Analysis of an HIV Pandemic Model with Cure Rate and CTL Response Delay

V. Geetha1, S. Balamuralitharan2*

1,2Dept of Mathematics, SRM Institute of science and technology, Kattankulathur-603203, Kancheepuram Dt., Tamil Nadu, India

*Corresponding author: balamurs@srmist.edu.in (Balamuralitharan)

Abstract - An HIV infection model with cure rate and Cytotoxic T-lymphocyte (CTL) response delay is investigated. The positivity and boundedness solutions of the proposed model were demonstrated. The stability of both virus-free equilibrium $I_0$ and the infected equilibrium $I_1$ is determined by the basic reproduction number $R_0$. Further, the existence of bifurcation in Hopf at the infected equilibrium of CTL immune response is also observed. Our empirical findings are shown by numerical simulations.

Keywords: HIV infection, model, CTL

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1. INTRODUCTION

Human Immunodeficiency Virus (HIV) appears to have become a global pandemic [1]. HIV is a retrovirus that induces the acquired immunodeficiency syndrome (AIDS) condition. A certain form immune system in the body called CD4 lymphocyte helper cells is infected by HIV virus. HIV kills these cells and makes it more difficult for the human body to resist other infections. HIV infection is caused by the transmission of blood, sperm, pre-ejaculate, vaginal fluid and breast milk. Some antiretroviral treatments currently available that support the immune system to prevent HIV [2, 3]. Reverse Transcriptase Inhibitors (RTIs) is one of the drugs that prevents virus RNA from being converted into DNA, which means that the viral population of the virus is reduced and the CD4+ count is higher and that the host will continue to be able to survive. Proteases (PIs) blocks viruses from actively infected cells.

Mathematical models are useful to understand the dynamics of HIV. Bonhoeffer et al [4], Nowak and Bangham [5] suggested the basic virus-host cell model. Several researchers have expanded the basic HIV pathogenesis model to incorporate other biological characteristics, such as antiretroviral therapy, therapeutic drugs, etc [6-7]. Culshaw et al. [8] improved the model by introducing logistic terms for the production of CD4 + T cells. Another development in viral dynamic modeling is the study of the rate of cure of infected cells. Lewin et al. [9] suggested an HBV cure rate model, which represents infected cells returning from their nucleus in the uninfected state. Zhou et al. [10] examined the infection of HIV model with the cure rate. In recent decades, various mathematical models have been developed that explain HIV dynamics [11-14]. CTLs play a major part in protecting antiviral by invading infected cells in most virus infections [15]. There has been a substantial concern to population dynamics in viral pathogens with CTL and several properties have been studied [16-18]. Some researchers suggest that the time lag in the immune response models can never be disregarded. [19-21].

2. Theoretical Framework

Motivated by the above-mentioned study, we introduce a model for HIV infection of CD4+ T-cells with cure rate and CTL response delay. The proposed model that contains an uninfected cells $T(t)$, infected cells $I(t)$, virus $V(t)$, and CTL response $Z(t)$ is given by

$$\dot{T} = \Lambda - dT + aT \left(1 - \frac{T}{T_{\text{max}}} \right) - \beta TI + \alpha I,$$
\[ \dot{I} = \beta TV - (\alpha + \delta)I - pIZ, \]
\[ \dot{V} = qI - kV, \]
\[ \dot{Z} = cI(t - \tau)Z(t - \tau) - bZ. \]  

(1)

Where \( \tau \) represents the production of CTL needs a time period.

The initial conditions for model (2) are
\[ T(\theta) = \varepsilon_1(\theta), I(\theta) = \varepsilon_2(\theta), V(\theta) = \varepsilon_3(\theta), Z(\theta) = \varepsilon_4(\theta), \]
\[ \varepsilon_i(\theta) \geq 0, \theta \in [-\tau, 0], i = 1, 2, 3, 4. \]  

(2)

3. Methodology

3.1 POSITIVITY AND BOUNDEDNESS

Theorem 1:

Let the solution \((T(t), I(t), V(t), Z(t))\) of (2) that satisfies the conditions (3)

Then the solution is positive and bounded.

Proof:

It is obvious that \(T(t) > 0\). If not then \(t_i > 0\) such that \(T(t_i) = 0\).

From (2) we get \(T(t_i) = \Lambda > 0\) then \(T(t) < 0\) for \(t \in (t_i - \varepsilon, t_i)\), where \(\varepsilon\) is a small positive constant, it leads to a contradiction.

Therefore \(T(t) > 0\).

From (1), we have
\[ I(t) = I(0)e^\int_0^t (\delta + \alpha + pZ(u))du + \int_0^t \beta I(\theta)V(\theta)e^\int_0^\theta (\delta + \alpha + pZ(u))du d\theta, \]
\[ V(t) = V(0)e^{-kt} + \int_0^t qI(\theta)e^{-k(t-\theta)}d\theta, \]
\[ Z(t) = Z(0)e^{-bt} + \int_0^t cI(\theta - \tau)Z(\theta - \tau)e^{-b(t-\theta)}d\theta. \]  

(3)

From these we get \(I(t), V(t), Z(t)\) are positive on the existing interval.

Now, we prove that system (2) is bounded.

From (2) we get
\[ \lim_{t \to \infty} \sup T(t) \leq T_0. \]  

(4)

Here \(T_0 = \frac{T_{\max}}{2a} \left[ (a - d) + \sqrt{(a - d)^2 + 4a\Lambda} \right]. \)  

(5)

We define \(E = T + I\) then we have
\[ \dot{E} \leq \Lambda + aT \left( 1 - \frac{T}{T_{\max}} \right) - hE \]
\[ \leq F - hE. \]

Where \(F = \Lambda + aT_{\max} \) and \(h = \min \{d, \delta\} .\)

Then we get \(E\) is ultimately bounded. From (5) it is clear that \(T(t)\) has an ultimate bound \(T_0\) and \(I(t)\) is ultimately bounded with some \(M^*_1\) and \(V(t)\) is ultimately bounded with some \(M^*_2\) and \(Z(t)\) is ultimately bounded with some \(M^*_3\).

Define \(M = \max \{M^*_1, M^*_2, M^*_3\} \) such that \(T(t) \leq T_0, I(t) \leq M^*_1, V(t) \leq M^*_2, Z(t) \leq M^*_3. \)
3.2. STABILITY ANALYSIS

The basic reproduction ratio of (2) is given by:

\[
R_0 = \frac{\beta q T_0}{k (\delta + \alpha)}. 
\]

We have the following non-negative equilibrium points of (2):

\[
(I, T, I, V, Z) = (0, 0, 0, 0) \quad \text{and} \quad (I, T, I, V, Z) = (I_1, T_1, I_2, V_2, Z_2).
\]

Here, \(T_0 = \frac{T_{\text{max}}}{2a} \left( (a - d) + \sqrt{(a - d)^2 + 4a \lambda} \right)\) and \(I = \frac{b}{c}, V = \frac{b q T - k (\delta + \alpha)}{kp}\).

And \(T\) is the following quadratic equation:

\[
B_T T^2 + B_T T - B_3 = 0,
\]

Where \(B_1 = a c k, B_2 = (c k (d - a) + \beta q T) T_{\text{max}}, B_3 = k (\Lambda c + a b) T_{\text{max}}\).

3.3. Local Stability of virus free equilibrium \((I_1)\)

**Theorem 2:**
If \(R_0 < 1\) then \(I_1\) is locally asymptotically stable.

**Proof:** The characteristic equation of \(I_1\) is

\[
\begin{vmatrix}
-d + a + \frac{2a T_0}{T_{\text{max}}} - \lambda & \alpha & -\beta T_0 & 0 \\
0 & -(\delta + \alpha) - \lambda & -\beta T_0 & 0 \\
0 & q & -k - \lambda & 0 \\
0 & 0 & 0 & -b - \lambda
\end{vmatrix} = 0
\]

From (7) we get the characteristic roots:

\[
\lambda_1 = -d + a + \frac{2a T_0}{T_{\text{max}}} = -\frac{a T_0}{T_{\text{max}}} + \frac{\Lambda}{T_0} < 0, \lambda_2 = -b < 0.
\]

And the other roots satisfy the following equation:

\[
\lambda^2 + \lambda (k + \delta + \alpha) + (k (\delta + \alpha) - \beta q T_0) = 0.
\]

The inequality \(R_0 < 1\) implies that \(k (\delta + \alpha) - \beta q T_0 > 0\).

In (8) all the roots of real part is negative then \(I_1\) is asymptotically stable.

3.4. Stability analysis and Hopf bifurcation of infected equilibrium \((I_2)\)

The characteristic equation of (2) at \(I_2\) is given by

\[
\begin{vmatrix}
-d + a + \frac{2a T}{T_{\text{max}}} - \beta V - \lambda & \alpha & -\beta T & 0 \\
0 & -(\delta + \alpha) - p Z - \lambda & -p I & 0 \\
0 & q & -k - \lambda & 0 \\
0 & e^{-\lambda \tau_c} & 0 & e^{-\lambda \tau_c} (I - b - \lambda)
\end{vmatrix} = 0
\]

Which is equivalent to the equation:

\[
A(\lambda, \tau) + B(\lambda, \tau) e^{-\lambda \tau} = 0,
\]

Where \(A(\lambda, \tau) = \lambda^4 + K_1 \lambda^3 + K_2 \lambda^2 + K_3 \lambda + K_4, B(\lambda, \tau) = L_1 \lambda^3 + L_2 \lambda^2 + L_3 \lambda + L_4, K_1 = -a_1 - a_5 - a_6 - a_{11}, K_2 = a_3 a_9 + a_4 a_9 + a_4 a_{11} + a_4 a_3 + a_3 a_{11} + a_2 a_4 - a_3 a_4, K_3 = -a_3 a_9 a_8 - a_4 a_9 a_{11} - a_4 a_8 a_{11} - a_4 a_9 a_8 - a_4 a_{11} a_8 + a_4 a_8 a_{11} - a_4 a_8 a_{11} - a_4 a_8 a_{11} + a_4 a_8 a_{11} - a_4 a_8 a_{11}, K_4 = a_3 a_3 a_9 a_{11} + a_4 a_3 a_{11} + a_4 a_3 a_{11} + a_3 a_3 a_{11} + a_3 a_3 a_{11},\)

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In which \( a_i = -d + a \frac{2aT}{T_{\text{max}}} \beta V, a_i = \alpha, a_j = -\beta \tau, a_4 = \beta V, a_1 = -\left( \delta + \alpha + p \right) \).

\[
a_i = -p I, a_4 = q, a_j = -k, a_5 = c Z, a_{10} = c I, a_{11} = -b.
\]

If \( \tau = 0 \) equation (9) becomes

\[
\begin{align*}
\dot{x}_1 &= -k x_1 - c z_1, \\
\dot{x}_2 &= -k x_2 - c z_2, \\
\dot{x}_3 &= -k x_3 - c z_3, \\
\dot{x}_4 &= -k x_4 - c z_4.
\end{align*}
\]

Lemma 1: If \( R_0 > 1 \) and \( \tau = 0 \), then \( I_2 \) of (2) is asymptotically stable locally provided (12) holds.

Proof:

By the above lemma we get (i) \( S_i > 0 \), \( i = 1, 2, 3, 4 \) and \( S_1 S_2 S_3 > S_1^2 S_4 + S_3^2 \) as provided by Routh-Hurwitz condition.

Hence all the roots are negative real part.

Therefore, we conclude that \( I_2 \) is locally asymptotically stable.

3.5. Existence of Hopf Bifurcation

We deduce the criteria for \( \tau > 0 \).

For \( \tau \neq 0 \), we consider \( \tau \) as bifurcation parameter and assume a purely imaginary solution of (10) is of the form

\[
\lambda = i\eta (\eta \neq 0).
\]

Substitute \( \lambda = i\eta \) in (10) we get

\[
\begin{align*}
(\eta^4 - K_2 \eta^2 + K_4), & \quad (-L_2 \eta^2 + L_4) \cos(\eta \tau) + (-L_1 \eta^3 + L_3 \eta) \sin(\eta \tau) = 0 \\
(-K_1 \eta^3 + K_3 \eta), & \quad (-L_1 \eta^3 + L_3 \eta) \cos(\eta \tau) - (-L_2 \eta^2 + L_4 \eta) \sin(\eta \tau) = 0
\end{align*}
\]

\[
\cos(\eta \tau) = \left( L_2 - L_1 \right) \eta^4 + (K_4, L_4 - K_3, L_3 + K_2, L_2) \eta^4
\]

\[
+ \left( (K_4, L_4 - K_3, L_3 + K_2, L_2) \eta^4 - K_1, L_1 \right) \eta^4
\]

\[
\sin(\eta \tau) = \left( L_2 - L_1 \right) \eta^4 + (K_4, L_4 - K_3, L_3 + K_2, L_2) \eta^4
\]

\[
+ \left( (K_4, L_4 - K_3, L_3 + K_2, L_2) \eta^4 - K_1, L_1 \right) \eta^4
\]

\[
\begin{align*}
b_1 &= L_2 - K_1, b_2 = K_1, L_2 - K_1, b_3 = K_1, L_3 - K_1, b_4 = -K_1, L_3, \\
b_5 &= L_2, b_6 = L_2, b_7 = L_2, b_8 = L_2, b_9 = L_2, b_{10} = K_1, L_3 - K_1, \\
b_{11} &= K_1, L_3 - K_1, b_{12} = K_1, L_3 - K_1.
\end{align*}
\]

(13)

From (13) we have \( \eta^4 + c_1 \eta^3 + c_2 \eta^2 + c_3 \eta + c_4 = 0 \).

From (12) we have \( c_1 \tau^{m-1} \).

Sub \( \eta^4 + c_1 \rho^4 + c_2 \rho^3 + c_3 \rho^2 + c_4 = 0 \).

If \( c_4 < 0 \) then (16) has one positive root

Incased (16) has four positive roots we have \( \eta_1 = \sqrt{\rho_1}, \eta_2 = \sqrt{\rho_2}, \eta_3 = \sqrt{\rho_3}, \eta_4 = \sqrt{\rho_4} \).

From (13) we have \( c_1 \tau^{m-1} \).

We choose \( \tau^* = \min(\eta_k^{(j)} \).

In order to determine a Hopf bifurcation at \( \tau = \tau^* \), we prove that \( R = \left( \frac{d\lambda}{d\tau} \right)_{\tau = \tau^*} = 0 \).

Taking derivative of the characteristic equation (10) with respect to \( \tau \), we get

\[
\left( \frac{d\lambda}{d\tau} \right)^{-1} = \left( (4 \lambda^3 + 3 K_3 \lambda^2 + 2 K_2 \lambda + K_1) + e^{-i\tau} \left( 3 L_2 \lambda^2 + 2 L_1 \lambda + L_0 \right) \right) \times \lambda e^{-i\tau} \left( L_0 \lambda^2 + L_2 \lambda^2 + L_4 \lambda + L_4 \right)^{-1} - \frac{\tau}{\lambda}.
\]
Sub $\lambda = i\eta$ in (18) we get
$$
\left(\frac{d\lambda}{d\tau}\right)^{-1}\bigg|_{\tau = \tau^*} = \frac{f_1 + if_2}{f_1 + f_2} - \frac{\tau}{\lambda}.
$$

Where
$$
\begin{align*}
& f_1 = \left(K_1 - 3K\eta^2\right) + \left(L_1 - 3L\eta\right)\cos\left(\eta,\tau\right) + \left(2L\eta\sin\left(\eta,\tau\right)\right), \\
& f_2 = \left(2K\eta - 4\eta\right) + \left(2L\eta\cos\left(\eta,\tau\right)\right) - \left(L_1 - 3L\eta\right)\sin\left(\eta,\tau\right), \\
& f_3 = \left(L\eta - L\eta\right)\cos\left(\eta,\tau\right) + \left(L\eta\right)\sin\left(\eta,\tau\right), \\
& f_4 = \left(L\eta - L\eta\right)\cos\left(\eta,\tau\right) + \left(L\eta\right)\sin\left(\eta,\tau\right).
\end{align*}
$$

Thus
$$
R\left(\frac{d\lambda}{d\tau}\right)^{-1}\bigg|_{\tau = \tau^*} = \frac{f_1 + if_2 + f_3 + f_4}{f_1 + f_3}.
$$

Note that
$$
sign\left(R\left(\frac{d\lambda}{d\tau}\right)^{-1}\bigg|_{\tau = \tau^*}\right) = sign\left(R\left(\frac{d\lambda}{d\tau}\right)^{-1}\bigg|_{\tau = \tau^*}\right).
$$

We arrive at the following lemma by illustrating the above results.

**Lemma 2:**
$I_2$ of (2) is asymptotically stable for $\tau \in \left[0, \tau^*_c\right]$ and unstable when $\tau > \tau^*_c$, system (2) undergoes Hopf bifurcation at $\tau = \tau^*_c$.

<table>
<thead>
<tr>
<th>Parameters and variables</th>
<th>Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\Lambda$</td>
<td>Uninfected cells production rate</td>
</tr>
<tr>
<td>$d$</td>
<td>depletion rate of uninfected cells</td>
</tr>
<tr>
<td>$a$</td>
<td>Rate of growth of T-cells</td>
</tr>
<tr>
<td>$T_{max}$</td>
<td>Maximum population density of T-cells</td>
</tr>
<tr>
<td>$\beta$</td>
<td>Rate of Infection</td>
</tr>
<tr>
<td>$\sigma$</td>
<td>Cure rate</td>
</tr>
<tr>
<td>$\delta$</td>
<td>Infected cells decay rate</td>
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<tr>
<td>$p$</td>
<td>Rate of decay for infected cells by immune response</td>
</tr>
<tr>
<td>$g$</td>
<td>Rate of infected cells reproduced</td>
</tr>
<tr>
<td>$k$</td>
<td>Free virus Clearance rate</td>
</tr>
<tr>
<td>$c$</td>
<td>CTL proliferation rate</td>
</tr>
<tr>
<td>$b$</td>
<td>Depletion rate of CTL</td>
</tr>
</tbody>
</table>

4. Results
We use Matlab to perform numerical illustrations in order to ascertain the main results. The values for parameters are considered in Table1. Based on the values of the given parameters, we get the infected equilibrium $I_2 (859.01, 16.6, 1666.6, 694)$ and the reproduction ratio $R_0 = 1.9719$ and the critical value $\tau^*_c = 0.114$. By Theorem 3.4, the infected equilibrium $I_2$ is stable when $\tau < \tau^*_c$ (Fig. 1); when $\tau = \tau^*_c$ occurs Hopf bifurcation and the equilibrium become unstable when $\tau > \tau^*_c$ (Fig 2). We also note that the infection will always maintain stable if the rate of cure $\alpha$ is higher (see fig3 (a)-(c)). The findings show that we are controlled by the disease if we increase the cure rate. Therefore, the cure rate is an important parameter can be inferred.
Fig. 1 Phase diagrams of (2) is asymptotically stable when $\tau = 0.09$
Fig. 2 Phase diagrams of (2) after Hopf bifurcation occurs when $\tau = 0.2$
Fig. 3 The diagrams show $T(t)$, $I(t)$, $V(t)$ for different cure rate values.

5. Discussion

In this study, we have provided a mathematical model describing CD4+ T-cell HIV infection including cure rate, logistic term with immune response delay. The virus-free equilibrium has been shown to be locally asymptotically stable if $R_0 < 1$. The virus will not maintain the infection in this situation and will go extinct. If $R_0 > 1$ becomes unstable and the equilibrium of HIV infection exists. $I_2$ is asymptotically stable in the delay independent. Therefore, $R_0$ is a sharp threshold parameter, which specifies that host viruses survive or become extinct. The result suggested in [22, 23] that the CTL immune delay can affect the periodic oscillation by Hopf bifurcation. Finally, it is possible to infer that we increase the cure rate values to reduce the risk of HIV infections.

6. Conclusion and Recommendation

In this article, we presented a model for cure rate and CTL response delay of an HIV infection. The local stability analysis of $I_1$ and $I_2$ is investigated. The existence of Hopf bifurcation was demonstrated and ascertained by numerical representations when the delay is used as the bifurcation parameter. This helps us to indicate that the system occurs periodic solutions if the delay crosses the critical value. Based on the numerical findings, it is apparent that HIV infection can easily be regulated by increasing the cure rate.

REFERENCES


