction ratio of immune response is greater than one then the concentration of free virus is reduced by the immune response. In 2019, Gupta and Dutta [13] proposed a model with the consideration that due to fusion effect a few portion of HIV-free $CD4^+$ T-cells and free virus get lossed during contact of HIV-free $CD4^+$ T cells and free virus. Also in [14], they incorporated fusion effect and used homotopy analysis method (HAM) to find analytic solutions of the model. In 2020, Geng *et al.* [26] studied a delayed differential equation model incorporating both the virus-to-cell and cell-to-cell infection processes along with proliferation of HIV-free and HIV-infected $CD4^+$ T cells. They established that destabilization of the infected equilibrium may occur due to time delays which leads to the existence of Hopf bifurcation.

In their study, Gupta and Dutta [13, 14] considered constant inflow rate for HIV-free healthy $CD4^+$ T cells which is an ideal situation as proliferation of existing $CD4^+$ T cells also leads to the formation of new $CD4^+$ T cells. So, we have proposed a more realistic mathematical model for HIV infection incorporating fusion effect and cure rate in this study. The model formulation and the basic properties of the model like non-negativity and boundedness of the solutions are discussed in the section 2. Also, we have discussed the stability conditions of the model in section 3. All the analytic results are verified numerically. Finally, the concluding remarks from the overall study are included in section 4.

2. MODEL FORMULATION

Here, we have formulated a model with the effect of fusion and cure rate to describe the in host HIV dynamics which is inspired by the models in [13, 14]. Our model constitutes of three populations: HIV-free $CD4^+$ T cells, HIV-infected $CD4^+$ T cells and free virus. Dynamics of each compartment and the overall model are discussed below:

2.1. HIV-free $CD4^+$ T cells. As discussed earlier, $CD4^+$ T cells are main target of HIV. To formulate the in-host HIV model, we divide the $CD4^+$ T cells in to two catagories: HIV-free $CD4^+$ T cells $x(t)$, which are healthy T cells and HIV-infected $CD4^+$ T cells $y(t)$, which are infected by HIV. Consider r is the rate at which HIV-free $CD4^+$ T-cells are produced from different sources like precursors in bone marrow and thymus. In different earlier studies [11, 12, 13, 14], they considered only this assumption for production of virus-free $CD4^+$ T cells. But, from the literatures of Biology it is found that proliferation of existing T cells can also produce new T cells and some researchers [15, 16, 17, 18, 19, 20] have already used a simplified logistic term $ax\left(1-\frac{x}{x_{max}}\right)$ to describe this phenomenom. Considering that during the infection total T cell population is $x+y$, different researchers have used a full logistic term $ax\left(1-\frac{x+y}{x_{max}}\right)$ in their works [20, 21, 22, 23, 24, 25] to describe this proliferation process. Here, a and x_{max} are the proliferation rate and maximum carrying capacity of T cells respectively. $-d_1x$ is the natural decay rate of HIV-free $CD4^+$ T cells. Therefore, the following equation represents dynamics of virus-free $CD4^+$ T cells when there is no HIV infection:

$$\frac{dx}{dt} = r - d_1x + ax\left(1-\frac{x}{x_{max}}\right) \tag{2.1}$$

If βzx is the infection rate of HIV-free cells and fzx is the decay rate of HIV-free $CD4^+$ T cells and free virus due to fusion effect. ρ is the cure rate of HIV-infected $CD4^+$ T cells to the HIV-free class. With all these considerations, the dynamics of the HIV-free $CD4^+$ T cells during HIV infection can be expressed by the following differential equation:

$$\frac{dx}{dt} = r - d_1x + ax\left(1-\frac{x+y}{x_{max}}\right) - fzx - \beta zx + \rho y \tag{2.2}$$

2.2. HIV-infected $CD4^+$ T cells. In addition to the assumptions discussed above, we consider d_2 is the natural death rate of HIV-infected $CD4^+$ T cells. Then, dynamics of HIV-infected

$CD4^+$ T can be described by the following differential equation:

$$\frac{dy}{dt} = \beta zx - d_2 y - \rho y \tag{2.3}$$

2.3. Free Virus. In order to model the dynamics of free virus, we consider during the lifetime, an HIV-infected $CD4^+$ T cell can produce N number of virus particles and natural clearance rate of virions is denoted by d_3. Then the dynamics of free virus can be represented by the following equation:

$$\frac{dz}{dt} = Nd_2 y - d_3 z - fzx \tag{2.4}$$

2.4. The Overall Model. Combining all the above equations, our overall model is:

$$\begin{aligned} \frac{dx}{dt} &= r - d_1 x + ax\left(1 - \frac{x+y}{x_{max}}\right) - fzx - \beta zx + \rho y, \\ \frac{dy}{dt} &= \beta zx - d_2 y - \rho y, \\ \frac{dz}{dt} &= Nd_2 y - d_3 z - fzx. \end{aligned} \tag{2.5}$$

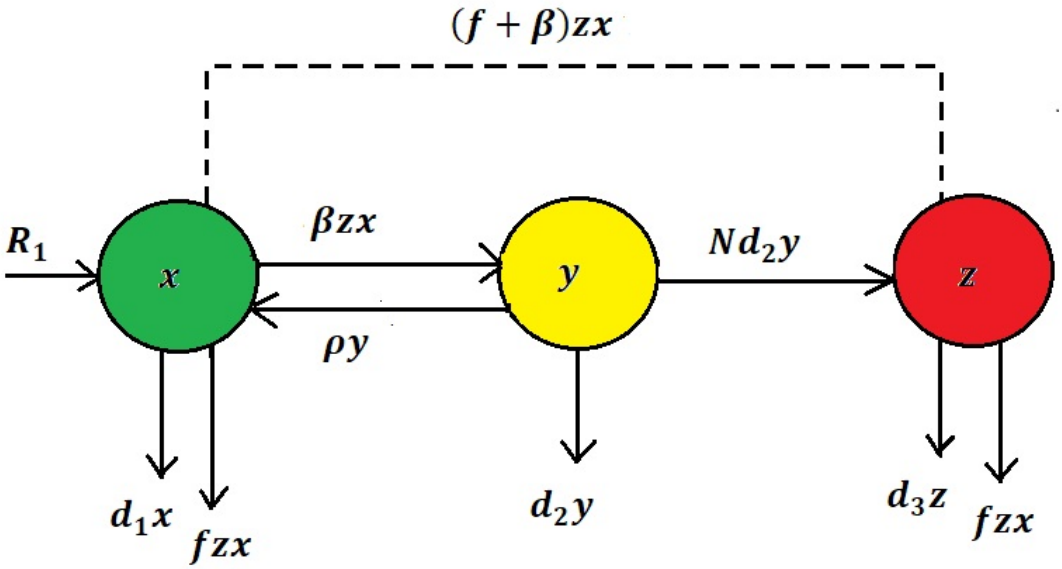

FIGURE 1. Pictorial representation of the model, where $R_1 = r + ax\left(1 - \frac{x+y}{x_{max}}\right)$.

2.5. Assumptions. We have considered following assumptions in this study:

(i) The HIV-free $CD4^+$ T cells are produced from the sources like precursors of bone marrow, thymus as well as by proliferation of existing cells.

(ii) Due to the fusion effect, a few portion of HIV-free $CD4^+$ T-cells and free virus get lossed during their contact process.

(iii) Consider $d_1 \leq d_2$ for the viral burden on the HIV infected $CD4^+$ T-cells.

(iv) For identifying the proliferation process of existing $CD4^+$ T-cells as compared to the normal rate $r - d_1 x$, we consider $d_1 \leq a$.

TABLE 1. Values of parameters for the model (2.5).

Parameters	Intervals	Set 1	Set 2	Units	Source
r	0-10	10	10	cells $mm^{-3}day^{-1}$	[20, 23, 26]
a	0.03-3	0.3	0.3	day^{-1}	[20, 23, 26]
x_{max}	1500	1500	1500	mm^{-3}	[20, 23, 26]
β	0.00025-0.5	0.00025	0.0027	virions mm^3day^{-1}	[20, 23, 26]
d_1	0.007-0.1	0.1	0.1	day^{-1}	[20, 26]
d_2	0.2-0.5	0.2	0.2	day^{-1}	[20, 23, 26]
d_3	2.4-3	2.4	2.4	day^{-1}	[20, 23, 26]
N	10-2500	10	10	virions/cell	[20, 26]
f	-	0.00002	0.00002	virions mm^3day^{-1}	Assumed
ρ	-	0.2	0.2	day^{-1}	Assumed

2.6. Basic Properties.

Theorem 1. *For the system* (2.5) *with the initial conditions* $x(0) = x_0 > 0, y(0) = y_0 \geq 0$ *and* $z(0) = z_0 \geq 0$*, we have* $x(t), y(t), z(t) \geq 0$ *for all* $t > 0$*.*

Proof. To prove that $x(t)$ is non-negative for $t \geq 0$, consider if possible there exists a t_0 such that

$$x(t_0) = 0, x^{'}(t_0) < 0, y(t) \geq 0, z(t) \geq 0, t \in [0, t_0).$$

From equation (2.2), we obtain $x^{'}(t_0) = r > 0$, a contradiction. Thus, $x(t) > 0$ for all $t > 0$.

In the same manner, it can be shown that $y(t) \geq 0$ and $z(t) \geq 0$ for all $t > 0$. Also using the

equation (2.3), it is obtained that

$$y(t) = e^{-(\rho+d_2)t}\left(y_0 + \int_0^t \beta z(\theta)x(\theta)e^{(\rho+d_2)\theta}d\theta\right) \geq 0.$$

Hence $y(t) \geq 0$ for all $t > 0$. Furthermore, using the equation (2.4), we get

$$z(t) = e^{-\int_0^t (d_3+fx(\sigma))d\sigma}\left(z_0 + \int_0^t Nd_2y(u)e^{\int_0^u (d_3+fx(\sigma))d\sigma}du\right) \geq 0.$$

which indicates that $z(t) \geq 0$ for all $t > 0$.

Therefore, all solutions $(x(t), y(t), z(t))$ of the system (2.5) exists and non-negative for all $t > 0$. □

Theorem 2. *For any solution of the model* (2.5)*, there exists* $B > 0$ *such that* $y(t) < B, z(t) < B$ *for all large* t.

Proof. From the equation (2.1), the T cell concentration during absence of infection becomes stable at a level x_0 which is given by,

$$x_0 = \frac{x_{max}}{2a}\left[(a-d_1) + \sqrt{(a-d_1)^2 + \frac{4ra}{x_{max}}}\right] \tag{2.6}$$

Also, $\lim_{t\to\infty} x(t) \leq x_0$.

Adding first two equations of the system (2.5), we get
$x' + y' = r - d_1x + ax\left(1 - \frac{x+y}{x_{max}}\right) - fzx - d_2y \leq r + ax_0 - d_1(x+y)$ (since $d_1 \leq d_2$). It follows that,

$$x + y \leq \frac{r+ax_0}{d_1} + Ce^{-dt} \tag{2.7}$$

where C is arbritary contant, which implies $x + y \to \frac{r+ax_0}{d_1}$ when $t \to \infty$. Therefore, $x + y$ is bounded by $\frac{r+ax_0}{d_1}$. Thus, y is bounded, say by $B_1 > 0$. From the third equation of model, we find z is bounded say by $B_2 > 0$. Take, $B = max\{B_1, B_2\}$. Then, any solution $(x(t), y(t), z(t))$ of the system (2.5) satisfies,

$$y(t) < B, z(t) < B \text{ for large } t.$$

Therefore, the solution $(x(t), y(t), z(t))$ of the model (2.5) are uniformly bounded. Thus, we have the region

$$\Omega = \{(x(t), y(t), z(t)) \in \mathbb{R}^3_+ : x \leq x_0, y < B, z < B\} \tag{2.8}$$

which is positively invariant w.r.t. the model (2.5). □

3. MATHEMATICAL ANALYSIS OF THE MODEL

In this section, we have calculated all stationary points of system (2.5) and investigated the dynamical behaviours of system (2.5) around existing stationary points.

3.1. HIV-free equilibrium point and Basic reproduction number. The system (2.5) always has a HIV-free equilibrium point $E_0 = (x_0, 0, 0)$, where x_0 is defined in equation (2.6). Using method of Driessche and Watmough [27], we can calculate the basic reproduction number of model (2.5) as follows:

Consider $S = (y, z, x)$, then our system (2.5) can be represented as:

$$\frac{dS}{dt} = E(S) - T(S) \tag{3.1}$$

where $E(S)$ is appearance rate of new infections and $T(S)$ is the transfer rate of population to another compartment in the system (2.5), given by

$$E(S) = \begin{pmatrix} \beta zx \\ 0 \\ 0 \end{pmatrix}, T(S) = \begin{pmatrix} d_2 y + \rho y \\ d_3 z + fzx - Nd_2 y \\ d_1 x + fzx + \beta zx - r - ax\left(1 - \frac{x+y}{x_{max}}\right) - \rho y \end{pmatrix}$$

The Jacobian matrix of $E(S)$ and $T(S)$ at the HIV-free equilibrium point E_0 are

$$DE(E_0) = \begin{pmatrix} e_{2\times 2} & 0_{2\times 1} \\ 0_{1\times 2} & 0 \end{pmatrix}, DT(E_0) = \begin{pmatrix} t_{2\times 2} & 0_{2\times 1} \\ \frac{ax_0}{x_{max}} - \rho & fx_0 + \beta x_0 \quad d_1 - a\left(1 - \frac{x_0}{x_{max}}\right) + \frac{ax_0}{x_{max}} \end{pmatrix}$$

where

$$e_{2\times 2} = \begin{pmatrix} 0 & \beta x_0 \\ 0 & 0 \end{pmatrix}, t_{2\times 2} = \begin{pmatrix} d_2 + \rho & 0 \\ -Nd_2 & d_3 + fx_0 \end{pmatrix}$$

Now

$$et^{-1} = \frac{1}{(d_2 + \rho)(d_3 + fx_0)} \begin{pmatrix} Nd_2\beta x_0 & \beta x_0(d_2 + \rho) \\ 0 & 0 \end{pmatrix}$$

Therefore, basic reproduction number (R_0) of the system (2.5) is given by spectral radius of et^{-1} and hence $R_0 = \dfrac{Nd_2\beta x_0}{(d_2 + \rho)(d_3 + fx_0)}$.

3.2. HIV-infected equilibrium point. HIV-infected stationary point $\overline{E} = (\overline{x}, \overline{y}, \overline{z})$ must satisfy

$$r - d_1\overline{x} + a\overline{x}\left(1 - \frac{\overline{x}+\overline{y}}{x_{max}}\right) - f\overline{z}\overline{x} - \beta\overline{z}\overline{x} + \rho\overline{y} = 0 \tag{3.2}$$

$$\beta\overline{z}\overline{x} - d_2\overline{y} - \rho\overline{y} = 0 \tag{3.3}$$

$$Nd_2\overline{y} - d_3\overline{z} - f\overline{z}\overline{x} = 0 \tag{3.4}$$

Equations (3.3) and (3.4) lead to

$$\overline{x} = \frac{d_3(d_2+\rho)}{Nd_2\beta - (d_2+\rho)f},$$
$$\overline{y} = \frac{d_3\beta}{Nd_2\beta - (d_2+\rho)f}\overline{z}.$$

Substituting $\overline{x}$ and $\overline{y}$ in the equation (3.2), we get

$$\overline{z} = \frac{rp^2 + (a-d_1)(d_2+\rho)d_3p - \dfrac{a(d_2+\rho)^2d_3^2}{x_{max}}}{pfd_3(d_2+\rho) + pd_2d_3\beta + \dfrac{a(d_2+\rho)\beta d_3^2}{x_{max}}}$$

where $p = Nd_2\beta - (d_2+\rho)f$. These non-trivial solutions of the system (2.5) exist whenever $R_0 > 1$. Thus, we have following proposition:

Proposition 1. When $R_0 \leq 1$, only HIV-free equilibrium point $E_0 = (x_0, 0, 0)$ exists in Ω for the system (2.5) and for $R_0 > 1$ there exists two equilibrium points: HIV-free equilibrium point $E_0 = (x_0, 0, 0)$ and HIV-infected equilibrium point $\overline{E} = (\overline{x}, \overline{y}, \overline{z}) \in int(\Omega)$.

3.3. Behaviour of the Model (2.5) **around** E_0**.** In this section, we have studied the local and global behaviour of our model (2.5) around HIV-free equilibrium point E_0.

Theorem 3. *The HIV-free equilibrium point E_0 is locally asymptotically stable for $R_0 < 1$, locally stable for $R_0 = 1$ and unstable otherwise.*

Proof. The Jacobian matrix $J(E_0)$ at HIV-free equilibrium point E_0 is,

$$J(E_0) = \begin{pmatrix} \left(-d_1 + a\left(1 - \dfrac{x_0}{x_{max}}\right) - \dfrac{ax_0}{x_{max}}\right) & \left(-\dfrac{ax_0}{x_{max}} + \rho\right) & (-fx_0 - \beta x_0) \\ 0 & -(d_2+\rho) & \beta x_0 \\ 0 & Nd_2 & -d_3 - fx_0 \end{pmatrix}$$

One characteristic root of $J(E_0)$ is

$$\lambda_1 = -d_1 + a\left(1 - \frac{x_0}{x_{max}}\right) - \frac{ax_0}{x_{max}} = -\frac{r}{x_0} - \frac{ax_0}{x_{max}} < 0.$$

Other two characteristic roots are given by the equation,

$$\lambda^2 + A_1\lambda + A_2 = 0 \tag{3.5}$$

where,

$$A_1 = d_2 + \rho + d_3 + fx_0 > 0$$

$$A_2 = (d_2+\rho)(d_3+fx_0) - Nd_2\beta x_0 = (d_2+\rho)(d_3+fx_0)(1-R_0).$$

Therefore, one characteristic root of $J(E_0)$ is negative. Also, for $R_0 < 1$, $A_2 > 0$. Therefore, Routh-Hurwitz criteria indicates that when $R_0 < 1$, HIV-free equilibrium point E_0 is locally asymptotically stable. For $R_0 = 1$, one eigen value is zero. $J(E_0)$ has a positive characteristic root when $R_0 > 1$ which leads to instability of the HIV-free equilibrium point E_0. This completes the proof. □

Theorem 4. *The HIV-free equilibrium point E_0 is globally asymptotically stable when $R_0 \leq 1$, unstable otherwise.*

Proof. Define Lyaponuv's functional as:

$$L = \frac{Nd_2}{d_2+\rho}y + z$$

Differentiating w.r.t. t,

$$\frac{dL}{dt} = \frac{Nd_2}{d_2+\rho}\frac{dy}{dt} + \frac{dz}{dt}$$

Putting $\frac{dy}{dt}$ and $\frac{dz}{dt}$ from the system (2.5),

$$\frac{dL}{dt} = z(d_3+fx)\left[\frac{Nd_2\beta x}{(d_2+\rho)(d_3+fx)} - 1\right] \leq z(d_3+fx_0)(R_0-1) \tag{3.6}$$

It is straightforward from equation (3.6) that if $R_0 \leq 1$, $\frac{dL}{dt} \leq 0$. We have, $\frac{dL}{dt} = 0$ for two cases: $z = 0$ or $R_0 = 1$ and $x = x_0$. Hence, as per Lyapunov- Lasalle theorem [28] when $R_0 \leq 1$, all solutions in the region Ω approaches to the HIV-free equilibrium point E_0.

Since $J(E_0)$ has one positive characteristic root when $R_0 > 1$, therefore HIV-free equilibrium point E_0 is unstable. □

Numerically, stability of the HIV-free equilibrium point E_0 are shown in the figure 2 which verifies the analytic results. From table 1, we get $R_0 = 0.541 < 1$ for parameters as in the data set 1. Thus, theorem 4 indicates that virus will be cleared out. Fig. 2(a) depicts the increase of

the HIV-free $CD4^+$ T cells in the first few days and then it goes to equilibrium state. Fig. 2(b) describes the rapid increase of HIV-infected $CD4^+$ T cells in the starting few days and then it decreases fastly and it becomes zero after some days. From fig. 2(c), it is clear that in the starting few days, free virus population decreases very fastly until it reaches the zero level.

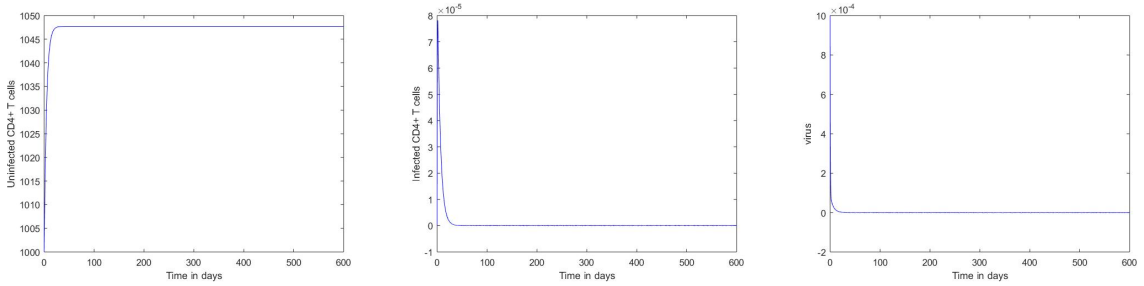

FIGURE 2. Dynamics of HIV-free $CD4^+$ T cells (a), HIV-infected $CD4^+$ T cells (b) and virus (c) *vs.* time for $R_0 = 0.541 < 1$.

3.4. Behaviour of the Model (2.5) **around** $\overline{E}$**.** In this section, we have studied both the local and global behaviour of the model (2.5) around the HIV-infected equilibrium point $\overline{E}$.

Theorem 5. *If*

(i) $R_0 > 1$,

(ii) $M_0 - \dfrac{\rho f \overline{z}}{d_2} \geq 0$ *where* $M_0 = d_1 - a + a\left(\dfrac{2\overline{x}+\overline{y}}{x_{max}}\right)$.

then, HIV-infected equilibrium point $\overline{E}(\overline{x},\overline{y},\overline{z})$ *is locally asymptotically stable.*

Proof. The Jacobian matrix $J(\overline{E})$ at HIV-infected equilibrium $\overline{E}$ is

$$J(\overline{E}) = \begin{pmatrix} -\overline{Z} & \left(-\dfrac{a\overline{x}}{x_{max}} + \rho\right) & (-f\overline{x} - \beta\overline{x}) \\ \beta\overline{z} & -(d_2+\rho) & \beta\overline{x} \\ -f\overline{z} & Nd_2 & -d_3 - f\overline{x} \end{pmatrix} \tag{3.7}$$

where

$$\overline{Z} = d_1 - a\left(1 - \frac{\overline{x}+\overline{y}}{x_{max}}\right) + \frac{a\overline{x}}{x_{max}} + f\overline{z} + \beta\overline{z} = \frac{r}{\overline{x}} + \frac{a\overline{x}}{x_{max}} + \frac{\rho\overline{y}}{\overline{x}} > 0.$$

The characteristic equation of $J(\overline{E})$ is

$$\lambda^3 + B_1\lambda^2 + B_2\lambda + B_3 = 0 \tag{3.8}$$

where

$$B_1 = \overline{Z} + d_2 + \rho + d_3 + f\bar{x} > 0,$$

$$B_2 = \left(\frac{r}{\bar{x}} + \frac{a\bar{x}}{x_{max}}\right)(d_2 + \rho + d_3) + \frac{\rho d_3 \bar{y}}{\bar{x}} + \frac{a\beta\bar{x}\bar{z}}{x_{max}} + f\bar{x}M_0,$$

$$B_3 = \left(\frac{a\bar{x}}{x_{max}} + d_2\right)\beta\bar{z}d_3 + f\bar{z}d_3(d_2 + \rho) > 0,$$

$$B_1B_2 - B_3 = B_2(\overline{Z} + \rho + f\bar{x}) + d_2\left\{\left(\frac{r}{\bar{x}} + \frac{a\bar{x}}{x_{max}}\right)(d_2 + \rho + d_3) + \frac{a\beta\bar{x}\bar{z}}{x_{max}} + f\bar{x}M_0\right\} +$$

$$d_3\left\{\left(\frac{r}{\bar{x}} + \frac{a\bar{x}}{x_{max}}\right)(\rho + d_3) + \frac{\rho d_3\bar{y}}{\bar{x}} + f\bar{x}M_0\right\} + d_2d_3\left(M_0 - \frac{\rho f\bar{z}}{d_2}\right),$$

$$M_0 = d_1 - a + a\left(\frac{2\bar{x} + \bar{y}}{x_{max}}\right).$$

From the above analysis, we have $B_2 > 0$ if $M_0 \geq 0$ and $B_1B_2 - B_3 > 0$ if $M_0 - \frac{f\rho\bar{z}}{d_2} \geq 0$. Using Routh-Hurwitz criteria, the HIV-infected equilibrium point $\overline{E}$ is locally asymptotically stable when $M_0 - \frac{\rho f\bar{z}}{d_2} \geq 0$. □

We know, the system (2.5) will be uniformly persistent in the region $int(\Omega)$ if there exists $\varepsilon > 0$, irrespective of initial data in $int(\Omega)$, such that for all solutions $(x(t), y(t), z(t))$ of the model (2.5)

$$\liminf_{t\to\infty} x(t) > \varepsilon, \liminf_{t\to\infty} y(t) > \varepsilon, \liminf_{t\to\infty} z(t) > \varepsilon$$

for $(x(0), y(0), z(0)) \in int(\Omega)$.

Theorem 6. *The system* (2.5) *is uniformly persistent when* $R_0 > 1$.

Proof. From equation (3.6), it is clear that for all solutions sufficiently close to E_0 and initiating in $int(\Omega)$, $\frac{dL}{dt} > 0$ when $R_0 > 1$. Thus, a neighborhood of E_0 is left by these solutions. Solutions on the x-axis which is positively invariant satisfies the equation,

$$\frac{dx}{dt} = r + ax\left(1 - \frac{x}{x_{max}}\right) - d_1x$$

Thus, $x \to x_0$ as $t \to \infty$. Thus, when $R_0 \leq 1$ all the solutions in Ω approaches to E_0 along x-axis. We can show that the uniform persistence of system (2.5) is implied by the local behaviors of solutions around E_0 along with the instability of E_0. Using a uniform persistence result from [29] and a similar argument from the proof of the Proposition 3.3 in [30], the proof of the theorem is completed. □

In our study, we have used global-stability criteria develoved by Li and Muldowney [31] to study the global behaviour of HIV-infected equilibrium point $\overline{E}$. We have, $int(\Omega)$ is simply connected and when $R_0 > 1$, $\overline{E}$ is the unique stationary point in $int(\Omega)$. From theorem 4, it is straightforward that an absorbing compact set $H \subset \Omega$ exists for the model (2.5). Also, already it is proved that the solutions of model (2.5) are ultimately bounded and the conditions

$$x(t) \leq x_0, y(t) < B, z < B \tag{3.9}$$

for $B > 0$ and all large t, are satisfied by any positive solution of the model (2.5) in $int(\Omega)$.

We have the following theorem regarding global behaviour of HIV-infected equilibrium point $\overline{E}$.

Theorem 7. *The HIV-infected equilibrium point $\overline{E}$ whenever it exists is globally asymptotically stable in the interior of H if*

$$v := Bf + v_0 < 0, \tag{3.10}$$

where

$$v_0 = \max\left\{-d_1 + a\left(1 - \frac{\varepsilon}{x_{max}}\right) + \frac{x_0 Bf}{\varepsilon}, -d_2 + \frac{ax_0}{x_{max}}\right\}$$

and ε is constant of uniform persistent and B is defined in equation (3.9)*.*

Proof. For a general solution $(x(t), y(t), z(t))$ of the model (2.5), associated Jacobian matrix J is

$$J(E) = \begin{pmatrix} -Z & -\frac{ax}{x_{max}} + \rho & -fx - \beta x \\ \beta z & -(d_2 + \rho) & \beta x \\ -fz & Nd_2 & -d_3 - fx \end{pmatrix} \tag{3.11}$$

$J^{[2]}$, corresponding second additive compound matrix [21, 31] of J is

$$J^{[2]} = \begin{pmatrix} -(Z + d_2 + \rho) & \beta x & fx + \beta x \\ Nd_2 & -(Z + d_3 + fx) & -\frac{ax}{x_{max}} + \rho \\ fz & \beta z & -(d_2 + \rho + d_3 + fx) \end{pmatrix}$$

where

$$Z = d_1 - a\left(1 - \frac{x+y}{x_{max}}\right) + \frac{ax}{x_{max}} + fz + \beta z$$

Define,

$$Q = Q(x,y,z) = \begin{pmatrix} 1 & 0 & 0 \\ 0 & \frac{y}{z} & 0 \\ 0 & 0 & \frac{y}{z} \end{pmatrix}$$

Now, we compute the directional derivative matrix Q_f in the direction of f [32] as follows,

$$Q_f = \begin{pmatrix} 0 & 0 & 0 \\ 0 & \frac{y'}{z} - \frac{yz'}{z^2} & 0 \\ 0 & 0 & \frac{y'}{z} - \frac{yz'}{z^2} \end{pmatrix}$$

Then,

$$Q_f Q^{-1} = \begin{pmatrix} 0 & 0 & 0 \\ 0 & \frac{y'}{y} - \frac{z'}{z} & 0 \\ 0 & 0 & \frac{y'}{y} - \frac{z'}{z} \end{pmatrix}$$

Define,

$$\begin{aligned} X :=& Q_f Q^{-1} + QJ^{[2]}Q^{-1} \\ =& \begin{pmatrix} -(Z+d_2+\rho) & \frac{\beta xz}{y} & \frac{(fx+\beta x)z}{y} \\ \frac{Nd_2 y}{z} & \frac{y'}{y} - \frac{z'}{z} - Z - d_3 - fx & -\frac{ax}{x_{max}} + \rho \\ fz & \beta z & \frac{y'}{y} - \frac{z'}{z} - d_2 - \rho - d_3 - fx \end{pmatrix} \\ =& \begin{pmatrix} X_{11} & X_{12} \\ X_{21} & X_{22} \end{pmatrix} \end{aligned}$$

where $X_{11} = -(Z+d_2+\rho), X_{12} = \begin{pmatrix} \frac{\beta xz}{y} & \frac{(fx+\beta x)z}{y} \end{pmatrix}, X_{21} = \begin{pmatrix} \frac{Nd_2 y}{z} \\ fz \end{pmatrix}$ and

$$X_{22} = \begin{pmatrix} \frac{y'}{y} - \frac{z'}{z} - Z - d_3 - fx & -\frac{ax}{x_{max}} + \rho \\ \beta z & \frac{y'}{y} - \frac{z'}{z} - d_2 - \rho - d_3 - fx \end{pmatrix}.$$

Let, (u,v,w) be a vector in $\mathbb{R}^3$, consider a norm in $\mathbb{R}^3$ as $|(u,v,w)| = max\{|u|, |v|+|w|\}$. Consider, the corresponding Lozinskii measure be μ. Then we have (see [33]):

$$\mu(X) \leq max\{g_1, g_2\} \tag{3.12}$$

with

$$g_1 = \mu_1(X_{11}) + |X_{12}|, g_2 = |X_{21}| + \mu_1(X_{22}) \tag{3.13}$$

Here, $|X_{12}|, |X_{21}|$ are matrix norm and μ_1 be the Lozinskii measure w.r.t. l_1 norm. Specifically,

$$\mu_1(X_{11}) = -Z - d_2 - \rho, |X_{12}| = \frac{(fx+\beta x)z}{y}, |X_{21}| = \frac{Nd_2 y}{z} + fz$$

To calculate $\mu_1(X_{22})$, we consider the solutions of system (2.5) from the interior of the compact set $H \subset \Omega$ which satisfies (3.9), then:

$$\begin{aligned}
\mu_1(X_{22}) &= max\left\{\frac{y'}{y} - \frac{z'}{z} - Z - d_3 - fx + \beta z, \frac{y'}{y} - \frac{z'}{z} - d_2 - \rho - d_3 - fx + \left|-\frac{ax}{x_{max}} + \rho\right|\right\} \\
&\leq \frac{y'}{y} - \frac{z'}{z} - fx - d_3 + max\left\{-d_1 + a\left(1 - \frac{2x+y}{x_{max}}\right) - fz, -d_2 + \frac{ax}{x_{max}}\right\} \\
&< \frac{y'}{y} - \frac{z'}{z} - fx - d_3 + v_0
\end{aligned}$$

where,

$$v_0 = \max\left\{-d_1 + a\left(1 - \frac{\varepsilon}{x_{max}}\right) + \frac{x_0 Bf}{\varepsilon}, -d_2 + \frac{ax_0}{x_{max}}\right\}.$$

From the system (2.5), we get

$$\begin{aligned}
\frac{y'}{y} &= \frac{\beta zx}{y} - d_2 - \rho \\
\frac{z'}{z} &= \frac{Nd_2 y}{z} - d_3 - fx
\end{aligned}$$

From (3.13), we have

$$\begin{aligned}
g_1 &= -Z - d_2 - \rho + \frac{(fx+\beta x)z}{y} = \frac{y'}{y} - Z + \frac{fxz}{y} < \frac{y'}{y} + v \\
g_2 &< \frac{Nd_2 y}{z} + fz + \frac{y'}{y} - \frac{z'}{z} - fx - d_3 + v_0 < \frac{y'}{y} + v
\end{aligned}$$

Therefore, we have

$$\mu(X) \leq \frac{y'}{y} + v$$

Define v with the help of (3.9) as:

$$v := Bf + v_0 < 0$$

Consider, $\bar{t}$ be sufficiently large time such that $(x(t),y(t),z(t)) \in H$ for all $t \geq \bar{t}$ and $(x(t),y(t),z(t))$ be any positive solution starting in the compact absorbing set $H \subset \Omega$. Then, along each solution $(x(t),y(t),z(t))$ with the condition $(x(0),y(0),z(0)) \in H$ and $t > \bar{t}$, we have

$$\frac{1}{t}\int_0^t \mu(X)ds \leq \frac{1}{t}\int_0^{\bar{t}} \mu(X)ds + \frac{1}{t}ln\frac{y(t)}{y(\bar{t})} + \left(\frac{t-\bar{t}}{t}\right)v.$$

Consequently,

$$\bar{q_2} := \lim_{t\to\infty}\sup\sup_{x_0\in H}\frac{1}{t}\int_0^t \mu(X(x(s,x_0)))ds < 0$$

From [31], we have globally asymptotically stability criteria for the HIV-infected equilibrium point $\overline{E}$ is that $v < 0$, which completes the proof. □

Numerical results for HIV-infected equilibrium $\overline{E}$ are shown in figure 3. From table 1, we get $R_0 = 5.8424 > 1$ for data set 2. Therefore, a unique HIV-infected equilibrium point $\overline{E}(178.042, 164.599, 136.962)$ exists. Global dynamics of the HIV-free $CD4^+$ T cells, HIV-infected $CD4^+$ T cells and free virus are depicted when $R_0 > 1$ i.e. whenever HIV-infected equilibrium exists. Also, for this parameter set 2, the conditions for the analytic results are satisfied and hence these analytic results are numerically verified.

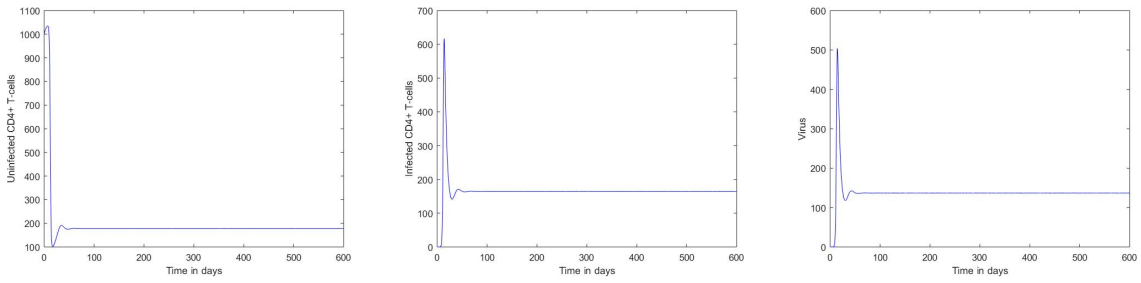

FIGURE 3. Dynamics of HIV-free $CD4^+$ T cells, HIV-infected $CD4^+$ T cells and virus *vs.* time for $R_0 = 5.8424 > 1$.

4. DISCUSSION

In this paper, we have considered the classical virus infection model with the effects of fusion and cure rate along with the consideration that multiplication of the existing $CD4^+$ T cells can occur and it follows full logistic growth term $ax\left(1-\frac{x+y}{x_{max}}\right)$. In the earlier studies of fusion effect and cure rate, constant inflow rate of the HIV-free $CD4^+$ T cells was considered by Gupta and Dutta [13, 14]. In our paper, we have studied the effects of fusion and cure rate with consideration of proliferation of healthy $CD4^+$ T cells. Essential criteria like non-negativity

and boundedness of the solutions for a biologically feasible model are proved. Also, basic reproduction number (R_0) is calculated for our model (2.5) and it is found to be a threshold parameter in our study. Our stability analysis indicates that if $R_0 \leq 1$ then T cell population will be free from HIV infection and HIV infection persists for $R_0 > 1$. Also, stability analysis of HIV-infected equilibrium point established that proliferation rate and the basic reproduction number are the important factors for stability of the HIV-infected equilibrium point. Therefore, proliferation of T cells cannot be ignored while analyzing the dynamics of HIV for better outcomes.

We can study the effect of fusion rate on the dynamics of the model by means of numerical simulations. For this purpose, we consider two different fusion rates (f) with other parameters same as data set 2. The effect of fusion rate (f) is shown in figure 4. It is observed that when the fusion rate is increased the HIV-infected $CD4^+$ T cell and virus population decrease.

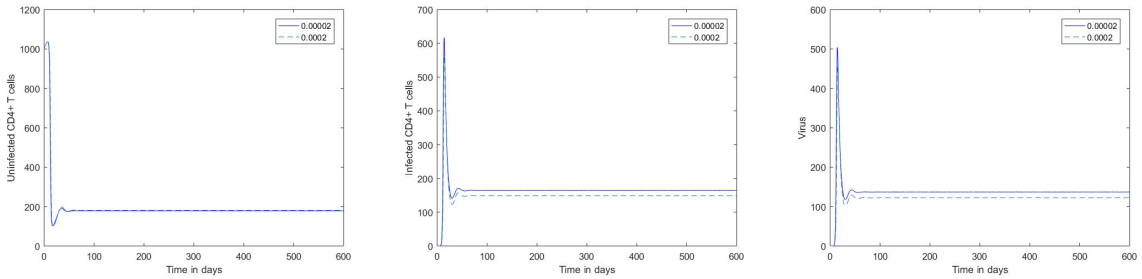

FIGURE 4. Dynamics of HIV-free $CD4^+$ T cells, HIV-infected $CD4^+$ T cells and virus *vs.* time for different values of f.

Similarly, the effects of cure rate (ρ) on the dynamics of the model are shown in figure 5. It is clear that when cure rate is increased the transition time of HIV-free $CD4^+$ T cell population increases and the HIV-infected $CD4^+$ T cell population and virus population decrease.

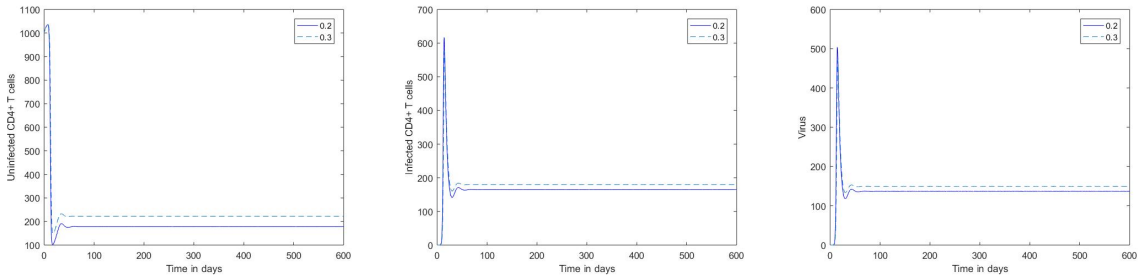

FIGURE 5. Dynamics of HIV-free $CD4^+$ T cells, HIV-infected $CD4^+$ T cells and virus *vs.* time for two different values of ρ.

From the overall study, it is clear that a treatment policy that can increase the transfer rate of HIV-infected $CD4^+$ T cells to HIV-free class along with the loss of free viruses due to the fusion effect will be effective to control HIV infection.

CONFLICT OF INTERESTS

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

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