

Mathematical modeling of liver enzyme elevation in HIV mono-infection

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ABSTRACT

HIV-infected individuals are increasingly becoming susceptible to liver disease and, hence, liver-related mortality is on a rise. The presence of CD4⁺ in the liver and the presence of C-X-C chemokine receptor type 4 (CXCR4) on human hepatocytes provide a conducive environment for HIV invasion.

In this study, a mathematical model is used to analyse the dynamics of HIV in the liver with the aim of investigating the existence of liver enzyme elevation in HIV mono-infected individuals. In the presence of HIV-specific cytotoxic T-lymphocytes, the model depicts a unique endemic equilibrium with a transcritical bifurcation when the basic reproductive number is unity. Results of the study show that the level of liver enzyme alanine aminotransferase (ALT) increases with increase in the rate of hepatocytes production. Numerical simulations reveal significant elevation of alanine aminotransferase with increase in viral load. The findings presuppose that while liver damage in HIV infection has mostly been associated with HIV/HBV coinfection and use of antiretroviral therapy (ART), it is possible to have liver damage solely with HIV infection.

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1. Introduction

Liver disease is emerging as the leading cause of morbidity and mortality among individuals infected with HIV [1–3]. Liver damage is clinically assessed by measuring the level of the liver enzymes aspartate aminotransferase (AST) or alanine aminotransferase (ALT) in the blood system. ALT is more specific to the liver as AST can be found in other organs [4].

Liver enzyme elevation in HIV patients has been largely associated with factors such as coinfection with viral hepatitis B (HBV), hepatitis C (HCV), the use of antiretroviral therapy (ART) and alcoholism [5–9]. Although significant correlation has been found between underlying coinfection with hepatitis, use of ART and liver enzyme elevation, the findings cannot rule out the possibility that HIV could infect hepatocytes (liver cells) and hence lead to elevation of ALT in the absence of ART or underlying coinfection with HBV/HCV.

HIV uses ribonucleic acid (RNA) to carry its genetic information. In addition to CD4 molecule, HIV uses C-X-C chemokine receptor to facilitate its entry into a target cell [10,11]. An *in vivo* study at Mayo Clinic [12] revealed that human hepatocytes possess C-X-C chemokine receptor type 4 (CXCR4). The researchers further proposed that HIV might cause hepatocyte apoptosis by signaling through CXCR4 without actually infecting the cell. This was further investigated by Svegliati-Baroni and de Minicis [13] whose

findings concurred with [12] that the presence of CXCR4 on the hepatocytes makes it possible for HIV to infect hepatocytes and hence replicate in these types of cell.

HIV infection of human hepatocytes supposedly partly explains current high levels of liver disease in HIV infected people. However, there are discrepancies in reports regarding HIV productive infection in hepatocytes. To some scholars [13–15], HIV productively infects hepatocytes, while to others [1,7,16], evidence regarding HIV infection and replication in liver cells remains scanty. However, there is consensus on HIV causing hepatocyte apoptosis by signaling through CXCR4.

In this paper we use a mathematical model to determine if the level of ALT in the blood system increases with increase in viral load. Elevated ALT in such a case would imply the possibility of liver injury in HIV mono-infected patients who are not using ART. To concur with [1,7,16], we assume that HIV replicates only in CD4⁺ cells that exist in the liver [17] and there is no productive infection in hepatocytes.

2. Model development

Like many researchers who have modeled HIV dynamics *in vivo* [18–22], this study considers the action of HIV-specific cytotoxic T lymphocytes (CTLs) in killing infected CD4⁺ cells and hepatocytes cells.

In the model formulation, we define eight variables as follows: uninfected CD4⁺ (T_c), CD4⁺ infected but not yet infectious or CD4⁺ in the eclipse phase (E), infected and virus producing CD4⁺ (I_c),

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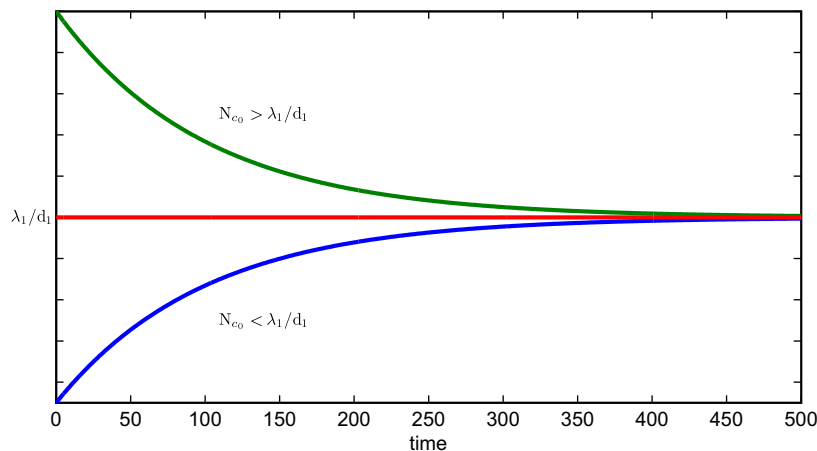


Fig. 1. Total number of CD4+ bounded by λ_1/d_1 during HIV infection. Time is in days and parameter values are as shown in Table 1.

uninfected hepatocytes (T_h), infected hepatocytes (I_h), HIV-specific cytotoxic T lymphocytes (L), HIV population (V) and the level of alanine aminotransferase in the blood system (A).

The model parameters are described as follows: CD4+ and hepatocytes are produced from within the body at rates λ_1 and λ_2 and die naturally at rates d_1 and d_4 respectively. HIV infects hepatocytes with probability p at a rate β_2 and infects CD4+ with probability $1 - p$ and rate β_1 . When HIV enters a resting CD4+ cell, the RNA may not be completely reverse transcribed into DNA and the un-integrated virus cell may decay with time before reverse transcription [23]. This results in a proportion of infected cells reverting to the uninfected state at a rate α . If reverse transcription takes place, the cell becomes infectious at a rate π . This implies that if reverse transcription takes place in a period $1/\alpha$, where $1/\alpha < 1/\pi$ then the exposed cell will revert to uninfected state, otherwise it will proceed to the infectious state. Infected CD4+ die due to infection at a rate d_2 .

CTLs kill both infected CD4+ and hepatocytes at rates k_2 and k_3 respectively. CTLs are stimulated at a rate $k_4 I_c L / (1 + \xi L)$, which is a saturation function of L . At high densities of CTLs, the proliferation rate converges to $k_4 I_c / \xi$. CTLs die at a rate d_5 . HIV is produced by infected CD4+ that die due to infection with burst size of n per dying cell, and virions die at a rate d_6 . ALT is generated in the blood by hepatocytes that die due to infection or are killed by CTLs at a rate k_5 . ALT is naturally cleared from the blood system at a rate d_7 . From description above, we arrive at the following system of ordinary differential equations.

$$\frac{dT_c}{dt} = \lambda_1 - d_1 T_c - (1 - p)\beta_1 T_c V + \alpha E \quad (2.1)$$

$$\frac{dE}{dt} = (1 - p)\beta_1 T_c V - d_1 E - (\alpha + \pi)E \quad (2.2)$$

$$\frac{dI_c}{dt} = \pi E - (d_1 + d_2 + k_2 L)I_c \quad (2.3)$$

$$\frac{dT_h}{dt} = \lambda_2 - d_3 T_h - p\beta_2 T_h V \quad (2.4)$$

$$\frac{dI_h}{dt} = p\beta_2 T_h V - d_4 I_h - k_3 I_h L \quad (2.5)$$

$$\frac{dL}{dt} = \frac{k_4 I_c L}{1 + \xi L} - d_5 L \quad (2.6)$$

$$\frac{dV}{dt} = n d_2 I_c - d_6 V \quad (2.7)$$

$$\frac{dA}{dt} = k_5 (d_4 I_h + k_3 I_h L) - d_7 A \quad (2.8)$$

3. Model analysis

3.1. Feasibility of solutions

The model (2.1)–(2.8) has solutions that are contained in the feasible solution $\Omega : (T_c \geq 0, E \geq 0, I_c \geq 0, T_h \geq 0, I_h \geq 0, L \geq 0)$.

Taking the total number of CD4+ and hepatocytes cells in the liver to be N_c and N_h respectively, where $N_c = T_c + E + I_c$ and $N_h = T_h + I_h$, and using Eqs. (2.1)–(2.3), we have

$$\frac{dN_c}{dt} = \lambda_1 - d_1 N_c - (k_2 L + d_2)I_c \quad (3.1)$$

Considering that all parameters and variables are non-negative, the last term of Eq. (3.1) is always positive otherwise the model would not be biologically feasible. Therefore,

$$\frac{dN_c}{dt} < \lambda_1 - d_1 N_c \quad (3.2)$$

$$N_c < \lambda_1/d_1 + (N_{c0} - \lambda_1/d_1)e^{-d_1 t} \quad (3.3)$$

N_{c0} is the total number of CD4+ at the time of infection. We note that for $N_{c0} > \lambda_1/d_1$ the upper bound of $N_c \rightarrow (\lambda_1/d_1)^+$ as $t \rightarrow \infty$ and for $N_{c0} < \lambda_1/d_1$ and for all values of t , the upper bound of $N_c \rightarrow (\lambda_1/d_1)^-$. This is shown in Fig. 1.

Using Eqs. (2.4) and (2.5), it can similarly be shown that as $t \rightarrow \infty$ then $N_h < \lambda_2/d_3$. However, as shown in Section (3.2) below, the total number of CD4+ cells at disease free is λ_1/d_1 and that of hepatocytes is λ_2/d_3 . For this reason, the number of CD4+ and hepatocytes cells at infection would not exceed λ_1/d_1 and λ_2/d_3 respectively. Thus, given $N_{c0} < \lambda_1/d_1$ all feasible solutions of CD4+ in the model (2.1)–(2.8) are in the region

$$\Omega_c = \{(T_c, E, I_c) \in \mathbb{R}^3 : N_c < \lambda_1/d_1\} \quad (3.4)$$

Similarly, given $N_{h0} < \lambda_2/d_3$ the feasible solutions for the hepatocytes in the model (2.1)–(2.8) are in the region

$$\Omega_h = \{(T_h, I_h) \in \mathbb{R}^2 : N_h < \lambda_2/d_3\} \quad (3.5)$$

Since $T_c + E + I_c < \lambda_1/d_1$ then $T_c < \lambda_1/d_1$, $E < \lambda_1/d_1$ and $I_c < \lambda_1/d_1$ for $T_c \geq 0$, $E \geq 0$ and $I_c \geq 0$. Letting $\lambda_1/d_1 = N_1$ where $N_1 \in \mathbb{R}^+$. From Eq. (2.7)

$$\frac{dV}{dt} = n d_2 I_c - d_6 V$$

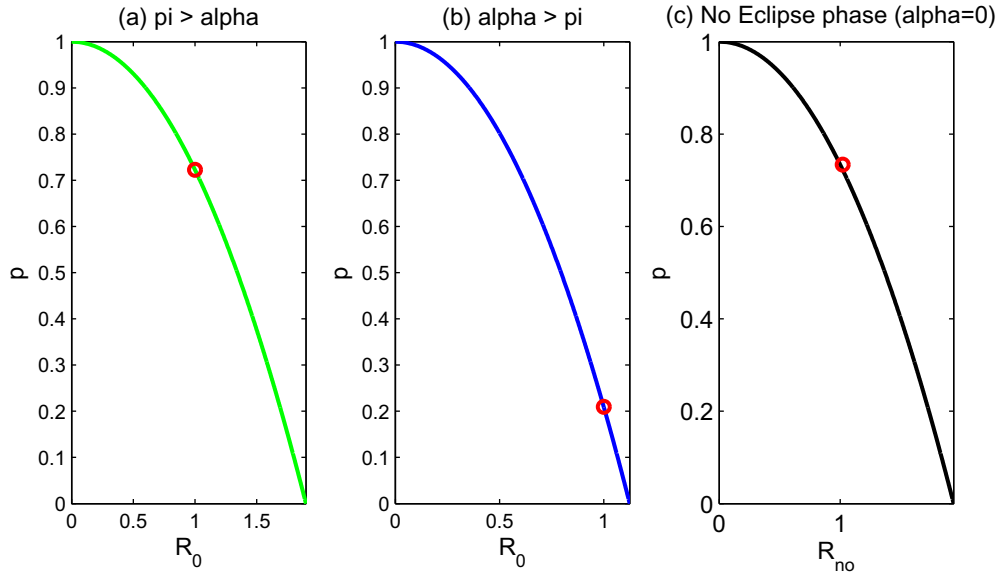


Fig. 2. Basic reproductive number (R_0) reduces with increase in probability (p) of hepatocyte infection by HIV.

Given that $I_c < N_1$ then $\frac{dV}{dt} < nd_2N_1 - d_6V$, letting $S = nd_2N_1$ for $S \in \mathbb{R}^+$, then

$$\frac{dV}{dt} < S - d_6V \tag{3.6}$$

Using the same approach as in Eq. (3.3), it can be shown that $V < N_3$ where $N_3 = S/d_6$ for some $N_3 \in \mathbb{R}^+$. Considering Eq. (2.6)

$$\frac{dL}{dt} = \frac{k_4 I_c L}{1 + \xi L} - d_5 L$$

Since $I_c < N_1$, then $\frac{dL}{dt} < \frac{k_4 N_1 L}{1 + \xi L} - d_5 L$. Given that $L > 0$ (biological feasibility), then

$$\frac{dL}{dt} < \frac{RL}{1 + \xi L} \tag{3.7}$$

for some real number R , where $R = k_4 N_1$.

$$L < e^{(-LambertW(\xi e^{-C+Rt}) - C + Rt)} \tag{3.8}$$

for some constant C . Lastly we consider Eq. (2.8)

$$\frac{dA}{dt} = k_5(d_4 I_h + k_3 I_h L) - d_7 A$$

From Eq. (3.5), suppose $N_2 = \lambda_2/d_3$ and $N_4 = e^{(-LambertW(\xi e^{-C+Rt}) - C + Rt)}$ for some $N_2, N_4 \in \mathbb{R}^+$, then $I_h < N_2$ and $L < N_4$. Therefore,

$$\frac{dA}{dt} < W - d_7 A \tag{3.9}$$

where $W = k_5(d_4 N_3 + k_3 N_3 N_4)$. Using same method as in Eq. (3.3), it can be shown that A is bounded by some real number Y , where $Y = \max\{N_1, N_2, N_3, N_4\}$. Therefore the feasible solution for the model (2.1)–(2.8) is

$$\Omega = \{(T_c, E, I_c, T_h, I_h, L, V, A) \in \mathbb{R}^8 : \tag{3.10}$$

$$(T_c + E + I_c) < N_1, (T_h + I_h) < N_2, V < N_3, L < N_4, A < Y\} \tag{3.11}$$

3.2. Existence and stability analysis of the disease-free equilibrium

By equating the right hand side of system (2.1)–(2.8) to zero, it can be shown that if there is no virus infection, the system settles to the disease-free equilibrium $E_0(T_c, E, I_c, T_h, I_h, L, V, A) = (\lambda_1/d_1, 0, 0, \lambda_2/d_3, 0, 0, 0)$.

In order to analyse the stability of E_0 we compute the basic reproductive number R_0 of the virus. The basic reproductive number R_0 for within-host models measures the average number of virus-producing target cells produced by a single virus-producing target cell during the entire infectious period in a entirely uninfected target cell population [24].

R_0 is computed using the method of next generation matrix [25] as,

$$R_0 = \sqrt{\frac{\pi}{(d_1 + \alpha + \pi)} \cdot \frac{(1-p)\beta_1 \lambda_1 n d_2}{d_1 d_6 (d_1 + d_2)}} \tag{3.12}$$

$$= \sqrt{R_c \cdot R_w} \tag{3.13}$$

where $R_c = \frac{\pi}{(d_1 + \alpha + \pi)}$ and $R_w = \frac{(1-p)\beta_1 \lambda_1 n d_2}{d_1 d_6 (d_1 + d_2)}$

The basic reproductive number is a combination of the reproductive number of the eclipse phase (latency infection, [23]) R_c and the basic reproductive number without the eclipse phase R_w . R_c is the fraction of CD4+ that survives the latency period and R_w is the transmission rate of HIV during the infectious period [19].

Increasing the probability (p) of hepatocyte infection by HIV reduces the chances of the infection to progress to the endemic state, Fig. 2(a) and (b). If HIV RNA can stay in the cell longer than required for reverse transcription, $\alpha > \pi$, then HIV in the liver will not progress faster to the endemic state.

As shown in Fig. 2(a) and (b), if $\alpha > \pi$ a lower probability of hepatocyte infection (p) is needed to reduce the basic reproductive number below unity, as compared to when $\alpha < \pi$. Respective threshold probabilities below which HIV will become endemic in the liver based on the parameters shown in Table 1 are 0.7228 and 0.2095, as shown in Fig. 2. This implies that even if fewer hepatocytes are infected by HIV ($p = 0.2095$), the endemicity of HIV in the liver can be avoided, provided the rate of progression of HIV from latency to infection (π) is less than the rate at which latently infected CD4+ become uninfected.

On the other hand if reverse transcription immediately takes place with no infected CD4+ returning to the uninfected state ($\alpha = 0$), the threshold value of $0 < p < 1$ below which the infection will become endemic, that is, $R_w > 1$ is $p < 0.7339$ (see Fig. 2).

It can also be shown from Eq. (3.12) that R_w depends on the rate at which HIV affiliates to CD4+ and is independent of the rate of

Table 1
Parameters for the basic model of HIV in the liver.

Parameter	Description	Value	Source
λ_1	Rate of creation of CD4+ from within the body	10 (ml)^{-1}	[30]
d_1	Natural death rate of uninfected CD4+	0.01	[31]
p	Probability that HIV infects hepatocytes	0.3	Estimate
β_1	Rate of transmission of HIV in CD4+	0.005 (ml)^{-1}	[30]
α	Rate at which exposed CD4+ become uninfected	0.01	[23]
π	Rate at which exposed CD4+ become infectious	0.23	[23]
d_2	Death rate of infected CD4+ due to infection	0.5	[19]
k_2	Rate at which CTLs kill infected CD4+	0.4	Estimate
λ_2	Rate of creation of hepatocytes from within the body	100 (ml)^{-1}	Estimate
d_3	Natural death rate of hepatocytes	0.002	[4]
β_2	Rate of transmission of HIV in hepatocytes	0.005 (ml)^{-1}	Estimate
d_4	Death rate of hepatocytes due to infection	0.05	Estimate
k_3	Rate at which CTLs kill infected hepatocytes	1	[18]
k_4	Rate of HIV-specific CTL proliferation	2.5	[19]
d_5	Rate of clearance of CTLs by all means	0.15	[18]
ξ	Saturation constant of CTLs	1	[19]
n	Number of virus produced by an infected CD4+	100	Estimate
d_6	Death rate of HIV	2	[19]
k_5	Rate of generation of liver enzyme in the blood	1000	Estimate
d_7	Rate of clearance of ALT from blood system	0.25	[4]

affiliation to hepatocytes. On the other hand, if all virions that attack the liver infect only CD4+, that is, $p = 0$, then the infection will become endemic only if the ratio of viral birth-rate to viral death-rate is greater than $d_1(d_1 + d_2)/\beta_1\lambda_1$, that is, if $nd_2/d_6 > d_1(d_1 + d_2)/\beta_1\lambda_1$.

Using Theorem 2 of van den Driessche and Watmough [25] we establish the following result.

Theorem 1. *The Disease-Free Equilibrium E_0 is locally asymptotically stable when $R_0 < 1$ and unstable when $R_0 > 1$.*

3.3. Global stability of DFE

Using the approach of Musekwa et al. [26] and van den Driessche and Watmough [25], we study the global stability of DFE.

Consider the infected compartments of system (2.1)–(2.8)

$$\begin{cases} \frac{dE}{dt} = (1 - p)\beta_1 T_c V - d_1 E - (\alpha + \pi)E \\ \frac{dI_c}{dt} = \pi E - (d_1 + d_2 + k_2 L) I_c \\ \frac{dI_h}{dt} = p\beta_2 T_h V - d_4 I_h - k_3 I_h L \\ \frac{dV}{dt} = nd_2 I_c - d_6 V \end{cases} \quad (3.14)$$

Taking \mathfrak{F}_i to be the rate of appearance of new infections in compartment i and $V_i = V_i^- - V_i^+$ to be the difference between the rate of transfer of individual cells out of and into compartment i by all other means, we write (3.14) in terms of $\mathfrak{F}_i - V_i$ (rate of transfer in compartment i), taking the Jacobian of \mathfrak{F}_i and V_i as F and V respectively. Then we have

$$\begin{bmatrix} \dot{E} \\ \dot{I}_c \\ \dot{I}_h \\ \dot{V} \end{bmatrix} = (F - V) \begin{bmatrix} E \\ I_c \\ I_h \\ V \end{bmatrix} - \begin{bmatrix} 0 \\ k_2 L I_c \\ k_3 I_h L \\ 0 \end{bmatrix} \quad (3.15)$$

Thus

$$\begin{bmatrix} \dot{E} \\ \dot{I}_c \\ \dot{I}_h \\ \dot{V} \end{bmatrix} < (F - V) \begin{bmatrix} E \\ I_c \\ I_h \\ V \end{bmatrix} \quad (3.16)$$

We write system (2.1)–(2.8) as $Df(x_i)$ for $i = 1, 2, \dots, n$, where $i = 1, 2, \dots, m$ are components in the infectious compartments,

$m < n$. Using E_0 as the DFE which is locally asymptotically stable and considering conditions (i) to (iv) of Lemma 1 in van den Driessche and Watmough [25], we rewrite the Jacobian matrix of system (2.1)–(2.8) at E_0 as a block matrix (3.17)

$$J_{E_0} = \begin{bmatrix} \Delta_1 & 0 \\ \Delta_2 & \Delta_3 \end{bmatrix} \quad (3.17)$$

Δ_1 is a non-singular matrix ($F - V$) and Δ_3 has eigenvalues with negative real parts. Based on van den Driessche and Watmough [25], inequality (3.16) is stable when $R_0 < 1$. And it follows from Musekwa et al. [26] that as $t \rightarrow \infty$ then $(E, I_c, I_h, V) \rightarrow E_0$, which implies that E_0 is globally asymptotically stable.

3.4. Existence of endemic equilibrium points

The endemic equilibrium point E_1 is a state where HIV infection persists in the liver. It exists when $T_c > 0, E > 0, I_c > 0, T_h > 0, I_h > 0, L > 0, V > 0, A > 0$ and is given by $E_1 = (T_c^*, E^*, I_c^*, T_h^*, I_h^*, L^*, V^*, A^*)$, where

$$T_c^* = \frac{d_6 \lambda_1 (d_1 + \pi + \alpha)}{d_6 d_1 (d_1 + \pi + \alpha) + (1 - p)\beta_1 n d_2 (d_1 + \pi) I_c^*} \quad (3.18)$$

$$E^* = \frac{(1 - p)\beta_1 n d_2 \lambda_1 I_c^*}{d_6 d_1 (d_1 + \pi + \alpha) + (1 - p)(d_1 + \pi)\beta_1 n d_2 I_c^*} \quad (3.19)$$

$$T_h^* = \frac{\lambda_2 d_6}{d_3 d_6 + p\beta_2 n d_2 I_c^*} \quad (3.20)$$

$$I_h^* = \frac{p\beta_2 \lambda_2 n d_2 d_5 \xi I_c^*}{(d_3 d_6 + p\beta_2 n d_2 I_c^*)(d_4 d_5 \xi - k_3 d_5 + k_3 k_4 I_c^*)} \quad (3.21)$$

$$L^* = \frac{k_4 I_c^* - d_5}{d_5 \xi} \quad (3.22)$$

$$V^* = \frac{n d_2 I_c^*}{d_6} \quad (3.23)$$

$$A^* = \frac{k_5 p\beta_2 \lambda_2 n d_2 I_c^*}{d_7 (d_3 d_6 + p\beta_2 n d_2 I_c^*)} \quad (3.24)$$

I_c^* is defined in terms of a cubic polynomial

$$I_c^* [a_0 (I_c^*)^2 + a_1 (I_c^*) + a_2] = 0 \quad (3.25)$$

where

$$a_0 = (1 - p)(d_1 + \pi)nd_2\beta_1k_2k_4 \tag{3.26}$$

$$a_1 = k_2k_4d_1d_6(\alpha + \pi + d_1) + (1 - p)(d_1 + \pi)nd_2\beta_1d_5(d_1\xi + d_2\xi - k_2) \tag{3.27}$$

$$a_2 = d_1d_6d_5k_2k_4(d_1\xi + d_2\xi - k_2)(\alpha + \pi + d_1) - (1 - p)\pi nd_2d_5\beta_1\lambda_1 \tag{3.28}$$

In Eq. (3.25), $I_c^* = 0$ corresponds to the disease-free equilibrium, a case when there is no virus in the liver. For at least one biologically meaningful endemic equilibrium (non-negative equilibrium points), we seek to have either $a_2 > 0$ and $a_1 < 0$ (for two non-negative roots) or $a_2 < 0$ and $a_1 > 0$ (for one non-negative root) in Eq. (3.29)

$$a_0(I_c^*)^2 + a_1(I_c^*) + a_2 = 0 \tag{3.29}$$

After the asymptomatic phase in HIV infection, the viral load increases and surpasses the action of CTLs triggering full blown Acquired Immune Deficiency Syndrome (AIDS) [27,28]. Since the AIDS stage is attained when the infection is endemic, we assume that at this stage, the death rate of infected CD4+ cells is greater than the rate at which infected CD4+ are killed by CTLs. Thus the endemic equilibrium will exist when $d_1\xi + d_2\xi > k_2$. If this holds, then $a_1 > 0$. This implies that it is not possible to have two biologically feasible endemic equilibrium points. We therefore seek to investigate for one positive root which exists when $a_2 < 0$ and $a_1 > 0$.

From Eq. (3.26), $a_0 > 0$. Given that $d_1\xi + d_2\xi > k_2$ then $a_2 < 0$ if $d_1d_6k_2k_4(d_1\xi + d_2\xi - k_2)(\alpha + \pi + d_1) < (1 - p)\pi nd_2\beta_1\lambda_1$ (3.30)

$$k_2k_4(d_1\xi + d_2\xi - k_2) < \frac{(1 - p)\pi nd_2\beta_1\lambda_1}{d_1d_6(\alpha + \pi + d_1)}$$

It is likely that when HIV is endemic, CD4+ will die both naturally and due to infection ($d_1 + d_2$) much faster than the action of CTLs on infected CD4+ will be negligible. Thus, letting $d_1\xi + d_2\xi \gg k_2$ such that $d_1\xi + d_2\xi - k_2 \approx d_1\xi + d_2\xi$ and letting $\xi = 1$ [19], then

$$k_2k_4 < \frac{(1 - p)\pi nd_2\beta_1\lambda_1}{d_1d_6(\alpha + \pi + d_1)(d_1 + d_2)} \tag{3.31}$$

Comparing Eqs. (3.12) and (3.31) we have

$$k_2k_4 < R_0 \tag{3.32}$$

$a_2 < 0$ if $R_0 > k_2k_4$. Since HIV is endemic when $R_0 > 1$, then there is an endemic equilibrium point when $k_2k_4 \geq 1$. Summarising the above analysis, we have the following lemma.

Lemma 1. Given $d_1\xi + d_2\xi \gg k_2$, the endemic equilibrium point for system (2.1)–(2.8) exists when $R_0 > 1$ provided $k_2k_4 \geq 1$.

3.4.1. Stability analysis of the endemic equilibrium point

To determine the stability of the endemic equilibrium we use bifurcation analysis at the disease-free equilibrium (E_0) using Centre Manifold Theorem as in [29].

Let $T_c = x_1$, $E = x_2$, $I_c = x_3$, $T_h = x_4$, $I_h = x_5$, $L = x_6$, $V = x_7$ and $A = x_8$. So we re-write system (2.1)–(2.8) in the form

$$\dot{x}_1 = f_1 = \lambda_1 - d_1x_1 - (1 - p)\beta_1x_1x_7 + \alpha x_2 \tag{3.33}$$

$$\dot{x}_2 = f_2 = (1 - p)\beta_1x_1x_7 - d_1x_2 - (\alpha + \pi)x_2 \tag{3.34}$$

$$\dot{x}_3 = f_3 = \pi x_2 - (d_1 + d_2 + k_2x_6)x_3 \tag{3.35}$$

$$\dot{x}_4 = f_4 = \lambda_2 - d_3x_4 - p\beta_2x_4x_7 \tag{3.36}$$

$$\dot{x}_5 = f_5 = p\beta_2x_4x_7 - d_4x_5 - k_3x_5x_6 \tag{3.37}$$

$$\dot{x}_6 = f_6 = \frac{k_4x_3x_6}{1 + \xi x_6} - d_5x_6 \tag{3.38}$$

$$\dot{x}_7 = f_7 = nd_2x_3 - d_6x_7 \tag{3.39}$$

$$\dot{x}_8 = f_8 = k_5(d_4x_5 + k_3x_5x_6) - d_7x_8 \tag{3.40}$$

Let p^* be the bifurcation parameter, that is, the value of p in Eq. (3.12) when $R_0 = 1$, then we have

$$p^* = \frac{\pi\lambda_1nd_2\beta_1 - d_1d_6(d_1 + d_2)(d_1 + \pi + \alpha)}{\pi\lambda_1nd_2\beta_1} \tag{3.41}$$

Let $(J_{E_0}(p^*) = J_{p^*})$ be the Jacobian matrix of system (3.33)–(3.40) at E_0 corresponding to p^*

$$J_{p^*} = \begin{bmatrix} -d_1 & \alpha & 0 & 0 & 0 & 0 & -\phi_1 & 0 \\ 0 & -(d_1 + \pi + \alpha) & 0 & 0 & 0 & 0 & \phi_1 & 0 \\ 0 & \pi & -(d_1 + d_2) & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & -d_3 & 0 & 0 & -\phi_2 & 0 \\ 0 & 0 & 0 & 0 & -d_4 & 0 & \phi_2 & 0 \\ 0 & 0 & 0 & 0 & 0 & -d_5 & 0 & 0 \\ 0 & 0 & nd_2 & 0 & 0 & 0 & -d_6 & 0 \\ 0 & 0 & 0 & 0 & k_5d_4 & 0 & 0 & -d_7 \end{bmatrix} \tag{3.42}$$

where $\phi_1 = (1 - p^*)\beta_1\lambda_1/d_1$ and $\phi_2 = p^*\beta_2\lambda_2/d_3$.

Zero is a simple eigenvalue of J_{p^*} , and the right eigenvector w of J_{p^*} associated with the zero eigenvalues is given by $w = (w_1, w_2, w_3, w_4, w_5, w_6, w_7, w_8)^T$ where

$$\begin{cases} w_1 = \frac{\alpha w_2}{d_1} - \frac{(1 - p^*)\beta_1\lambda_1 w_7}{d_1} \\ w_2 = \frac{(1 - p^*)\beta_1\lambda_1 w_7}{d_1(d_1 + \pi + \alpha)} \\ w_3 = \frac{\pi w_2}{d_1 + d_2} \\ w_4 = -\frac{p^*\beta_2\lambda_2 w_7}{d_3} \\ w_5 = \frac{p^*\beta_2\lambda_2 w_7}{d_4} \\ w_6 = 0 \\ w_7 = w_7 > 0 \\ w_8 = \frac{k_5 d_4 w_5}{d_7} \end{cases} \tag{3.43}$$

The left eigenvector v of J_{p^*} associated with the zero eigenvalues is given by $v = (v_1, v_2, v_3, v_4, v_5, v_6, v_7, v_8)^T$ where

$$\begin{cases} v_1 = v_4 = v_6 = 0 \\ v_2 = \frac{\pi v_3}{(d_1 + \pi + \alpha)} \\ v_3 = v_3 > 0 \\ v_5 = \frac{d_3(d_1d_6v_7 - (1 - p^*)\lambda_1\beta_1v_2)}{d_1p^*\beta_2\lambda_2} \\ v_7 = \frac{(d_1 + d_2)v_3}{nd_2} \\ v_8 = \frac{v_5}{k_4} \end{cases} \tag{3.44}$$

From system (3.33)–(3.40), the non zero partial derivatives are

$$\begin{aligned} \frac{\partial^2 f_1}{\partial x_1 \partial x_7} &= \frac{\partial^2 f_1}{\partial x_7 \partial x_1} = -(1 - p^*)\beta_1, & \frac{\partial^2 f_2}{\partial x_1 \partial x_7} &= \frac{\partial^2 f_2}{\partial x_7 \partial x_1} \\ &= (1 - p^*)\beta_1, & \frac{\partial^2 f_3}{\partial x_3 \partial x_6} &= \frac{\partial^2 f_3}{\partial x_6 \partial x_3} = -k_2, \\ \frac{\partial^2 f_4}{\partial x_4 \partial x_7} &= \frac{\partial^2 f_4}{\partial x_7 \partial x_4} = -p^*\beta_2, & \frac{\partial^2 f_5}{\partial x_4 \partial x_7} &= \frac{\partial^2 f_5}{\partial x_7 \partial x_4} = p^*\beta_2, \\ \frac{\partial^2 f_5}{\partial x_5 \partial x_6} &= \frac{\partial^2 f_5}{\partial x_6 \partial x_5} = -k_3, & \frac{\partial^2 f_6}{\partial x_3 \partial x_6} &= \frac{\partial^2 f_6}{\partial x_6 \partial x_3} = \frac{(1 + \xi x_6)k_2 - \xi k_4 x_6}{(1 + \xi x_6)^2}, \\ \frac{\partial^2 f_8}{\partial x_5 \partial x_6} &= \frac{\partial^2 f_8}{\partial x_6 \partial x_5} = k_3k_5, & \frac{\partial^2 f_1}{\partial x_7 \partial p^*} &= \beta_1x_1, & \frac{\partial^2 f_1}{\partial x_1 \partial p^*} &= \beta_1x_7, \end{aligned}$$

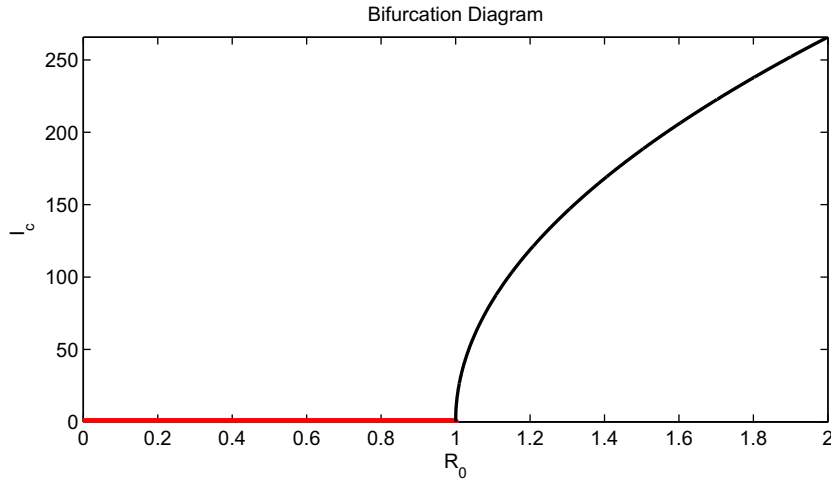


Fig. 3. Bifurcation diagram of model (2.1)–(2.8). Parameter values are as indicated in Table 1.

$$\begin{aligned} \frac{\partial^2 f_2}{\partial x_7 \partial p^*} &= -\beta_1 x_1, & \frac{\partial^2 f_2}{\partial x_1 \partial p^*} &= -\beta_1 x_7, & \frac{\partial^2 f_4}{\partial x_7 \partial p^*} &= -\beta_2 x_4, \\ \frac{\partial^2 f_4}{\partial x_4 \partial p^*} &= -\beta_2 x_7, & \frac{\partial^2 f_5}{\partial x_7 \partial p^*} &= \beta_2 x_4, & \frac{\partial^2 f_5}{\partial x_4 \partial p^*} &= \beta_2 x_7 \end{aligned} \quad (3.45)$$

We therefore compute for a

$$a = \sum_{i,j,k=0}^n v_k w_i w_j \frac{\partial^2 f_k}{\partial x_i \partial x_j} (0, 0) \quad (3.46)$$

$$a = \frac{2(1-p^*)\beta_1\pi(\alpha w_2 - \gamma w_7)}{d_1(\alpha + \pi + d_1)} - 2\lambda_2 v_2 \left(\frac{p^* \beta_2 w_7}{d_3} \right)^2 \quad (3.47)$$

where $\gamma = \frac{(1-p^*)\beta_1 \lambda_1}{d_1}$.

Considering the first part of Eq. (3.47), if $\alpha w_2 > \gamma w_7$, that is $\alpha/\gamma > w_7/w_2$, then the first part will be positive. From (3.43) $w_2/w_7 = \gamma/(\alpha + \pi + d_1)$. Therefore, $\alpha/\gamma > (\alpha + \pi + d_1)/\gamma$, but since $\pi, d_1 > 0$ then $\alpha < (\alpha + \pi + d_1)$. Therefore, the first part is negative and hence $a < 0$.

We now derive the expression for b as

$$b = \sum_{i,k=0}^n v_k w_i \frac{\partial^2 f_k}{\partial x_i \partial \phi} (0, 0) \quad (3.48)$$

$$b = \sum_{i,k=0}^n v_k w_i \frac{\partial^2 f_k}{\partial x_i \partial \phi} (E_0) = w_7(v_5 \beta_2 x_4 - v_2 \beta_1 x_1) \quad (3.49)$$

If

$$\frac{v_5}{v_2} > \frac{\beta_1 x_1}{\beta_2 x_4} \quad (3.50)$$

then $b > 0$. From Eq. (3.44)

$$\frac{v_5}{v_2} = \frac{d_3[d_1 d_6(d_1 + d_2)(d_1 + \pi + \alpha) - (1-p^*)\beta_1 n d_2 \pi \lambda_1]}{d_1 d_2 \beta_2 n \pi p^*} \quad (3.51)$$

From Eq. (3.41) it can be shown that $\frac{v_5}{v_2} = 0$. If $\frac{v_5}{v_2} = 0$, then using Eq. (3.50), $b > 0$ only if $\frac{\beta_1 x_1}{\beta_2 x_4} < 0$. Since all variables and parameters are non-negative, then $\frac{\beta_1 x_1}{\beta_2 x_4} > 0$. Using the condition leading to Eq. (3.50), it is hence implied that $b < 0$.

Using point (ii) of Theorem 1 in [29], the bifurcation parameter $p \in (0, 1)$, and since there exists a positive unstable equilibrium, then a unique endemic equilibrium exists when $R_0 > 1$.

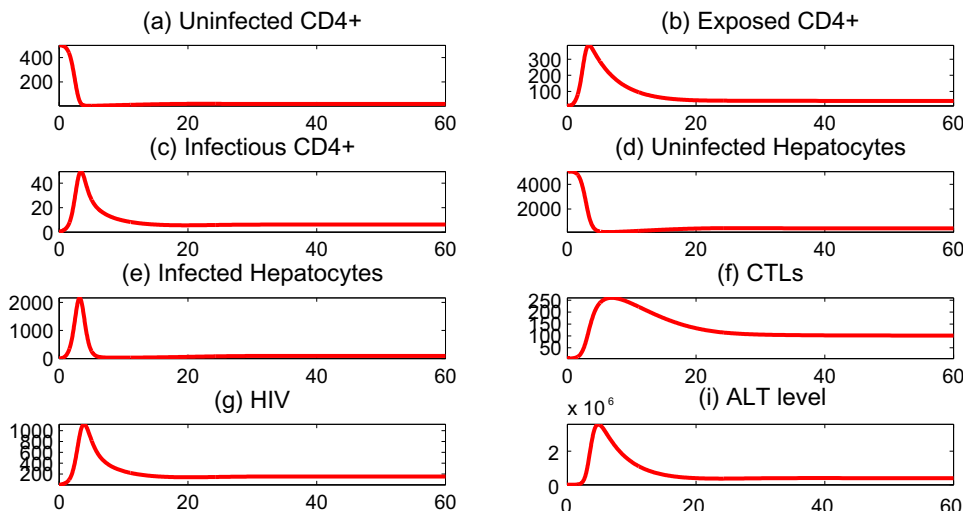


Fig. 4. General dynamics of HIV infection in the liver as demonstrated in the model with $\alpha < \pi$. Vertical axes represent the variables and horizontal axes are time in days. Parameter values are as indicated in Table 1.

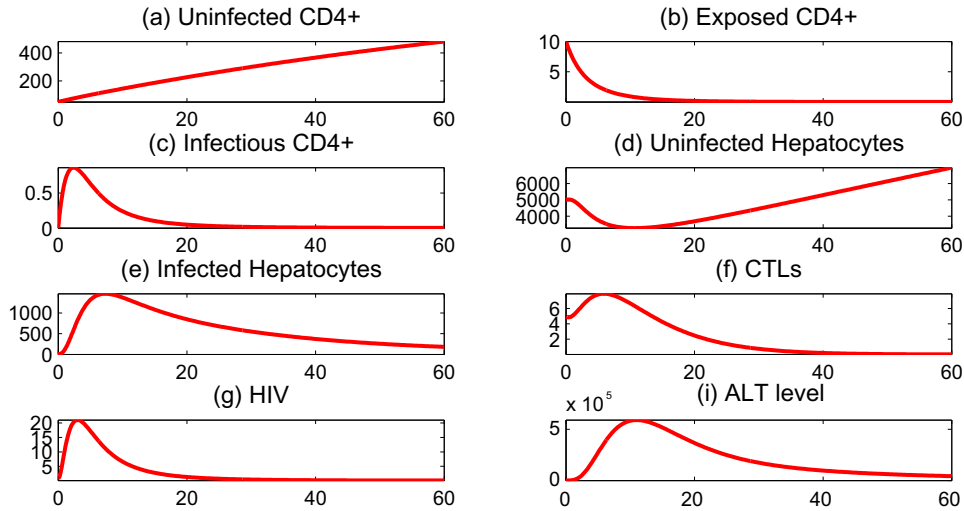


Fig. 5. General dynamics of HIV infection in the liver as demonstrated in the model with $\alpha > \pi$. Vertical axes represent the variables and horizontal axes are time in days. Parameter values are as indicated in Table 1.

HIV may establish an infection without the presence of an immune response (endemic equilibrium when $L = 0$) when the infection is limited by the availability of target cells. This equilibrium is stable when $R_0 > 1$ if the number of infected CD4+ in the absence of an immune response is given by a threshold $I_c < d_5/k_4$ [19]. Otherwise, with immune response in play, there exists a unique endemic equilibrium for all $R_0 > 1$ with a transcritical bifurcation at $R_0 = 1$ and an exchange of stability between the disease-free equilibrium and endemic equilibrium, as depicted in Fig. 3. Unlike infections like tuberculosis where the infection can be shielded by the host cells, during HIV infection, every infected cell is exposed to CTLs killing and hence there is no possibility of endemicity when the basic reproductive number is below unity. The existence of a transcritical bifurcation would inform public health that if R_0 can be reduced below unity, then HIV in the liver can be controlled given a suitable choice of epidemiological parameters.

4. Numerical simulations

To observe the dynamics of the variables in the system of differential equations (2.1)–(2.8) over time, we used MatLab programming language. The initial values for the variables were set as $T_{c0} = 500$, $E_0 = 10$, $I_{c0} = 0$, $T_{h0} = 5000$, $I_{h0} = 0$, $L_0 = 5$, $V_0 = 1$, $A_0 = 0$. Liver enzyme elevation was regarded as the enzyme level of alanine aminotransferase above the normal level, thus the normal level was assumed to be zero. Time is in days and all the rates are per day. The fixed parameters used are shown in Table 1.

Fig. 4 shows the general dynamics of HIV in the liver, given that replication is only in CD4+. When the viral load increases (g), the number of infected CD4+ (b), exposed CD4+ (c) and infected hepatocytes (e) increase. Correspondingly, the number of uninfected CD4+ (a) and uninfected hepatocytes (d) decrease. The increase in infected CD4+ and hepatocytes leads to an increase in CTL proliferation (f). Antigen-dependent death and cytotoxic killing of infected hepatocytes consequently lead to elevation of liver enzymes (i).

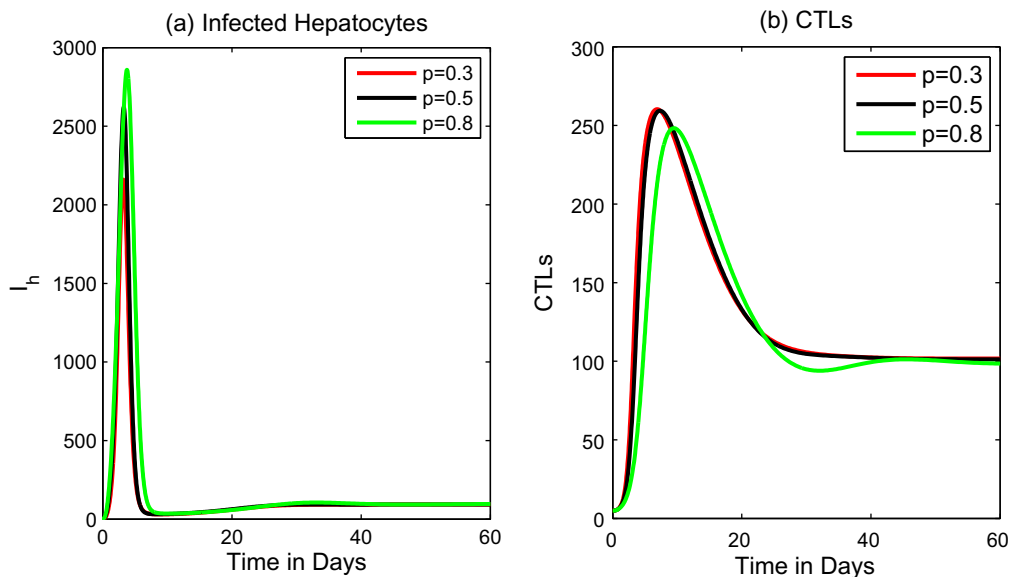


Fig. 6. Dependence of the number of infected hepatocytes (a) and the number of cytotoxic T lymphocytes (b) on the probability that HIV in the liver infects hepatocytes. Parameter values are as indicated in Table 1.

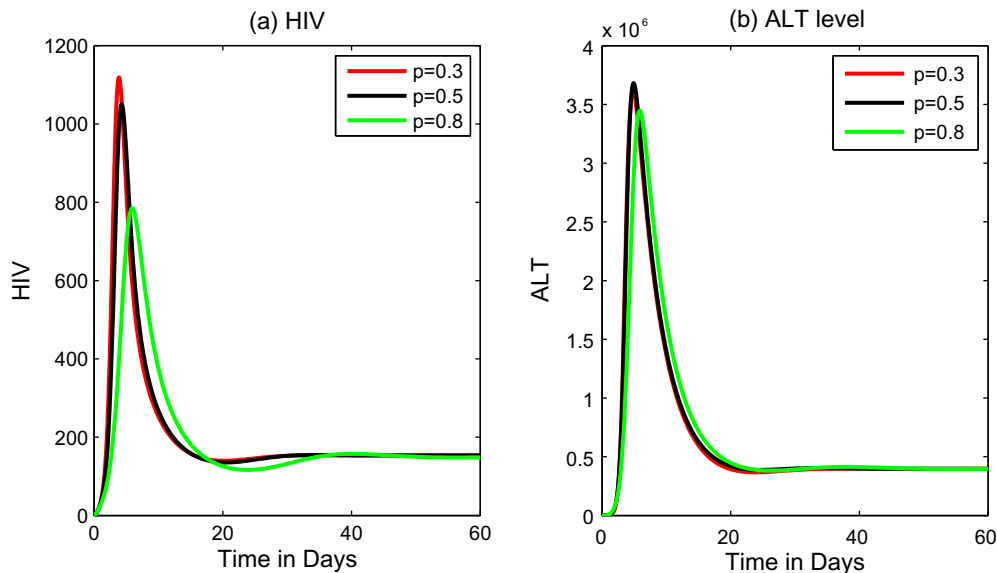


Fig. 7. Dependence of the viral load (a) and the level of alanine aminotransferase in the blood steam (b) on the probability that HIV in the liver infects hepatocytes. Parameter values are as indicated in Table 1.

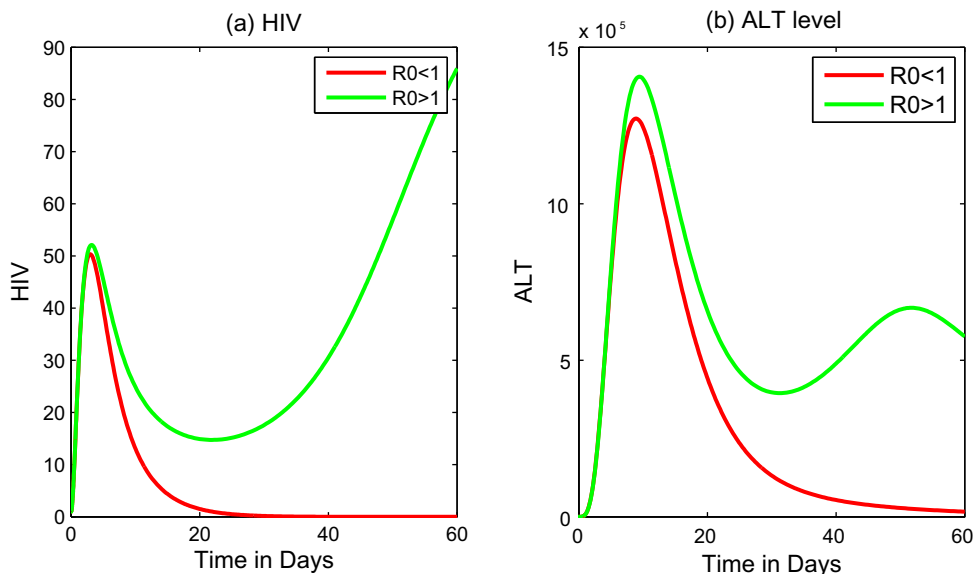


Fig. 8. Dynamics of HIV (a) and level of alanine aminotransferase in the blood system (b) when $R_0 < 1$ and when $R_0 > 1$. Parameter values are as indicated in Table 1.

If the time it takes for reverse transcription is greater than the length of time it would take for the virus to die within the exposed cell ($1/\alpha < 1/\pi$) then uninfected cells (CD4+ and hepatocytes) grow logistically. However, exposed CD4+, infectious CD4+, viral load, CTLs and ALT levels will decay to extinction, Fig. (5).

Comparing the level of CTLs in cases where $\alpha < \pi$, (Fig. 4) and $\alpha > \pi$, (Fig. 5). Since the model considers only antigen-dependant proliferation rate of CTLs, if more exposed cells return to uninfected state as compared to those becoming infectious then CTLs proliferate very slowly due to fewer number of infectious cells.

The dynamics of HIV in the liver is dependent on the probability that HIV infects either of the cells on invasion. When the probability of HIV infection in hepatocytes increases then the number of infected hepatocytes increases. A decrease in probability ($p = 0.3$) leads to an increase in the number of infected CD4+, leading to

an increase in viral load. This triggers an increase in the action of CTL proliferation, (Fig. 6).

Unlike other variables that are consistent with the biological logic resulting from increasing the probability p that HIV infects hepatocytes, ALT shows a different behaviour. ALT levels are maximised when HIV is equally likely to infect CD4+ cells or hepatocytes (Fig. 7). This is in agreement with Eq. (3.24) which indicates that at high viral load, the level of ALT is independent of p . The independence of ALT on p would suppose that for as long as HIV prevails, there will be ALT elevation in the blood system regardless of the type of cells that are infected most.

Fig. 8 shows that when $R_0 < 1$ the viral load (a) and level of ALT in blood (b) will first increase then decay to extinction. When $R_0 > 1$ then there is a biphasic decay of ALT due to the action of CTLs. This action is significant at low viral load but at higher viral load (possibly AIDS) this action becomes negligible.

5. Discussion and conclusion

In the formulation of the mathematical model, it was considered that HIV infects and replicates in CD4+ cells, while the virus infects and causes apoptosis to hepatocytes by signaling through C-X-C chemokine receptor type 4 without replication.

Liver disease in HIV infected people has been largely associated with the use of ART and coinfection with HBV or HCV [1,2,8]. However, the numerical simulations in this study show that there is an increase in the level of alanine aminotransferase in the blood system (an indicator of liver damage), even though the model does not incorporate the use of ART. This is in agreement with Xiao et al. [15], who reported that liver abnormalities occur solely as a result of HIV infection. The level of alanine aminotransferase in the blood system is seen in the numerical simulations to be highest when HIV is equally likely to infect CD4+ cells or hepatocytes. Increase in ALT with increase in the viral load is an indicator of liver damage in HIV mono-infected people. Thus, the study suggests that liver disease can be experienced by HIV mono-infected people prior to initiation of ART.

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