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Analysis of an In-host Model for HIV Dynamics with Saturation Effect and Discrete Time Delay

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Abstract: We present an in-host HIV/AIDS model with saturation effect and a discrete time delay. It is shown that infection is endemic when $\mathcal{R}_0 > 1$ but dies out when $\mathcal{R}_0 < 1$. The switching phenomenon for the stable equilibria is observed when a discrete time delay is incorporated. The parameters that can control the disease transmission are also discussed. Numerical simulations are carried out to verify and support the analytical results and illustrate possible behavior scenarios of the model.

Keywords: *HIV/AIDS; stability; delay; switching.*

Mathematics Subject Classification (2000): 92B05, 92C60, 92D30.

1 Introduction

Throughout the ages and despite all medical and sanitary progress humankind has severely been afflicted by infectious diseases. The spread of human immune virus (HIV) is alarming today and becomes a global crisis of the modern era. No other disease engenders as much fear, revulsion, despair and utter helplessness as acquired immunodeficiency syndrome (AIDS). In a survey carried out in 2009, it was noted that about 33.3 million people are living with HIV/AIDS and 2.6 million people have newly been infected during this year only. Further, in this 2009 the number of AIDS-related deaths is estimated as 1.8 million [1]. The sexually active and risk groups such as truck drivers, commercial sex workers, bathhouse customers, and drinkers are known to play a central role in HIV population dynamics.

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HIV infection typically begins when an HIV particle containing two copies of the HIV RNA encounters a cell with a surface molecule called cluster designation 4 (CD4). Although these CD4+ T cells appear to be the main targets of HIV, other immune system cells with and without CD4 molecules on their surfaces are infected as well. Among these cells, monocytes and macrophages act as reservoirs of HIV by harboring a large amount of the virus without being killed. CD4+ T cells also serve as important reservoirs of HIV; a small proportion of these cells harbor HIV in a stable and inactive form. Normal immune processes may activate these cells, which leads to the production of new HIV virions [2]. HIV causes AIDS by destroying a type of white blood cells (T cells or CD4 cells) that the immune system must have to fight infection. AIDS is the final stage of HIV infection. It can take about 5 to 15 years for a person infected with HIV, even without treatment, to reach this stage [3]. In brief, HIV carries copies of its DNA and inserts this into the host cell's (mainly CD4+ T cells) DNA. The host cell after being stimulated to reproduce, it reproduces copies of HIV virus. Further the count of CD4+ T cells is a primary indicator used to measure progression of HIV infection. Chronic HIV infection causes gradual depletion of the CD4+ T cells' pool, and thus progressively compromises the host's immune response to opportunistic infections, leading to AIDS. Three main stages of disease progression after HIV virus is introduced into the body are as follows: the first one is the initial transient — a relatively short period of time when both the T cell population and the virus population increase greatly. This is followed by the second stage, clinical latency — a period of time when there are extremely large numbers of virus and T cells undergoing incredible dynamics, the overall result of which is an appearance of latency (disease steady state). The AIDS stage follows finally, and it is characterized by a drop in T cells to a very low number (or zero) and the virus grows without any bound and leads to death. In particular cell-cell fusions also have an important pathogenic role in vivo [4].

Wodarz and Nowak [5] showed through a diversity threshold model that evolution of virus can drive disease progression and also destruct the immune system. They also pointed out that mathematical models may be used to correlate the long-term immunological control of HIV and designing of therapy that convert a progressing patient into a state of long-term non-progression. Culshaw and Ruan [6] modified the model proposed by Perelson *et al.* [7] by introducing discrete time delay and studied the effect of time delay on the stability of equilibria. Further, Nelson and Perelson [8] developed and studied a set of models that include intercellular delays, combination antiretroviral therapy and the dynamics of both infected and uninfected T cells. The role of drug efficacy was highlighted along with general stability results of non-linear delay differential equation while Bachar and Dorfmayr [9] modeled the latent period and the delayed onset of positive treatment effects in the patients and carried out stability analysis of the system with numerical simulations depending on the size of the treatment-induced delay. On the other hand Banks and Bortz [10] studied cellular HIV infection models by using sensitivity methodology for non-linear delay system and carried out a typical sensitivity investigation. Zhou *et al.* [11] investigated the dynamics of a model of HIV infection of CD4+ T-cells with cure rate and obtained threshold conditions on $\mathcal{R}_0$ for persistence and periodic solutions. Mukandavire *et al.* [12] analyzed a mathematical model for HIV/AIDS with time delay due to incubation period and remarked that prolonged incubation period due to medical interventions may yield higher HIV/AIDS prevalence whereas Pastore [13] studied an HIV model incorporating mutation and discussed the effects of a virus attack on the human immune system in the presence of HIV infection

and the break down of the immune system. Stilianakis and Schenzle [14] studied an intra-host dynamics of HIV-1 infection by incorporating the effect of the permanently increasing susceptibility of CD4+T cell clones and suggested that the HIV evolutionary speed plays a crucial role in the progression of disease. Li and Shu investigated an in-host viral model with intracellular delay [15] and observed that for $\mathcal{R}_0 > 1$, the infection persists and the chronic-infection equilibrium is locally as well as globally asymptotically stable. They further stated that without cell division no sustained oscillations regime exists even if in the presence of intracellular delays.

The interaction between HIV and the human immune system is a highly dynamic and multifactorial process and as a result it is essential to base therapeutic interventions on a more solid theoretical ground than it has been the case until now. Previous studies considered different aspects on models of HIV/AIDS, namely, effect of mutation, cellular HIV infection, inter-cellular delays, delay due to incubation period only to mention a few. To the best of our knowledge, none of the studies considered the saturation effects and latent class. For in-host models of HIV/AIDS to be more realistic, the saturation effects should be incorporated together with the effect of delay on the latently infected class. Actually saturation effect is applicable because of the presence of large number of virions. Hence we incorporate both these effects into the model system and our interest is to explore the effects of various parameters involved in the development of infection using analytic and numerical methods. The main thrust of the paper is to highlight the effect of delay and also the role of the rate of production of new virions.

The paper is organized as follows: in Section 2 we present the mathematical model and assumptions made in the formulation. Conditions for boundedness and existence of equilibria of the model are derived in Section 3. The basic reproductive number, $\mathcal{R}_0$, is also computed in this section. The local stability behaviour of the infection-free and endemic equilibria of the model in the absence of delay is discussed in Section 4 where global stability behaviour of the endemic equilibrium is also studied. In Section 5, stability switching behaviour is addressed. A brief discussion rounds up the paper in Section 6 with numerical simulations.

2 Mathematical Model

In [16] we note that some cells after being infected by the HIV, enter a latent class. Although these cells do not produce new virions while in this class, they are reactivated later to do so. On basis of these views, here we formulate an in-host HIV model with a latent infected class and incorporate a discrete time delay along with saturation effect.

The relationship between the virus and the uninfected cells is similar to the relationship between predator and prey in ecological problem and with this analogy βX is the functional response of the viruses to the uninfected cells. Further, we assume that the function that describes the rate at which uninfected cells are produced by the host is a decreasing function of virions. When the numbers of virions tend to zero then the uninfected cells are produced at a constant rate. Thus one can infer that virions affect the production of uninfected cells by the host. In other words uninfected cells are produced by the organism at the rate $\frac{c}{k+V}$ which depends on the number of virions in an organism. This is analogous to assuming that not all newborn cells are uninfected. Then infected cells and latent cells are produced by the organism at certain rates (vertical transmission of HIV/AIDS). Consequently, we consider uninfected cells being produced by the host at the rate $\frac{c}{k+V}$.

The following system of differential equations specifies the model

$$\begin{aligned}
\frac{dV}{dt} &= aY_1 - bV, \\
\frac{dX}{dt} &= \frac{c}{k+V} - dX - \beta XV, \\
\frac{dY_1}{dt} &= q_1\beta XV - f_1Y_1 + \delta Y_2\,(t-\tau)\,, \\
\frac{dY_2}{dt} &= q_2\beta XV - f_2Y_2 - \delta Y_2,
\end{aligned} \tag{1}$$

where $V(t), X(t), Y_1(t), Y_2(t)$ represent the number of virions, number of uninfected target cells, number of productive infected cells and number of latent infected cells respectively at any time, in a host.

The virus is replicated by the infected cells, so its rate of production, a is assumed to be proportional to Y_1. Virions die at a specific rate b. The uninfected cells are produced by the host at a specific rate $\frac{c}{k+V}$. They die at a rate d, and become infected by the virus at a specific rate βV, entering Y_1 class and Y_2 class respectively,in proportions. A proportion q_1 of the infected cells become productively infected while the remaining proportion, $q_2 = (1 - q_1)$ become latently infected. Productive infected cells and latent infected cells die at specific rates $f_1 = e_1 + d$ and $f_2 = e_2 + d$, respectively, where d is the natural death rate, e_1 and e_2 are the additional death rates due to infection. Only the Y_1 cells produce virions, and Y_2 cells move to the Y_1 class at a per capita rate δ. Further, $\tau\,(0 < \tau < \infty)$ is the delay due to the formation of productive infected class from the latent infected class. The parameter c is a constant and k is the half saturation constant.

3 Boundedness and Equilibria

In this section we first show that the solutions of model system (1) are bounded.

Lemma 3.1 *If $a < f_1$ then the solutions of model system (1) are bounded.*

Proof Define the function $U = V + X + Y_1 + Y_2$. Now

$$\dot{U} < \frac{c}{k} - bV - dX + (a - f_1)Y_1 - f_2Y_2.$$

For each $\lambda > 0$ the following inequality is fulfilled:

$$\dot{U} + \lambda U \leq \frac{c}{k} - (b - \lambda)V - (d - \lambda)X - (f_1 - a - \lambda))Y_1 - (f_2 - \lambda)Y_2.$$

If we choose $\lambda < \min\{b, d, f_1 - a, f_2\}$, then right hand side is bounded $\forall (V, X, Y_1, Y_2) \in \mathbb{R}^4_+$. Thus, $\dot{U} + \lambda U \leq \frac{c}{k}$. Applying a theorem on differential inequality we have

$$0 \leq U \leq \frac{c}{k\lambda} + \frac{1}{e^{\lambda t}}U(V(0), X(0), Y_1(0), Y_2(0))$$

and $0 \leq U \leq \frac{c}{k\lambda}$ for $t \to 0$. Thus, all solutions of system (1) enter the region

$$B = \{(V(t), X(t), Y_1(t), Y_2(t)) : U \leq \frac{c}{k\lambda} + \epsilon, \forall \epsilon > 0\}.$$

The assumption $a < f_1$ indicates that to keep the population under control, the production rate of virions must be below the specific death rate of productive infected cells. The system has two equilibrium points given by:

(1) $E_1(0, \frac{c}{kd}, 0, 0)$, (2) $E_2(\frac{aY_1^*}{b}, \frac{b^2c}{(kb+aY_1^*)(bd+a\beta Y_1^*)}, Y_1^*, \frac{f_1q_2Y_1^*}{f_2q_1+\delta q_1+\delta q_2})$, provided

$a > \frac{bdkf_1(f_2+\delta)}{\beta c(f_2q_1+\delta q_1+\delta q_2)}$, $Y_1^* = \frac{1}{2a^2\beta}\left[-ad(d+k\beta)+\sqrt{a^2b^2(d-k\beta)^2+\frac{4a^3bc\beta^2(f_2q_1+\delta q_1+\delta q_2)}{f_1(f_2+\delta)}}\right]$.

Latent infected cells Y_2, become productive infected cells Y_1, at a rate δ after a period of time $\frac{1}{\delta+f_2}$. Hence, adding contributions from cells $Y_1$and Y_2 cells, the basic reproductive number becomes $\mathcal{R}_0 = \frac{\beta ac}{bdkf_1}(q_1+q_2\frac{\delta}{\delta+f_2})$. The inequality $\mathcal{R}_0 > 1$ represents the same threshold condition as the expression $a > \frac{bdkf_1(f_2+\delta)}{\beta c(f_2q_1+\delta q_1+\delta q_2)}$. Hence E_2 exists only when $\mathcal{R}_0 > 1$.

4 Stability Analysis without Delay

In this section we investigate the local stability characteristics of the infection-free equilibrium point, E_1 and endemic equlibrium point, E_2 of the system. Global stability of E_2 is also discussed.

4.1 Local stability analysis

The Jacobian matrix of model system (1) is as follows:

$$J = \begin{pmatrix} -b & 0 & a & 0 \\ -\beta X - \frac{c}{(k+V)2} & -(d+\beta V) & 0 & 0 \\ q_1\beta X & q_1\beta V & -f_1 & \delta \\ q_2\beta X & q_2\beta V & 0 & -(f_2+\delta) \end{pmatrix}.$$

Theorem 4.1 *The infection-free equilibrium E_1 is locally asymptotically stable if $\mathcal{R}_0 < 1$ and is unstable if $\mathcal{R}_0 > 1$.*

Proof The characteristic equation of the Jacobian matrix of model system (1) at E_1 is $\lambda^3 + A\lambda^2 + B\lambda + C = 0$, where

$$A = b+f_1+f_2+\delta,\ B = (b+f_1)(f_2+\delta)+bf_1-\frac{ac\beta q_1}{kd},\ C = (\delta+f_2)(bf_1-\frac{ac\beta q_1}{kd})-\frac{ac\beta\delta q_2}{kd}.$$

Now $C > 0$ implies that $a < \frac{bdkf_1(f_2+\delta)}{\beta c(f_2q_1+\delta q_1+\delta q_2)}$. Again if $a < \frac{bdkf_1(f_2+\delta)}{\beta c(f_2q_1+\delta q_1+\delta q_2)}$ then $AB - C > 0$.

Further the inequality $\mathcal{R}_0 < 1$ represents the same threshold condition as the expression $a < \frac{bdkf_1(f_2+\delta)}{\beta c(f_2q_1+\delta q_1+\delta q_2)}$. Hence, the result follows by Routh-Hurwitz criterion for the equilibrium point E_1.

Theorem 4.2 *The equilibrium point E_2 is locally asymptotically stable if $D_i > 0$, for $i = 1, 2, 3, 4$; where $D_1 = P, D_2 = PQ - R, D_3 = P(QR - PS) - P^2$ and $D_4 = SD_3$.*

Proof The characteristic equation of the Jacobian matrix of model system (1) at E_2 is given by

$$\lambda^4 + P\lambda^3 + Q\lambda^2 + R\lambda + S = 0,$$

where $P = b + d + \delta + f_1 + f_2 + \beta V^*$,
$Q = bf_1 + (b + f_1)(d + \beta V^* + f_2 + \delta) + (d + \beta V^*)(f_2 + \delta) - aq_1\beta X^*$,
$R = bf_1(d+\beta V^* + f_2 + \delta) + (b+f_1)(d+\beta V^*)(f_2+\delta) + aq_1\beta V^*\{\beta X^* + \frac{c}{(k+V^*)^2}\} - a(d+\beta V^*)q_1\beta X^* - aq_1\beta X^*(f_2+\delta) - aq_2\delta\beta X^*$,
$S = a\{q_1\beta V^*(f_2+\delta) + q_2\delta\beta V^*\}\{\beta X^* + \frac{c}{(k+V^*)^2}\} - a\delta q_2\beta X^*(d+\beta V^*) - aq_1\beta X^*(f_2+\delta)(d+\beta V^*) + bf_1(d+\beta V^*)(f_2+\delta)$.

Hence, by Routh–Hurwitz criterion E_2 is locally asymptotically stable if $D_i > 0$, for $i = 1, 2, 3, 4$; where $D_1 = P, D_2 = PQ - R, D_3 = P(QR - PS) - P^2$ and $D_4 = SD_3$.

4.2 Global stability analysis of the endemic equilibrium

We now show that the endemic equilibrium point $E_2(V^*, X^*, Y_1^*, Y_2^*)$ is globally asymptotically stable in the set B as its domain of attraction under certain conditions as follows. Define

$$W(V, X, Y_1, Y_2) = \frac{1}{2}(V - V^*)^2 + \frac{1}{2}(X - X^*)^2 + \frac{1}{2}(Y_1 - Y_1^*)^2 + \frac{1}{2}(Y_2 - Y_2^*)^2.$$

The time derivative of W along the solution of model system (1) is

$$\begin{aligned}
\dot{W} &= (V - V^*)\dot{V} + (X - X^*)\dot{X} + (Y_1 - Y_1^*)\dot{Y_1} + (Y_2 - Y_2^*)\dot{Y_2} \\
&= (V - V^*)(aY_1 - bV) + (X - X^*)(\frac{c}{k+V} - dX - \beta XV) \\
&+(Y_1 - Y_1^*)(q_1\beta XV - f_1Y_1 + \delta Y_2) + (Y_2 - Y_2^*)(q_2\beta XV - f_2Y_2 - \delta Y_2) \\
&\leq -b(V - V^*)^2 - (d + \beta V^*)(X - X^*)^2 - f_1(Y_1 - Y_1^*)^2 - (f_2 + \delta)(Y_2 - Y_2^*)^2 \\
&+\frac{c}{k}(\frac{1}{k+V^*} + \frac{\beta}{d})\,|V - V^*|\,|X - X^*| + (a + \frac{q_1\beta c}{dk})\,|V - V^*|\,|Y_1 - Y_1^*| \\
&+\frac{q_2\beta c}{dk}\,|V - V^*|\,|Y_2 - Y_2^*| + q_1\beta V^*\,|X - X^*||Y_1 - Y_1^*| + q_2\beta V^*\,|X - X^*|\,|Y_2 - Y_2^*| \\
&+\delta\,|Y_1 - Y_1^*|\,|Y_2 - Y_2^*| \\
&= -a_{11}(V - V^*)^2 - a_{22}(X - X^*)^2 - a_{33}(Y_1 - Y_1^*)^2 - a_{44}(Y_2 - Y_2^*)^2 \\
&+2a_{12}\,|V - V^*|\,|X - X^*| + 2a_{13}\,|V - V^*|\,|Y_1 - Y_1^*| + 2a_{14}\,|V - V^*|\,|Y_2 - Y_2^*| \\
&+2a_{23}\,|X - X^*|\,|Y_1 - Y_1^*| + 2a_{24}\,|X - X^*|\,|Y_2 - Y_2^*| + 2a_{34}\,|Y_1 - Y_1^*|\,|Y_2 - Y_2^*| \\
&= -X^T M X,
\end{aligned} \tag{2}$$

where $X^T = \{|V - V^*|, |X - X^*|, |Y_1 - Y_1^*|, |Y_2 - Y_2^*|\}$ and $M = [a_{ij}]_{4\times4}$. Elements of the matrix M are given by: $a_{11} = b$, $a_{22} = d + \beta V^*$, $a_{33} = f_1$, $a_{44} = f_2 + \delta$, $a_{12} = a_{21} = -\frac{c}{2k}\left(\frac{1}{V^*+k} + \frac{\beta}{d}\right)$, $a_{13} = a_{31} = -\frac{1}{2}(a + \frac{q_1\beta c}{dk})$,$a_{14} = a_{41} = -\frac{q_2\beta c}{2dk}$,$a_{23} = a_{32} = -\frac{q_1\beta V^*}{2}$,$a_{24} = a_{42} = -\frac{q_2\beta V^*}{2}$, $a_{34} = a_{43} = -\frac{\delta}{2}$.

Here, M is positive definite if the following inequalities

$$\begin{vmatrix} a_{11} & a_{12} \\ a_{21} & a_{22} \end{vmatrix} > 0, \quad \begin{vmatrix} a_{11} & a_{12} & a_{13} \\ a_{21} & a_{22} & a_{23} \\ a_{31} & a_{32} & a_{33} \end{vmatrix} > 0, \quad \begin{vmatrix} a_{11} & a_{12} & a_{13} & a_{14} \\ a_{21} & a_{22} & a_{23} & a_{24} \\ a_{31} & a_{32} & a_{33} & a_{34} \\ a_{41} & a_{42} & a_{43} & a_{44} \end{vmatrix} > 0$$

hold simultaneously.

Theorem 4.3 *Suppose $a < f_1$, E_2 is globally asymptotically stable, if M is positive definite where $M = [a_{ij}]_{4\times 4}$.*

Proof Since B is a global attractor we may restrict our attention to solutions initiating in $\overset{\circ}{B}$. From the above inequalities, the right hand side of equation (2), which is considered as a quadratic form in the variables $|V - V^*|, |X - X^*|, |Y_1 - Y_1^*|, |Y_2 - Y_2^*|$is negative definite for $(V, X, Y_1, Y_2) \in \overset{\circ}{B}$. Hence $\dot{W}(V, X, Y_1, Y_2)$ is negative definite about E_2 and consequently $W(V, X, Y_1, Y_2)$ is a Lyapunov function for $(V, X, Y_1, Y_2) \in \overset{\circ}{B}$. This completes the proof.

5 Stability Analysis with Delay

In this section, dynamical behaviour of the system near the equilibrium points E_1 and E_2 are discussed in the presence of delay.

5.1 Local stability analysis

Before stating the theorems we require the following result in Kuang [17]. For a scalar differential equation

$$\sum_{k=0}^{n} a_k \frac{d^k}{dt^k} X(t) + \sum_{k=0}^{m} b_k \frac{d^k}{dt^k} X(t-\tau) = 0, \quad a_n \neq 0, \quad n \geq m.$$

The characteristic equation takes the form

$$P(\lambda) + Q(\lambda) e^{-\lambda\tau} = 0, \qquad P(\lambda) = \sum_{k=0}^{n} a_k \lambda^k, \quad Q(\lambda) = \sum_{k=0}^{m} b_k \lambda^k. \tag{3}$$

Theorem 5.1 *Consider equation (3), where $P(\lambda)$ and $Q(\lambda)$ are analytic functions in $Re\lambda > 0$ and satisfy the following conditions:*

(i) $P(\lambda)$*and* $Q(\lambda)$ *have no common imaginary root;*

(ii) $\bar{P}(-iy) = P(iy)$, $\bar{Q}(-iy) = Q(iy)$ *for real y; '-' denotes complex conjugate;*

(iii) $P(0) + Q(0) \neq 0$*;*

(iv) $\limsup [|Q(\lambda)/P(\lambda)| : |\lambda| \to \infty, Re\lambda \geq 0] < 1$*;*

(v) $F(y) = |P(iy)|^2 - |Q(iy)|^2$ *for real y has at most a finite number of real zeros.*

Then the following statements are true:

(a) If $F(y) = 0$ has no positive roots, then no stability switch may occur;

(b) If $F(y) = 0$ has at least one positive root and each of them is simple, then as τ increases, a finite number of stability switches may occur, and eventually the considered equation becomes unstable.

Now we state and prove our results.

Theorem 5.2 *Stability switches occur or do not occur near the equilibrium point E_1 as τ increases when $\mathcal{R}_0 > 1$ or $\mathcal{R}_0 < 1$ respectively.*

Proof The characteristic equation of the system with delay at E_1 is given by

$$\lambda^4 + \epsilon_1\lambda^3 + \eta_1\lambda^2 + \mu_1\lambda + \omega_1 + \zeta_1\lambda e^{-\lambda\tau} + \rho_1 e^{-\lambda\tau} = 0,$$

where $\epsilon_1 = b + d + f_1 + f_2 + \delta$, $\eta_1 = bd + (b+d)(f_1 + f_2 + \delta) + f_1(f_2 + \delta) - \frac{aq_1\beta c}{kd}$,
$\mu_1 = bd(f_1 + f_2 + \delta) + f_1(b+d)(f_2 + \delta) - \frac{aq_1\beta c}{kd}(d + f_2 + \delta)$,
$\omega_1 = (f_2 + \delta)(bdf_1 - \frac{aq_1\beta c}{kd}), \zeta_1 = -\frac{aq_2\delta\beta c}{kd}$ and $\rho_1 = -\frac{aq_2\delta\beta c}{k}$.

Again this equation is of the form

$$P(\lambda) + Q(\lambda)e^{-\lambda\tau} = 0,$$

where $P(\lambda) = \lambda^4 + \epsilon_1\lambda^3 + \eta_1\lambda^2 + \mu_1\lambda + \omega_1$ and $Q(\lambda) = \zeta_1\lambda + \rho_1$. Clearly $P(\lambda)$ and $Q(\lambda)$ have no common imaginary root. Obviously $\bar{P}(-iy) = P(iy)$, $\bar{Q}(-iy) = Q(iy)$ for real y. Also $P(0) + Q(0) \neq 0$. Now, $\limsup[|Q(\lambda)/P(\lambda)| : |\lambda| \to \infty, Re\lambda \geq 0] < 1$,
$F(y) = |P(iy)|^2 - |Q(iy)|^2$
$= y^8 + (\epsilon_1^2 - 2\eta_1)y^6 + (\eta_1^2 + 2\omega_1 - 2\epsilon_1\mu_1)y^4 + (\mu_1^2 - \zeta_1^2 - 2\eta_1\omega_1)y^2 + (\omega_1^2 - \rho_1^2)$.

Putting $y^2 = z$ we get

$$z^4 + (\epsilon_1^2 - 2\eta_1)z^3 + (\eta_1^2 + 2\omega_1 - 2\epsilon_1\mu_1)z^2 + (\mu_1^2 - \zeta_1^2 - 2\eta_1\omega_1)z + (\omega_1^2 - \rho_1^2) = 0.$$

We have $(\omega_1^2 - \rho_1^2) > 0$ which implies that $a < \frac{bdkf_1(f_2+\delta)}{\beta c(f_2q_1+\delta q_1+\delta q_2)}$. Consequently, $F(y) = 0$ has a positive root when $a > \frac{bdkf_1(f_2+\delta)}{\beta c(f_2q_1+\delta q_1+\delta q_2)}$, which is simple. Further when $a < \frac{bdkf_1(f_2+\delta)}{\beta c(f_2q_1+\delta q_1+\delta q_2)}$, $F(y) = 0$ does not have a positive root. The result follows by the application of Theorem 5.1.

Theorem 5.3 *The endemic equilibrium E_2 remains stable if $\sigma > 1$ and switches from its stability to instability if $\sigma < 1$, where*

$$\sigma = \frac{(f_2 + \delta)^2[bf_1(d + \beta V^*) + aq_1\beta[\frac{cV^*}{(k+V^*)^2} - dX^*]]^2}{[aq_2\beta\delta[\frac{cV^*}{(k+V^*)^2} - dX^*]]^2}.$$

Proof Proceeding along the lines of proof of Theorem 5.2 we obtained the result.

6 Numerical Simulations and Discussion

We modeled the interaction inside the body between the HIV virus and uninfected target cells. A virus particle (or virion) does absolutely nothing on its own. Virion hijacks the machinery of the cell for its own replication when it gets entry to the host cell. It then leaves the cell, and the process is repeated. In this way our immune system loses its control over our body. In this study βX is the functional response of the virus to the infected cell. Saturation effect due to virions and the effect of time delay due to production of new virions from the latent infected class to the productive infected class are also considered. The current study does not consider the effects of immune response but this will be considered elsewhere. We now explain the dynamical behavior of the model

using hypothetical set of parameter values for different situations and if experimental data are available, one can give more insight of the dynamics of our model. All numerical simulations are generated using MATLAB® (The Mathworks, Inc., Version 7.10.0.499, R2010a).

Figure 1 demonstrates that infection free equilibrium exists and is locally asymptotically stable as shown in Theorem 4.1. The parameter values used are: $a = 0.5$ per month; $b = 1$ per month; $c = 10$ per month; $k = 1$; $d = 1$ per month; $\beta = 0.2$ per month; $q_1 = 0.3$; $f_1 = 1$ per month; $\delta = 2$ per month; $q_2 = 0.7$; $f_2 = 0.1$ per month. Here $\mathcal{R}_0 = 0.97$. In other words infection dies out in this situation.

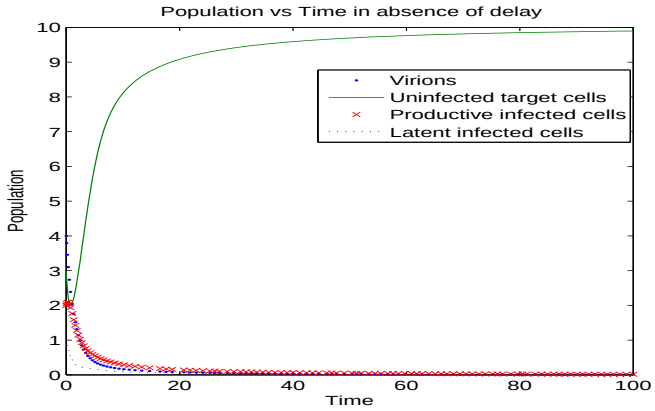

Figure 1: The figure shows that the infection-free equilibrium is locally asymptotically stable.

Existence of the endemic equilibrium is shown in Figure 2. Conditions for local asymptotic stability of this equilibrium are obtained in Theorem 4.2. Figure 2 is generated with the choice of the parameter values $a = 5$ per month; $b = 1$ per month; $c = 10$ per month; $k = 1$; $d = 1$ per month; $\beta = 0.2$ per month; $q_1 = 0.3$; $f_1 = 1$ per month; $\delta = 2$ per month; $q_2 = 0.7$; $f_2 = 0.1$ per month. It is important to note that in this case $\mathcal{R}_0 = 9.7$. Hence infection is endemic in nature and prevails in the human body.

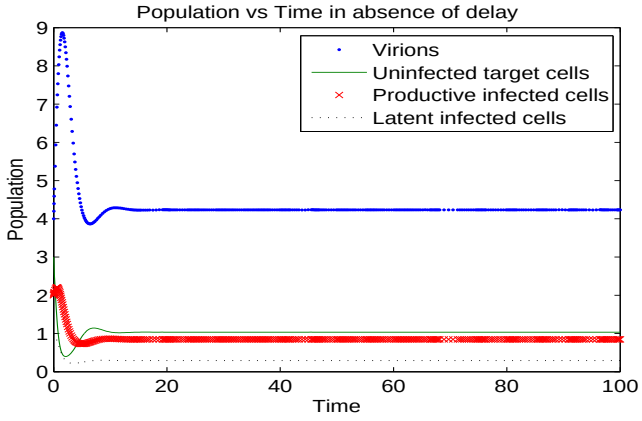

Figure 2: The figure demonstrates that the endemic equilibrium is locally asymptotically stable.

With the choice of parameter values $a = .5$ per month; $b = 1$ per month; $c = 10$ per month; $k = 1$; $d = 1$ per month; $\beta = 0.2$ per month; $q_1 = 0.3$; $f_1 = 1$ per month; $\delta = 2$ per month; $q_2 = 0.7$; $f_2 = 0.1$ per month and $\tau = 18$ months, we note from Figure 3 that infection-free equilibrium exists and is locally asymptotically stable without any stability switching as shown in Theorem 5.2. This implies no possibility of infection occurs. Further in this case $\mathcal{R}_0 = 0.97$.

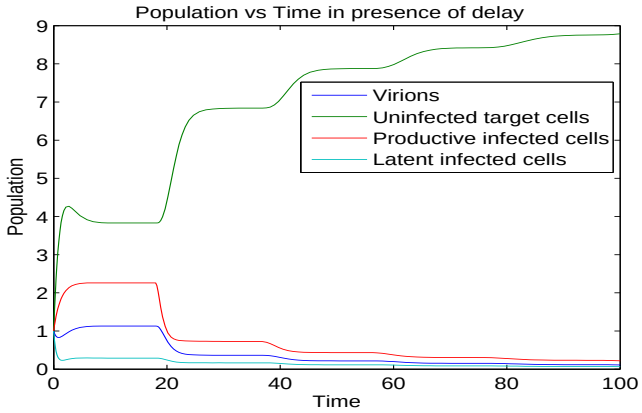

Figure 3: The figure depicts that the infection-free equilibrium remains stable in the presence of delay

With the following choice of parameter values: $a = 5$ per month; $b = 1$ per month; $c = 10$ per month; $k = 1$; $d = 1$ per month; $\beta = 0.2$ per month; $q_1 = 0.3$; $f_1 = 1$ per month; $\delta = 2$ per month; $q_2 = 0.7$; $f_2 = 0.1$ per month and $\tau = 18$ months, Figure 4 is obtained. From this set of values we get $\sigma > 1$ and $\mathcal{R}_0 = 9.7$. The figure shows that the system remains asymptotically stable through slight oscillations. Again by increasing τ no sustained oscillations are observed for the system. Biologically the disease prevails within the human body with slight ups and downs.

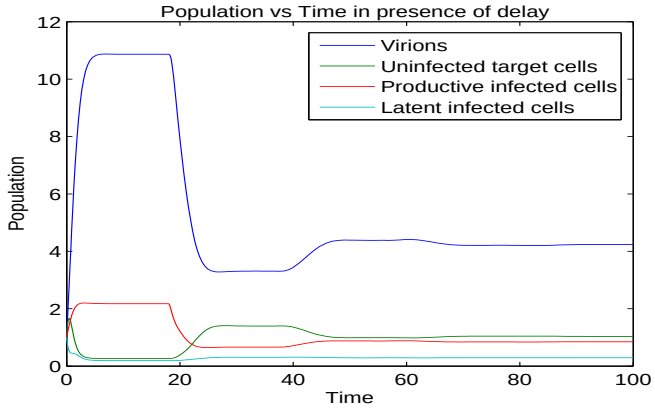

Figure 4: The figure shows that the endemic equilibrium, in the presence of delay, ultimately remains stable when $\sigma > 1$.

Figure 5 is obtained by using the following parameter values: $a = 5$ per month; $b = 1$ per month; $c = 10$ per month; $k = 1$; $d = 1$ per month; $\beta = 200$ per month; $q_1 = 0.3$; $f_1 = 1$ per month; $\delta = 2$ per month; $q_2 = 0.7$; $f_2 = 0.1$ per month and $\tau = 18$ months. This set of values of the parameters gives $\sigma < 1$. This figure depicts that the system switches from its stability to instability to stability etc. in the presence of delay. On the basis of Figure 5, we may interpret biologically that the disease spreads randomly with unusual manner within the individual. It is important to note that $\mathcal{R}_0 \gg 1$ in this situation and β plays a vital role.

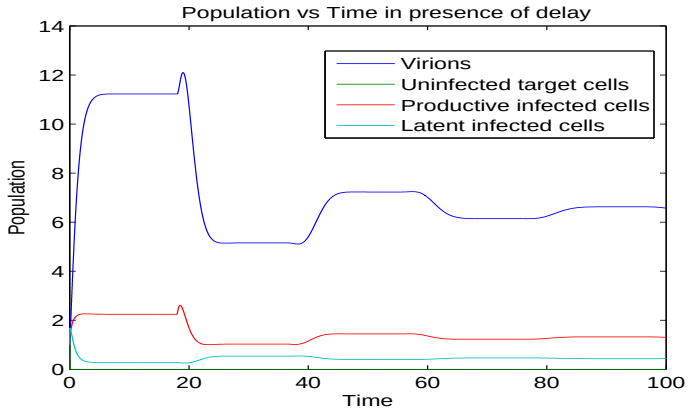

Figure 5: The figure shows that the endemic equilibrium becomes unstable in the presence of delay when $\sigma < 1$.

From the analysis and numerical simulations we observe that endemic establishment of the infection occurs for $\mathcal{R}_0 > 1$ whereas the infection dies out when $\mathcal{R}_0 < 1$. Again, if the rate of production of virus, a, is dominated by the specific death rate of productive infected cells, f_1, then the population cannot be explored although infection remains there. In brief, from the analysis we observed that the rate of production of virus through replication by infected cell has an important role over the stability of the system. Thus, we may reduce HIV infection that leads to AIDS by controlling the rate of production of virus through replication. It is important to note that delay has destabilizing effect on the system in the presence of latent class. Hence the latent class has a major role on the dynamics of the system which is clear from our analytical findings and numerical simulations.Saturation effects give more intricate dynamics also. Further β, δ and q_1 are also the key parameters of the system.Hence, in order to restore the outbreak of the disease, we have to take some control measures on these parameters with great care.

A definite AIDS cure is still under research. The current model can be extended by incorporating immune response, age structure and other modifications. We hope that some interesting results will be found in near future to save us from this fatal disease.

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