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Analysis of HIV therapy in the liver using optimal control and pharmacokinetics

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Abstract

The main burden in treating human immunodeficiency virus (HIV) infection currently, is the side effects of the antiretroviral therapy (ART) used, because each treatment is toxic to the liver. This study uses optimal control theory applied to a mathematical model that describes the dynamics of HIV infection in the liver. The optimal controls are presented as therapy efficacy of reverse transcriptase inhibitors (RTIs), integrase inhibitors (INs) and protease inhibitors (PIs). An objective function is defined with an aim to investigate the optimal control strategy that minimises toxicity, viral load and cost of first-line and second-line HIV regimen. Results indicate that, in the first-line regimen with INs, a patient has to take medication for at least 98% of the treatment time and the regimen should be close to 100% efficacious regardless of the intervention cost. For second-line regimen, the period of drug administration of PIs largely depends on the weight constants. Inclusion of INs in the first-line regimen yields better HIV DNA suppression, as they are more efficacious than NRTIs. Of all drugs studied, nevirapine is highly efficacious but most toxic. The study recommends routine transaminase tests because results indicate liver enzyme elevation even with very low viral load. Numerical results with pharmacokinetic parameters further indicate an increase in HIV load at initiation of therapy, due to viral redistribution in plasma.

Keywords: HIV; Antiretroviral therapy; Optimal control; Pharmacokinetics

1 Introduction

Liver-related complications are the leading cause of morbidity and mortality in human immunodeficiency virus (HIV)-infected persons, due to the role played by the organ in the pathogenesis of the virus [2]. HIV predominately infects CD4+ cells, however, there is evidence that HIV can manifest in hepatic cells and causes elevation of liver transaminases even in the absence of antiretroviral therapy (ART) [11, 23, 32].

HIV infected people in most settings get ART prescription according to the stage of HIV progression in their bodies. Persons who have just been diagonised with HIV are given the first-line regimen, which is a combination of different drugs depending on other underlying conditions. In the event that the first-line regimen fails to suppress the viral load for any other reason like drug resistance, a patient is then advanced to the second-line regimen, with different drug combination. About 50% of deaths among HIV-infected patients on antiretroviral therapy (ART) is associated with liver problems [4]. Research

shows that HIV ART is not as effective in curbing HIV in hepatocytes as compared to its effectiveness in CD4+ cells. As a result, hepatocytes may act as reservoirs of HIV and thus leading to higher HIV DNA in the liver during ART administration [1, 4].

In addition to liver fibrosis caused by HIV, life-time treatment of HIV-infected individuals has also heavily contributed to hepatotoxicity (drug induced liver injury). This has been attributed to some drugs such as nevirapine and efavirenz, which inhibit bile acid transport, that causes cholestasis and, consequently, apoptosis of hepatocytes [2]. Modern drugs have also been identified to cause non-alcoholic fatty liver disease and non-cirrhotic portal hypertension in HIV monoinfected patients [4]. There is no ART regimen that is free of toxicity, but it is crucial that the resultant hepatotoxicity is kept at the minimum.

Ezhilarasan *et al.* [2] recommend that careful observation is necessary especially during and after initiation of ART to study drug-induced liver diseases. They further propose that one of the ways to overcome liver disease is routine checks for basic liver function, such as transaminase levels after commencing ART for the first 3 months. In most developing nations, where the population accessing the free medication is sizable, financial constraints do not allow such checks to be carried out. It is therefore of great interest to identify a strategy of dealing with hepatotoxicity in different settings. This study proposes optimisation of three important components of medication, namely efficacy, toxicity and other systemic costs associated with the use of ART in HIV-infected people.

Various mathematical models with varying methodologies and cost functions have embraced optimal control theory as a strategy to mitigate infectious diseases [14, 29, 33]. Mainly the Pontryagin's maximum principle [30] has been adopted to obtain the most optimal control strategy. Recently, [27] used a model similar to that of [20] to study optimal therapy among reverse transcriptase inhibitors, fusion inhibitors and protease inhibitors. They found that protease inhibitor plays a very important role in virus suppression. Garira *et al.* [5] used optimal control approach to investigate drug toxicities, efficacy and cost of PIs and NRTIs. Their results indicate that for highly toxic drugs, small dosage sizes and allowing drug holidays make a better impact in both improving the quality of life and reducing costs of medication. They further concluded that, for less toxic drugs, uninterrupted therapy is the most effective strategy.

HIV therapy consisting of three or more drugs has proved to be extremely effective in suppressing the plasma viral load below detection limit in most HIV-infected patients. However, over time, some adverse effects of these drugs unfold and lead to discontinuation of ART or changing the regime. Magombedze *et al.* [20] suppose that these challenges stem from the unfavourable pharmacokinetics of ART, which play a very crucial role in drug effectiveness and toxicity.

Effectiveness of a control to manage viral replication highly depends on how the drug has been metabolised by hepatocytes [18]. Metabolism of toxic ART coupled with HIV infection results in hepatocellular apoptosis, with dangers ranging from elevation of transaminase levels to hepatic failure (cirrhosis, hepatocellular circinoma) and death [1]. In our previous work, we analysed hepatotoxicity in HIV-infected patients [24] and HIV/HBV coinfection [25]. However, we did not use the optimal control approach, neither did we consider the key pharmacokinetic (PK) parameters which play a very crucial role in defining drug efficacy and toxicity [14]. In this study we analyse a mathematical model of HIV infection in the liver with optimal control methods. We apply three controls: RTIs, INs and

PIs and assess the best control strategies for both first-line and second-line regimens. Pharmacokinetic parameters defining effectiveness and toxicity of medication are included.

Generally, the existing literature on optimal control analysis of HIV within-host mathematical models hinge on HIV dynamics in CD4+ immune cells with corresponding cytotoxic killing of the infected cells. Most objective functions aim at attaining an optimal therapy that will increase CD4+ T cells in a host as well as minimising the systemic costs of drugs administered. The main contribution of this study is that it considers optimising HIV therapy, given that the virus infects both immune cells and hepatic cells, which are responsible for metabolising the medication. The aim is to identify a regimen that improves the count of both immune cells and hepatic cells with minimal systemic cost.

2 HIV in immune and hepatic cells

According to Ganesan et al. [4] there is clinical evidence that HIV directly infects hepatocytes. A study carried out on 59 patients who were neither coinfected with viral hepatitis nor on therapy, shows that there is a positive correlation between transaminases elevation and HIV viral load, concluding that the virus on its own causes hepatic damage [21]. This is in agreement with other studies which propose that, there is an association between HIV viral load and liver fibrosis [11, 12, 31]. In our previous study, we also verified mathematically that in absence of coinfection and medication, there is significant liver enzyme elevation in HIV-infected patients [23]. HIV also has a direct cytopathic effect on hepatocytes, primarily triggering apoptosis via the HIV gp120 protein-receptor signalling pathway [11].

HIV gains access to a host immune cell through binding on a CD4+ receptor or coreceptors on the surface of a CD4+T cell. Likewise, HIV infects hepatocytes through C-X-C chemokine receptor type 4 (CXCR4) [32]. This is followed by fusion into the host cell, where viral RNA is released into the host cell. Direct cytotoxicity, which is seen as the primary cause of liver disease in the HIV-infected patient, is as a result of HIV infection of hepatocytes [4]. The next step involves HIV enzyme reverse transcriptase converting the single-stranded HIV RNA to a double stranded DNA through the process of reverse transcription. If reverse transcription has been successful, the next step will involve integration of the newly formed double strand DNA (DsDNA) into the host cell nucleus using an enzyme integrase to form a provirus. The provirus can remain in the host cell for many years without replication, implying that the host cell will be latently infected with HIV. After successful integration, HIV uses host cell enzyme called RNA polymerase for transcription in order to create copies of the HIV genomic materials. Then, HIV enzyme protease converts the newly formed HIV genetic materials into smaller and multiple copies of HIV RNA which are then ready to infect other susceptible cells [20].

3 Optimal control model

In model formulation, we define eight variables as follows: uninfected CD4+ cells (T_c), latently infected CD4+ cells (E_c), infectious CD4+ cells (I_c), uninfected hepatocytes (T_h), productively infected hepatocytes (I_h), HIV-specific cytotoxic T lymphocytes (L), viral load (V) and the level of enzyme alanine aminotransferase (ALT) in blood (A), which is an indicator of hepatocyte loss.

Model parameters are as follows: CD4+ cells and hepatocytes are produced from the thymus and the liver at rates α_1 and α_2 and die naturally at rates d_1 and d_4, respectively.

HIV infects target hepatocytes with probability q at rate β_3 and target CD4+ cells with probability $1-q$ at rate β_1. HIV infection in hepatocytes is much lower than that in CD4+ cells [11]. Healthy hepatocytes are cleared from the liver due to hepatotoxicity at a rate n_1. It is assumed that all hepatocytes that are exposed to viral entry will produce viral copies. Infectious CD4+ cells die at rate d_5 and are cleared by HIV-specific cytotoxic T-lymphocytes (CTLs) at a rate k_1.

Infectious hepatocytes are killed by CTLs at rate k_2, cleared naturally and due to infection at a rate d_5, and due to hepatotoxicity at rate n_2. With or without any pathogen in the body CTLs proliferate naturally at rate x. The antigen-dependant proliferation rate of CTLS is k_3. CTLs are cleared at rate d_6. The number of HIV virions produced per infectious CD4+ cell and hepatocyte are s_1 and s_2, respectively, and they die at rate d_7.

Without infection, the level of ALT in the blood system is generated from naturally dying hepatocytes at rate r [6]. During HIV infection, ALT level is increased by HIV-induced hepatocytes death, CTLs killing and drug metabolism [19]. Infection induced hepotocytes death lead to enzyme ALT elevation in the blood stream, thus, k_4 is assumed to be the average amount of enzyme ALT per hepatocyte that is leaked in the blood [24]. ALT is cleared from the blood naturally at rate d_8.

HIV antiretroviral therapy is manufactured with an aim of disabling all the enzymes that aid viral progression at different stages. In this study we shall consider three enzyme inhibitors: (i) reverse transcriptase inhibitors (RTIs), meaning both nucleoside reverse transcriptase inhibitors (NRTIs) and non nucleoside reverse transcriptase inhibitors (NNRTIs), (ii) integrase inhibitors (INs) and (iii) protease inhibitors (PIs). RTIs reduce the rate of infection β_1 by $\beta_1(1-\mu_{RT}(t))$, where $\mu_{RT}(t)$ defines the efficacy/effectiveness of RTIs medication administered. Integrase inhibitors disable the activity of integrase which reduce the rate at which exposed cells become infectious, thus β_2 becomes $(1-\mu_{IN}(t))\beta_2$, where $\mu_{IN}(t)$ is the efficacy of integrase inhibitors. The last stage of viral production is slowed down by administering protease inhibitors leading to fewer viral copies produced. Thus, s_1 and s_2 become $(1-\mu_{PI}(t))s_1$ and $(1-\mu_{PI}(t))s_2$ respectively, where $\mu_{PI}(t)$ is the efficacy of PIs. Hepatocytes are the primary cells responsible for drug metabolism in the liver. However, when the drug is toxic, some hepatocytes burst/die during the process (hepatotoxicity). It is assumed that $\psi(t)$ is time-dependant likelihood that a hepatocyte will die during drug metabolism depending on the level of cacinology of the drug in the body at a specific time [25].

We summarise the above dynamics with the following system of ordinary differential equations:

$$\dot{T}_c = \alpha_1 - (1-\mu_{RT}(t))(1-q)\beta_1 T_c V - d_1 T_c, \tag{3.1}$$

$$\dot{E}_c = (1-\mu_{RT}(t))(1-q)\beta_1 T_c V - (1-\mu_{IN}(t))\beta_2 E_c - d_2 E_c, \tag{3.2}$$

$$\dot{I}_c = (1-\mu_{IN}(t))\beta_2 E_c - k_1 I_c L - d_3 I_c, \tag{3.3}$$

$$\dot{T}_h = \alpha_2 - (1-\mu_{RT}(t))q\beta_3 T_h V - d_4 T_h - n_1\psi(t)T_h, \tag{3.4}$$

$$\dot{I}_h = (1-\mu_{RT}(t))q\beta_3 T_h V - k_2 I_h L - n_2\psi(t)I_h - d_5 I_h, \tag{3.5}$$

$$\dot{L} = x + k_3(I_c + I_h)L - d_6 L, \tag{3.6}$$

$$\dot{V} = (1-\mu_{PI}(t))s_1 I_C + (1-\mu_{PI}(t))s_2 I_h - d_7 V, \tag{3.7}$$

$$\dot{A} = r + k_4[(d_5 + n_2\psi(t) + k_2 L)I_h + n_1\psi(t)T_h] - d_8 A \tag{3.8}$$

3.1 Positivity and boundedness of solutions

Here we show the state variables in (3.1)-(3.8) are non-negative for all $t > 0$ given that the initial variables at $t = 0$ are non-negative. We further investigate for the invariant region, using an approach similar to that in [24].

Theorem 3.1 *The solution to the model system* (3.1)-(3.8) *with non-negative starting values remain non-negative for all* $t > 0$.

Proof Let $T_{c0} > 0$, $E_{c0} > 0$, $I_{c0} > 0$, $T_{h0} > 0$, $I_{h0} > 0$, $L_0 > 0$, $V_0 > 0$ and $A_0 > 0$, be initial variables for $T_c, E_c, I_c, T_h, I_h, L, V$ and A, respectively. For biological consistency, all parameters in model equations (3.1)-(3.8) are positive for all $t > 0$. Considering equation (3.1),

$$\dot{T}_c = \alpha_1 - (1 - \mu_{RT}(t))(1 - q)\beta_1 T_c V - d_1 T_c.$$

Since all parameters are positive for all $t > 0$ then

$$\begin{aligned}
\frac{dT_c}{dt} &\geq -[(1 - \mu_{RT}(t))(1 - q)\beta_1 V + d_1]T_c \\
\int_{T_{c0}}^{T_c(t)} \frac{dT_c}{T_c} &\geq -\int_0^t [(1 - \mu_{RT}(t))(1 - q)\beta_1 V + d_1]dt \\
T_c(t) &\geq T_{c0} e^{-\int_0^t [(1-\mu_{RT}(t))(1-q)\beta_1 V + d_1]dt}. \qquad (3.9)
\end{aligned}$$

Using the same approach, it can be shown that

$$E_c(t) \geq E_{c0} e^{-\int_0^t [(1-\mu_{IN}(t))\beta_2 + d_2]dt} \qquad (3.10)$$

$$I_c(t) \geq I_{c0} e^{-\int_0^t [k_1 L + d_3]dt} \qquad (3.11)$$

$$T_h(t) \geq T_{h0} e^{-\int_0^t [(1-\mu_{RT}(t))q\beta_3 V + d_4 + n_1\psi(t)]dt} \qquad (3.12)$$

$$I_h(t) \geq I_{h0} e^{-\int_0^t [k_2 L + n_2\psi(t) + d_5]dt} \qquad (3.13)$$

$$L(t) \geq L_0 e^{-\int_0^t d_6 dt} \qquad (3.14)$$

$$V(t) \geq V_0 e^{-\int_0^t d_7 dt} \qquad (3.15)$$

$$A(t) \geq A_0 e^{-\int_0^t d_8 dt}. \qquad (3.16)$$

Thus from equations (3.9)-(3.16), it can be seen that all variables are non-negative for all $t > 0$. □

Theorem 3.2 *The solution sets of system* (3.1)-(3.8) *with non-negative initial values in* $\mathbb{R}^8$ *are feasible for all* $t > 0$ *if they enter the invariant region* Ω *where*

$$\Omega = \{(T_c, E_c, I_c, T_h, I_h, L, V, A) \in \mathbb{R}^8 :$$
$$(T_c, E_c, I_c) < \frac{\alpha_1}{d_1}, (T_h, I_h) < \frac{\alpha_2}{d_4}, L < \Gamma, V < \frac{Y}{d_7}, A < \frac{Q}{d_8}\}$$

Proof Let $\Omega = \{(T_c, E_c, I_c, T_h, I_h, L, V, A) \in \mathbb{R}^8$ be a solution set to system (3.1)-(3.8) with non-negative initial values as $T_{c0} > 0$, $E_{c0} > 0$, $I_{c0} > 0$, $T_{h0} > 0$, $I_{h0} > 0$, $L_0 > 0$, $V_0 > 0$ and

$A_0 > 0$. The control functions μ_{RT}, μ_{IN} and μ_{PI}, are all bounded in $[0, 1]$, that is, 0 indicates a therapy that has no inihibition while 1 implies that the therapy is 100% efficient. Define N_D and N_H as the total number of CD4+ cells and hepatocytes, respectively. Then $\dot{N_D} = \dot{T_c} + \dot{E_c} + \dot{I_c}$ and $\dot{N_H} = \dot{T_h} + \dot{I_h}$. Thus

$$\dot{N_D} = \alpha_1 - d_1 T_c - d_2 E_c - k_1 L I_c - d_3 I_c.$$

We assume that the decay rates for CD4+ cells as well as hepatocytes increases with the level of viral infection. That is $d_1 < d_2 < d_3$ and $d_4 < d_5$. Define some constants $m_1, m_2 \in \mathbb{R}$, then $d_2 = d_1 + m_1$ and $d_3 = d_1 + m_2$.

$$\begin{aligned}\dot{N_D} &= \alpha_1 - d_1 N_D - m_1 E_c - m_2 I_c - k_1 L I_c,\\ &< \alpha_1 - d_1 N_D.\end{aligned}$$

Thus,

$$N_D < \frac{\alpha_1}{d_1} + (N_{D0} - \frac{\alpha_1}{d_1}) e^{-d_1 t},$$

where N_{D0} is the total CD4+ cells population at $t = 0$. Using the same approach, it can be derived that

$$N_H < \frac{\alpha_2}{d_4} + (N_{H0} - \frac{\alpha_2}{d_4}) e^{-d_4 t},$$

where N_{H0} is the total number of hepatocytes at $t = 0$. When $N_{D0} > \frac{\alpha_1}{d_1}$ and $N_{H0} > \frac{\alpha_2}{d_4}$, the upper bound of N_D and N_H decreases and asymptotically approaches the value of $\frac{\alpha_1}{d_1}$ and $\frac{\alpha_2}{d_4}$, respectively. On the other hand, when $N_{D0} < \frac{\alpha_1}{d_1}$ and $N_{H0} < \frac{\alpha_2}{d_4}$, the upper bound of N_D and N_H increases and asymptotically approaches the value of $\frac{\alpha_1}{d_1}$ and $\frac{\alpha_2}{d_4}$, respectively. This indicates that N_D and N_H are bounded and consequently, T_C, E_c, I_c, T_h and I_h are bounded. Let D be the upper bound of CD4+ cells and H be the upper bound for hepatocytes, then;

$$\dot{L} < x + k_3(D + H)L - d_6 L.$$

Noting that x is a natural proliferation rate of cytotoxic T lymphocytes, biologically, this rate is bounded. Unlike in [24], where this rate was ignored, in this study we shall consider it as a constant. Letting $-k_3(D + H) + d_6 = W$, then,

$$\begin{aligned}\dot{L} &< x - WL\\ L &< \frac{x}{W} + (L_0 - \frac{x}{W}) e^{-Wt}.\end{aligned}$$

If $k_3(D + H) < d_6$, then, L is bounded by $\frac{x}{W}$, that is, as $t \to \infty$, then $L < \frac{x}{W}$. Otherwise, $L < \Theta$, for some $0 < \Theta < \infty$. Letting $\Gamma = \text{Max}\{\Theta, \frac{x}{W}\}$, then, $L < \Gamma$. The boundness of CTLs, will depend on the population size of the infectious cells embedded in $D + H$, that will trigger the antigen-depended proliferation rate k_3 of the Lymphocytes.

Similarly,

$$\dot{V} < (1 - \mu_{PI}) s_1 D + (1 - \mu_{PI}) s_2 H - d_7 V.$$

Assuming that the efficacy of PI is bounded by some E such that $0 < E < 1$, then

$$\dot{V} < Y - d_7 V,$$
$$V < \frac{Y}{d_7} + (V_0 - \frac{Y}{d_7})e^{-d_7 t},$$

where $Y = (1-E)s_1 D + (1-E)s_1 H$ and V_0 is the viral load at $t = 0$. Therefore V is bounded by $\frac{Y}{d_7}$, given that the efficacy of the PIs is not 100% otherwise, the viral load will decay exponentially until when there is no viral copy in the liver.

Finally,

$$\dot{A} = r + k_4[(d_5 + n_2\psi(t) + k_2 L)I_h + n_1\psi(t)T_h] - d_8 A,$$
$$\dot{A} < r + k_4[(d_5 + n_2\psi(t) + k_2 L)N_H + n_1\psi(t)N_H] - d_8 A,$$
$$\dot{A} < Q - d_8 A,$$
$$A < \frac{Q}{d_8} + (A_0 - \frac{Q}{d_8})e^{-d_8 t},$$

where $Q = F + k_4[(d_5 + n_2 G + k_2 L)N_H + n_1 G N_H]$, in which F is the upper bound of the normal level of alanine aminotransferase enzyme in the blood stream, and G is the upper bound of the likelihood that the drug is cacinogenic, for which $0 < G < 1$. Therefore, A is bounded by $\frac{Q}{d_8}$. We suppose that, since all parameters in the model system (3.1)-(3.8) are positive and $\Gamma > 0$, $\frac{Y}{d_7} > 0$, $\frac{Q}{d_8} > 0$, and from the positivity of solutions as shown in Theorem 3.1, we have the following deduction. Suppose the feasible solutions set of CD4+ cells in the liver lie in the region Ω_C, then

$$\Omega_C = \{(T_c, E_c, I_c) \in \mathbb{R}^3 : N_D < \frac{\alpha_1}{d_1}\}.$$

Likewise, suppose hepatocytes lie in the region Ω_H, then

$$\Omega_H = \{(T_h, I_h) \in \mathbb{R}^2 : N_H < \frac{\alpha_2}{d_4}\}.$$

Therefore, all possible solutions of model (3.1)-(3.8) that begin in the region

$$\Omega = \{(T_c, E_c, I_c, T_h, I_h, L, V, A) \in \mathbb{R}^8 :$$
$$(T_c, E_c, I_c) < \frac{\alpha_1}{d_1}, (T_h, I_h) < \frac{\alpha_2}{d_4}, L < \Gamma, V < \frac{Y}{d_7}, A < \frac{Q}{d_8}\}$$

remain in that region for all $t > 0$. We thus, deduce that the domain Ω is positively invariant, that is, for all values of $t > 0$, the solution is well-posed and biologically meaningful. □

3.2 Analysis of therapy efficacy

Drugs considered in this study include: (i) five RTIs: abacavir (ABC), lamivudine (3TC), zidovudine (AZT), tenofovir (TDF), nevirapine (NVP) and efavirenz (EFV), (ii) one intrgrase inhibitor: dolutegravir (DGT), and (iii) one protease inhibitor: atanazavir (ATV).

Within-host mathematical models, generally assign drug efficacy any value from interval [0, 1]. However, according to [16], there has been desire to find efficacy value given that, even though a pill may be taken with a highly potent anti-viral drug, the medication may have trouble finding the entire corpus of infected cells before it is cleared by the body. In our previous work [24–26], we modelled efficacy as a dose-response Hill function. However, the role of pharmacokinetic (PK) parameters in drug metabolism that define time dependent efficacy can not be under estimated. Concentration of a drug at a given time $C(t)$ is one of the key parameters that contribute to effectiveness of the medication. Time-dependent efficacy of therapy is defined as a sigmoid function of concentration as shown in [13]. Thus, for a given drug efficacy $\mu_D(t)$

$$\mu_D(t) = \frac{C(t)}{C(t) + IC_{50}}, \tag{3.17}$$

in which

$$C(t) = \begin{cases} C(0) + \frac{t}{T_{max}}(C_{max} - C(0)), \text{for } 0 \leq t \leq T_{max}, \\ C_{max}e^{-w(t-T_{max})}, \text{for } T_{max} \leq t \leq \tau, \end{cases} \tag{3.18}$$

where

- IC_{50} is the intracellular concentration of drug that is necessary to inhibit viral replication by 50%,
- $w = \frac{log(2)}{t_{1/2}}$,
- $t_{1/2}$ is the serum half life of the drug, i.e. the time it takes for the plasma concentration or the amount of drug in the body to be reduced by 50%,
- τ is the dosing interval,
- C_{max} is peak plasma concentration of the drug,
- T_{max} is the time it takes to reach C_{max}.

It is assumed that at the time the pill is taken, the serum concentration $C(0)$ (extrapolated plasma concentration) is equal to the trough concentration (C_{min}).

In addition to therapeutic effects of ART, we also analyse the toxic effect. It is assumed that the therapeutic and toxic effects of all metabolic substances are associated with the concentration of the substance absorbed in the body. It is assumed that toxicity is also defined by concentration of the drug in the same way. Thus

$$\psi(t) = \frac{C(t)}{C(t) + TD_{50}}, \tag{3.19}$$

where, TD_{50} is concentration of the drug that will give carcinogenic reaction (hepatotoxicity in this case) to 50% of the exposed substances. The pharmacokinetic and carcinogenic parameter values are shown in Table 1.

Using the lower bound of the IC_{50} and other parameters in Table 1, simulation results in Fig. 1 demonstrate the resulting concentration profiles for each drug over a period of 48 hours. The higher the drug's plasma concentration, the more efficacious the drug is. Thus Fig. 2 indicates that all drugs in this study are highly efficacious with NVP as the most efficacious. DGT is more efficacious than EFV, ABC and AZT, which justifies its inclusion to replace a second NRTI. As visible from Fig. 3 NNRTIs are the most toxic

Table 1 Pharmacokinetic and carcinogenic parameter values. C_{min}, C_{max}, IC_{50}, TD_{50} are expressed in μM while τ, T_{max} and $t_{1/2}$ are in hours

Drug	Class	C_{min}	C_{max}	τ	IC_{50}	T_{max}	$t_{1/2}$	TD_{50}	Ref
3TC	NRTI	0.1744	8.722	24	3.125×10^{-5}-0.234375	1.25	6	170.53	[9]
TDF	NRTI	0.21 1	1.068	24	4.31×10^{-4}-0.09159	1	17	39.3381	[9]
AZT	NRTI	0.0748	8.232	24	$(1.806\text{-}7.839) \times 10^{-4}$	1	1.1	216.79	[9]
ABC	NRTI	0.0149	4.47	12	0.0052-0.08	1.5	1.5	22.89	[9]
FTC	NRTI	0.36	7.28	24	0.0013-0.64	1.5	10	263.056	[9]
EFV	NNRTI	5.575	12.892	24	0.0054-0.0054	4	47.5	38.523	[9]
NVP	NNRTI	14.007	21.555	24	0.00025-0.0025	2	27.5	31.6	[9]
DGT	IN	2.515	4.472	24	$(2.389\text{-}2.3864) \times 10^{-4}$	2.25	14	96.9	[9]
ATV	PI	0.387	4.472	24	0.0136-0.0136	2	7	85.1185	[9]

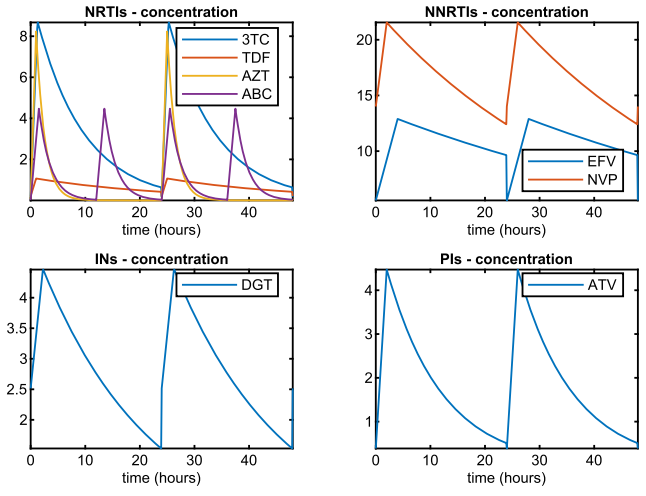

Figure 1 Concentration of antiretroviral drugs for PK parameters shown in Table 1

especially NVP [22, 24, 28], followed by NRTIs. ATV is the least toxic followed by DGT. The efficacy level of NVP partly explains, why despite its criticism as a very toxic drug, it is still widely used in most resource-poor nations in first-line regimen. This is because a potent drug is judged on its ability to suppress viral load which is routineley monitored as opposed to elevation of liver transaminases.

Steming from the fact that ART is used in combinations, we also draw the resulting efficacies for different regimen in Figs. 4 and 5 for first- and second-line regimens, as well as their respective toxicities in Figs. 6 and 7.

3.3 Objective function

Defining μ_{RT}, μ_{IN} and μ_{PI} as control strategies to inihibit viral replication in the body, we define an objective function as

$$J(\mu_{RT}, \mu_{IN}, \mu_{PI}) = \int_0^{T_f} T_c + T_h - (V + A + \frac{m_1\mu_{RT}^2}{2M} + \frac{m_2\mu_{IN}^2}{2M} + \frac{m_3\mu_{PI}^2}{2M})dt, \tag{3.20}$$

subject to state and control variables in system (3.1)-(3.8) with initial state variables as, $T_c(0) = T_{c0}$, $E_c(0) = E_{c0}$, $I_c(0) = I_{c0}$, $T_h(0) = T_{h0}$, $I_h(0) = I_{h0}$, $L(0) = L_0$, $V(0) = V_0$ and $A(0) = A_0$, such that, $T_{c0} \geq 0$, $E_{c0} \geq 0$, $I_{c0} \geq 0$, $T_{h0} \geq 0$, $I_{h0} \geq 0$, $L_0 \geq 0$, $V_0 \geq 0$, $A_0 \geq 0$.

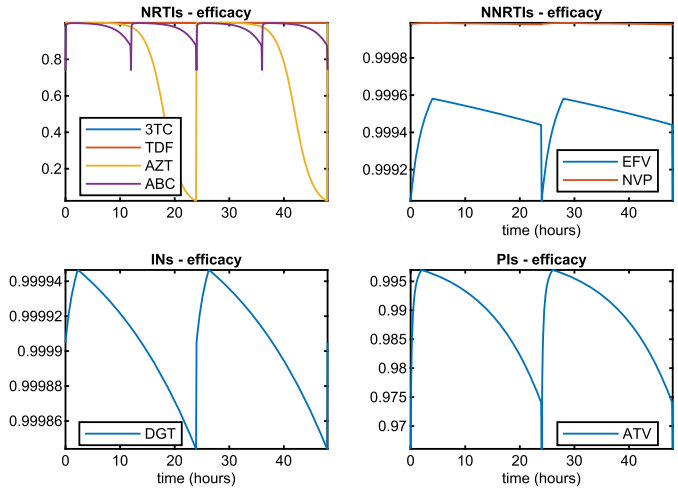

Figure 2 Efficacy of antiretroviral drugs for PK parameters shown in Table 1

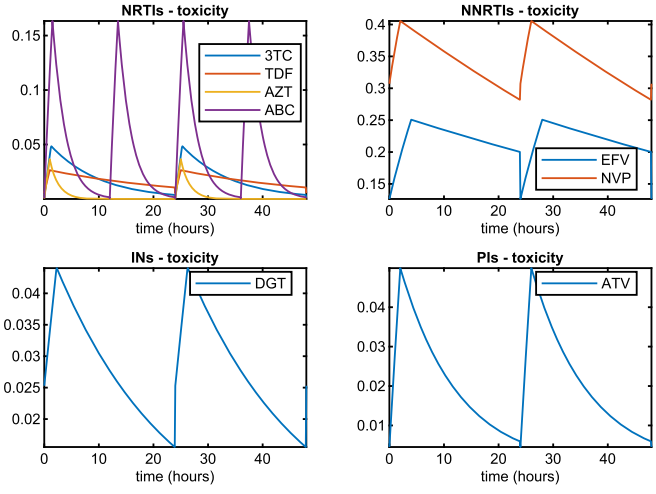

Figure 3 Toxicities of antiretroviral drugs for PK parameters shown in Table 1

The objective is to maximise the benefit of therapy on CD4+ cells and hepatocytes, while minimising the viral load, the level of alanine aminotransferase in the blood and the systemic cost based on the percentage effect of therapy. The positive constants m_1, m_2 and m_3, where $M = m_1 + m_2 + m_3$, represent desired weight on the benefit and cost and due to the synergistic effect that is attained in administering drugs in combination, we consider the relative cost of each drug type. High drug concentrations are very harmful to the body, $\mu_{RT}(t)$, $\mu_{IN}(t)$, $\mu_{PI}(t)$ should be minimised together with the other systemic costs and the cost of therapy. The cost function is assumed to be quadratic where, $\mu_{RT}(t)^2$, $\mu_{IN}(t)^2$, $\mu_{PI}(t)^2$ represent the severity of the side effects of ART. The choice of a non-linear cost function is on the assumption that there is no linear relationship between the effect of ART on CD4+ cells, hepatocytes, viral load and the level of ALT [5, 10]. Time $t = 0$ is the time when treatment is initiated and time $t = T_f$ is the time when treatment is stopped. It is assumed that treatment cannot be continued for infinite period due to their side effects.

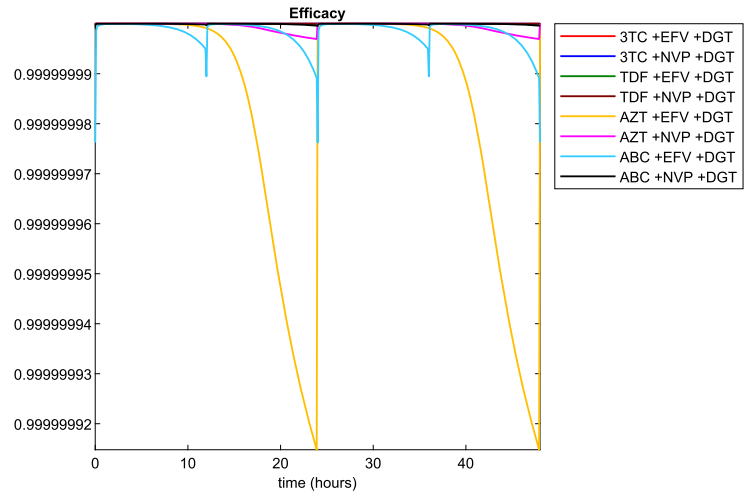

Figure 4 Efficacy of first-line regimen for PK parameters shown in Table 1

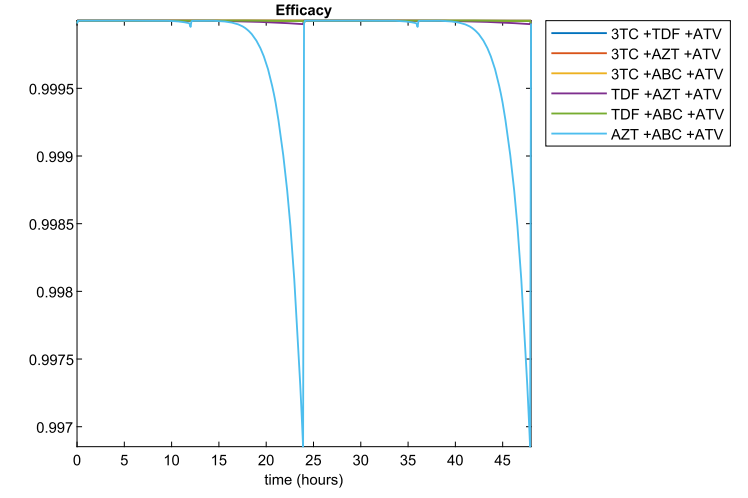

Figure 5 Efficacy of second-line regimen for PK parameters shown in Table 1

Moreover, HIV can mutate and develop resistance after some finite time [5]. Most studies have generalised the systemic cost associated with antiretroviral therapy [10, 20, 27], with some mentioning drug toxicity as common cost [5]. We include ALT elevation, an indicator of drug toxicity as one variable to be minimised. The Controls $\mu_{RT}(t)(t)$, $\mu_{IN}(t)$, $\mu_{PI}(t)$ are bounded, Lebesgue integrable functions, [8], and $\{\mu^*_{RT}, \mu^*_{IN}, \mu^*_{PI}\}$ are assumed to be the most desired therapeutic effects that reduce HIV transmission in the liver.

Thus, we seek an optimal control set $\{\mu^*_{RT}, \mu^*_{IN}, \mu^*_{PI}\}$ such that;

$$J(\mu^*_{RT}, \mu^*_{IN}, \mu^*_{PI}) = \max\{J(\mu_{RT}, \mu_{IN}, \mu_{PI}) | (\mu_{RT}, \mu_{IN}, \mu_{PI}) \in U\}, \tag{3.21}$$

where $U = \{(\mu_{RT}, \mu_{IN}, \mu_{PI}) | (\mu_{RT}, \mu_{IN}, \mu_{PI} measurable, 0 \leq a_{11} \leq \mu_{RT} \leq b_{11} \leq 1, 0 \leq a_{22} \leq \mu_{IN} \leq b_{22} \leq 1, 0 \leq a_{33} \leq \mu_{PI} \leq b_{33} \leq 1, t \in [0, T_f])\}$, for some $(a_{11}, a_{22}, a_{33}, b_{11}, b_{22}, b_{33}) \in \mathbb{R}$, is the control set.

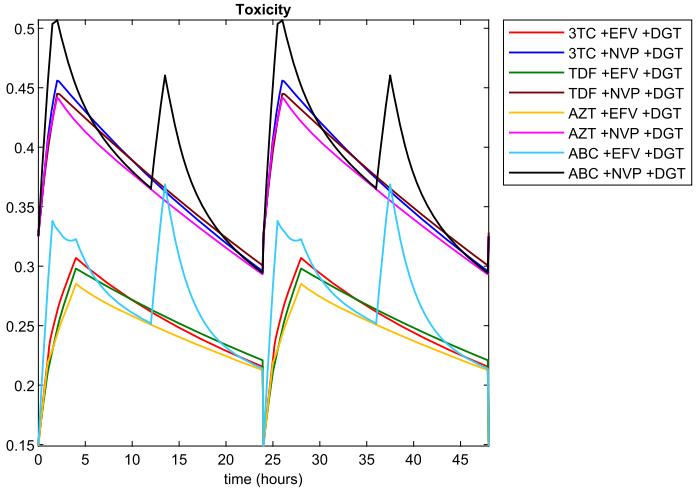

Figure 6 Toxicities of first-line regimen for PK parameters shown in Table 1

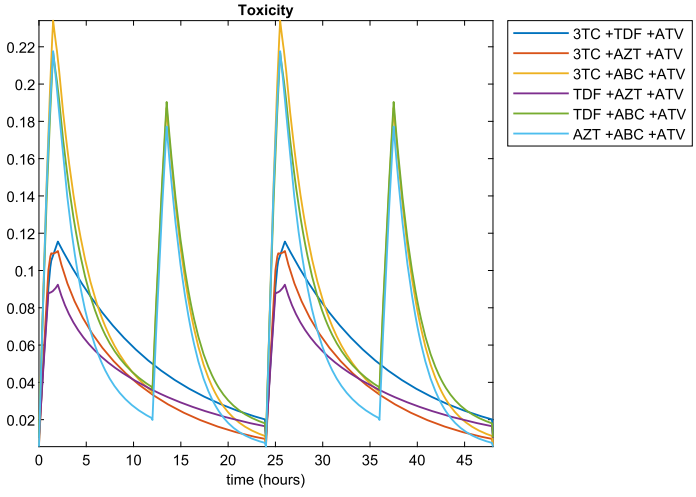

Figure 7 Toxicities of second-line regimen for PK parameters shown in Table 1

3.4 Existence of optimal control set

The existence of the optimal control set can be obtained by using a result by Fleming and Rishel [3].

Theorem 3.3 *The objective functional in* (3.20) *is maximised subject to state and control variables in system* (3.1)-(3.8)*, with initial state variables as,* $T_c(0) = T_{c0}$, $E_c(0) = E_{c0}$, $I_c(0) = I_{c0}$, $T_h(0) = T_{h0}$, $I_h(0) = I_{h0}$, $L(0) = L_0$, $V(0) = V_0$ *and* $A(0) = A_0$, *such that,* $T_{c0} \geq 0$, $E_{c0} \geq 0$, $I_{c0} \geq 0$, $T_{h0} \geq 0$, $I_{h0} \geq 0$, $L_0 \geq 0$, $V_0 \geq 0$, $A_0 \geq 0$.

There exist optimal controls $(\mu^*_{RT}, \mu^*_{IN}, \mu^*_{PI} \in U)$ *such that* $J(\mu^*_{RT}, \mu^*_{IN}, \mu^*_{PI}) = max\{J(\mu_{RT}, \mu_{IN}, \mu_{PI}) | (\mu_{RT}, \mu_{IN}, \mu_{PI}) \in U\}$, *if the following conditions are met*:

i. *The set of controls* μ_{RT}, μ_{IN}, μ_{PI} *and corresponding state variables is nonempty.*

ii. *The admissible control* U *set is convex and closed.*

iii. *The right hand side of the state system* (3.1)-(3.8) *is bounded by a linear function in the state and control variables.*
iv. *The integrand of the objective functional* $J(\mu_{RT}, \mu_{IN}, \mu_{PI})$ *is concave on* U.
v. *There exists constants* $c_1, c_2 > 0$ *such that the integrand* $J(\mu_{RT}, \mu_{IN}, \mu_{PI})$ *is bounded above by* $c_2 - c_1(|\mu_{RT}|^2 + |\mu_{IN}|^2 + |\mu_{PI}|^2)$.

Proof The set of state variables of system (3.1)-(3.8) with control set $\{\mu_{RT}, \mu_{IN}, \mu_{PI}) \in U\}$ where (μ_{RT}, μ_{IN} and μ_{PI} are integrable functions on $[0, T_f]$, is not empty and is non-negative, as shown in Sect. 3.1 and according to the definition of our control set, [5]. This satisfies condition (i). From equation (3.21), the control set is closed and convex, which satisfies condition (ii) of Fleming and Rishel Theorem. To prove condition (iii) we write the right-hand side of system (3.1)-(3.8) as $f(t, \Psi, \mu)$ where $\Psi = (T_c, E_c, I_c, T_h, I_h, L, V, A)$ and $\mu = (\mu_{RT}, \mu_{IN}, \mu_{PI})$. There are functions f_1 and f_2 such that

$$f(t, \Psi, \mu) = f_1(t, \Psi) + f_2(t, \Psi)\mu, \tag{3.22}$$

where

$$f_1(t, \Psi) = \begin{bmatrix} \alpha_1 - (1-q)\beta_1 T_c V - d_1 T_c \\ (1-q)\beta_1 T_c V - \beta_2 E_c - d_2 E_c \\ \beta_2 E_c - k_1 I_c L - d_3 I_c \\ \alpha_2 - q\beta_3 T_h V - d_4 T_h - n_1 \psi(t) T_h \\ q\beta_3 T_h V - k_2 I_h L - n_2 \psi(t) I_h - d_5 I_h \\ x + k_3(I_c + I_h)L - d_6 L \\ s_1 I_C + s_2 I_h - d_7 V \\ r + k_4[(d_5 + n_2\psi(t) + k_2 L)I_h + n_1 \psi(t) T_h] - d_8 A \end{bmatrix} \tag{3.23}$$

and

$$f_2(t, \Psi,) = \begin{bmatrix} (1-q)\beta_1 T_c V & 0 & 0 \\ -(1-q)\beta_1 T_c V & \beta_2 E_c & 0 \\ 0 & -\beta_2 E_c & 0 \\ q\beta_3 T_h V & 0 & 0 \\ -q\beta_3 T_h V & 0 & 0 \\ 0 & 0 & 0 \\ 0 & 0 & -s_1 I_c - s_2 I_h \\ 0 & 0 & 0 \end{bmatrix}. \tag{3.24}$$

Applying norm inequality on equation (3.22) we have

$$|f(t, \Psi, \mu)| \leq |f_1(t, \Psi)| + |f_2(t, \Psi)||\mu|,$$

where f_1 and f_2 are continuous functions in state variables. It has been shown in Sect. 3.1 that the state variables are bounded, indicating that f_1 and f_2 are bounded. Suppose that, there exist some numbers θ_1 and θ_2, such that, $|f_1| \leq \theta_1$ and $|f_2| \leq \theta_2$, and for some κ =

Table 2 Parameters values used in simulations

Par	Description	Value (ml^{-1} day^{-1})	Source
α_1	rate of creation of CD4+ cells from within the body	10	[27]
β_1	rate of transmission of HIV in CD4+ cells	0.005	[27]
d_1	natural death rate of uninfected CD4+ cells	0.01	[27]
q	probability a hepatocyte becomes infected by HIV	0.01	assum.
β_2	rate of transmission of HIV in CD4+ cells	0.023	[20]
d_2	death rate of latently infected CD4+ cells	0.02	[8]
k_1	rate at which CTLs kill infectious CD4+ cells	0.4	[27]
d_3	death rate of infectious CD4+ cells	0.025	[20]
α_2	rate of creation of hepatocytes from within the body	100	[27]
β_3	rate at which latently infected cells become infectious	0.0005	[8]
k_2	rate at which CTLs kill infectious hepatocytes	0.0025	[19]
d_4	natural death rate of uninfected hepatocytes	0.011	[19]
n_1	rate of clearance of healthy hepatocytes due to drug metabolism	0.2	assum.
n_2	rate of clearance of infectious hepatocytes due to drug metabolism	0.0025	assum.
d_5	death rate of infectious hepatocytes	0.5	[27]
x	antigen-independent CTLs proliferation rate	10	[7]
k_3	antigen-dependent proliferation rate of CTLs	0.004	[27]
d_6	rate of clearance of CTLs by all means	0.06	[27]
s_1	average rate of production of virions by an infected CD4+	100	[27]
s_2	average rate of production of virions by an infectious hepatocyte	10	assum.
d_7	death rate of HIV	1.5	[20]
r	natural rate of generation of ALT in the liver	14	[19]
d_8	rate of clearance of ALT from blood system	0.25	[19]
k_4	amount of ALT generated in the blood	2000	[19]

$max\{\theta_1.\theta_2\}$, then

$$\begin{aligned}|f(t,\Psi,\mu)| &\leq |f_1(t,\Psi)| + |f_2(t,\Psi)||\mu|,\\ &\leq \theta_1 + \theta_2|\mu|,\\ &\leq \kappa + \kappa|\mu|,\\ &\leq \kappa(1+|\mu|).\end{aligned}$$

Therefore, condition (iii) is satisfied. Condition (iv) is also fulfilled, since the integrand of our objective functional is concave. For the last condition, the integrand of the objective function $J(U,t)$, that is, $T_c + T_h - (V + A + \frac{m_1\mu_{RT}^2}{2M} + \frac{m_2\mu_{IN}^2}{2M} + \frac{m_3\mu_{PI}^2}{2M}$ satisfies the condition

$$T_c + T_h - (V + A + \frac{m_1\mu_{RT}^2}{2M} + \frac{m_2\mu_{IN}^2}{2M} + \frac{m_3\mu_{PI}^2}{2M} \leq c_2 - c_1(|\mu_{RT}|^2 + |\mu_{IN}|^2 + |\mu_{PI}|^2),$$

where $c_1 > 0$, $m_1 > 0$, $m_2 > 0$, $m_3 > 0$ and $M > 0$ and c_2 depends on the upper bounds of CD4+ cells, hepatocytes, viral load and the level of alanine aminotransferase in the body. Therefore, the optimal control set exists. □

4 Numerical simulations of optimality system

The optimality system is solved using an iterative method with Runge-Kutta fourth order scheme [17]. Starting with a guess for the adjoint variables, the state equations are solved forward in time. Then those state values are used to solve the adjoint equations backward in time, and the iterations continue until convergence with boundary conditions $0 \leq t \leq T_f$, [17]. In all cases the simulations are ran using parameters listed in Table 2 and system initial values as shown in Table 3. We simulate the optimality system for the first-line regi-

Table 3 Initial values of variables

Initial variable	Initial value
T_{c0}	500 cells ml^{-1}
E_{c0}	100 cells ml^{-1}
I_{c0}	100 cells ml^{-1}
T_{h0}	27,000 cells ml^{-1}
I_{h0}	500 cells ml^{-1}
L_0	100 cells ml^{-1}
V_0	100 copies ml^{-1}
A	14 units ml^{-1}

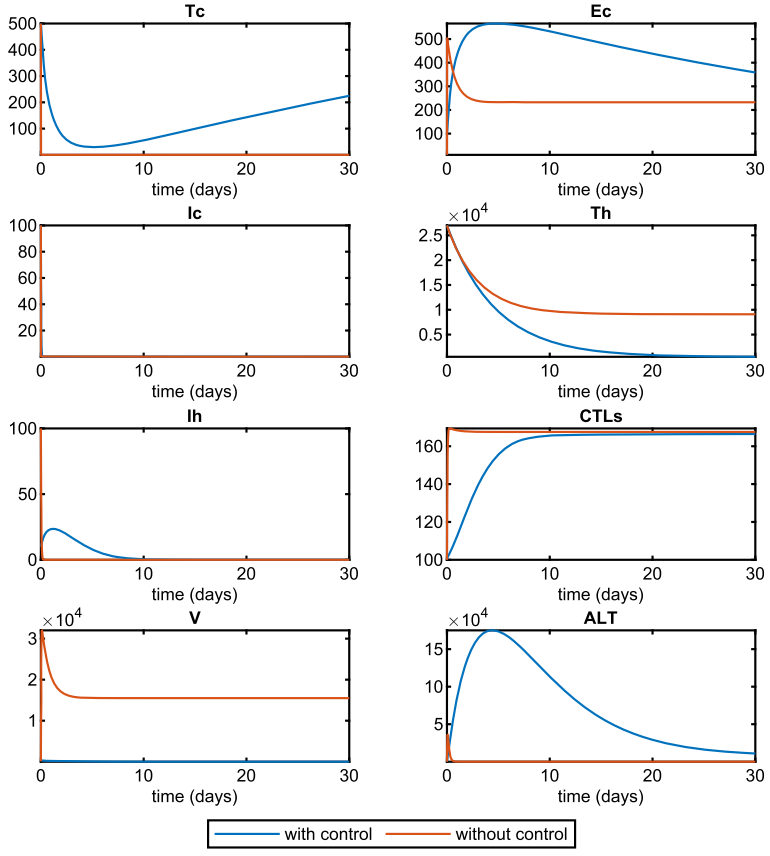

Figure 8 Dynamics of all variables with and without the first-line controls. The horizontal axes represent period of controls in months. Parameter values are as shown in Table 2 with initial values in Table 3

men, considering a combination of one NRTI combined with one NNRTI and one IN, with corresponding weight constants m_1 and m_2. However, in the second-line regimen, we consider two NRTI combined one PI and corresponding weight constants m_1 and m_3 as indicated in the equation (3.20). Simulation results in Fig. 8 and Fig. 9 for first-line and second-line regimen, respectively, indicate that therapy is able to increase CD4+ cells in the liver and suppress viral load. Due to drug toxicity, many hepatocytes are lost, and it is reflected in the level of ALT during treatment. Initially the level of ALT is higher without than with medication. This could be attributed to higher cytotoxic killing of infectious hepatocytes.

The significant difference between first-line and second-line medication is the effectiveness of protease inhibitors in improving CD4+ cells as compare to hepatocytes. There is

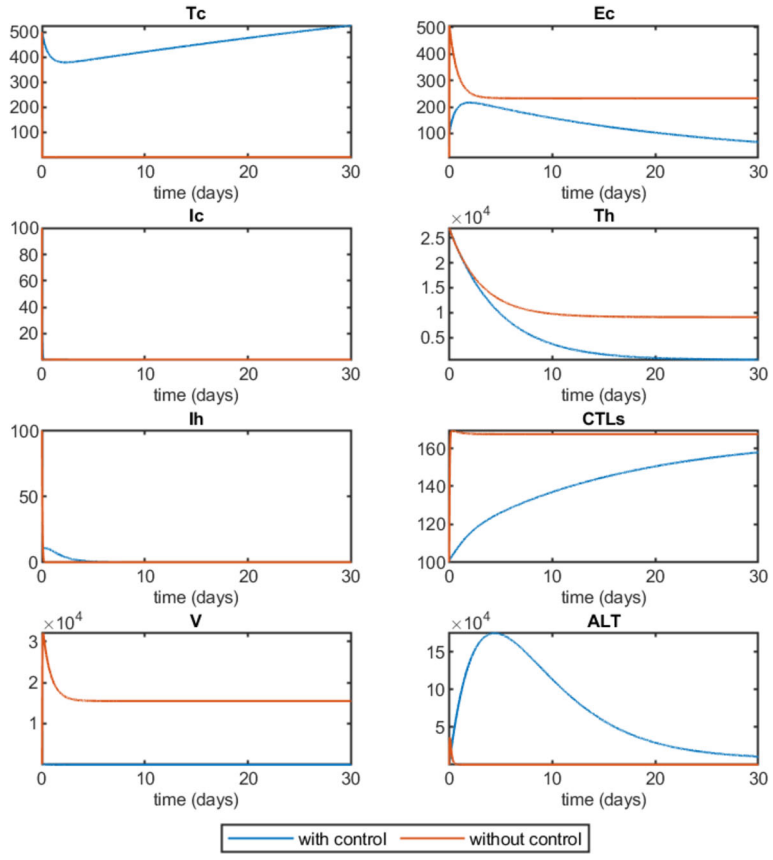

Figure 9 Dynamics of all variables with and without second-line controls. The horizontal axes represent period of controls in months. Parameter values are as shown in Table 2 with initial values in Table 3

also a reduction in CTLs which could be attributed to the reconstituted immune system or due to the reduction of the retroviral activity on the cells [27]. Second-line treatment gives less viral load than first-line but they consequently give more enzyme levels.

The corresponding control profile for first-line in Fig. 10 indicate that both integrase and reverse transcriptase inhibitors have to be taken at maximum intensity for close to a month. After 22 days, control μ_{RT} goes to the lower bound until the end of the control period. This is an indication that RTIs are neutral and can not be used on their own but rather with other controls. Integrase inhibitors on the other hand, if given at maximum effectiveness, then they can be used without another control and are able to provide an optimal control. This is consistent with second-line regimen as shown in Fig. 11. When the weight constant for RTIs is greater than the weight constant of either IN or PI, then the second drug is applied for a longer period at an upper bound. This indicates that in order to use the more potent drug for a longer time, a deliberate effort should be made to keep their systemic cost as low as possible.

4.1 Analysis of variables with inclusion all pharmacokinetic and carcinogenic parameters

Dynamics of system (3.1)-(3.8) when, the controls $\mu_{RT}(t)$, $\mu_{IN}(t)$ and $\mu_{PI}(t)$ are replaced by efficacy equation (3.17) and $\psi(t)$ is repalced by carcinology equation (3.19). The aim

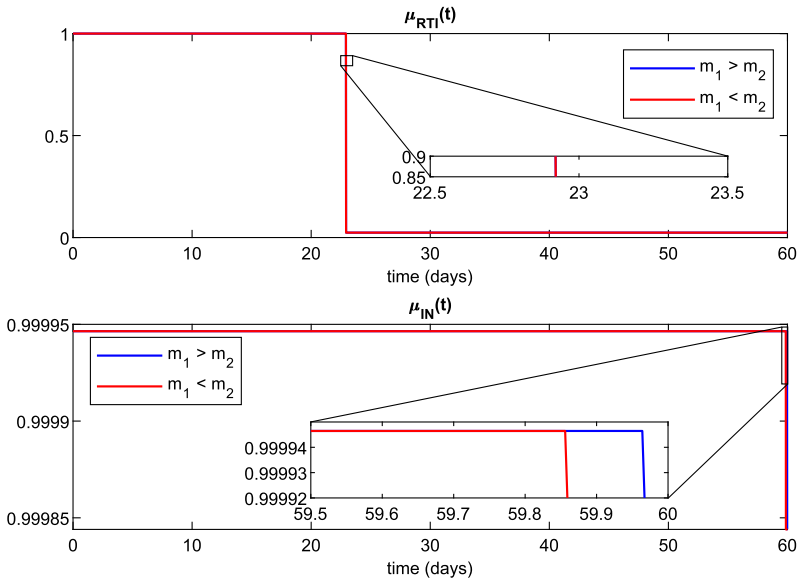

Figure 10 Control profile of first-line medication with average monthly cost of all medication used. Parameter values are as shown in Table 2 with initial values in Table 3

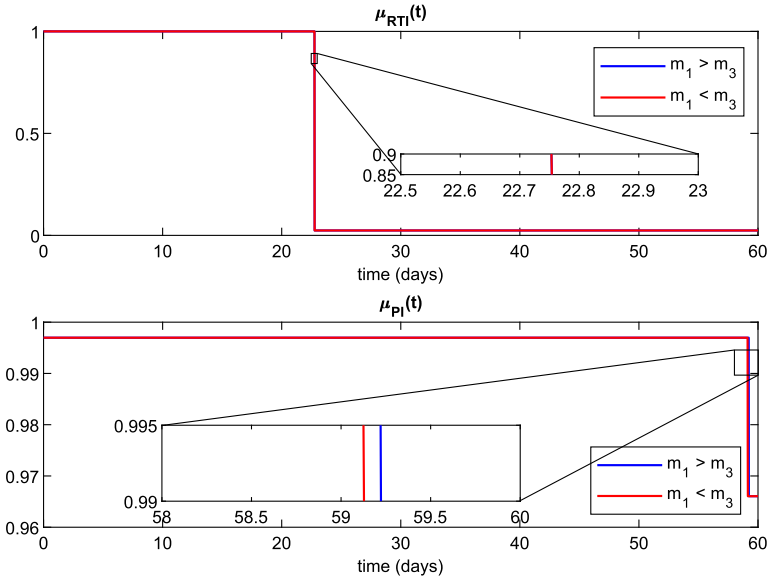

Figure 11 Control profile of second-line medication with average monthly cost of all medication used. Parameter values are as shown in Table 2 with initial values in Table 3

is to ascertain the performance of either regimen, given the corresponding efficacy and toxicity of individual drugs.

Numerical results for; the first-line regimen in Fig. 12 and Fig. 13 and the second-line regimen in Fig. 14 and Fig. 15, indicate that all combinations are able to increase CD4+ cells and reduce exposed and infectious CD4+ cells. All drugs reduce infectious hepatocytes, however, not as fast as infectious CD4+ cells, because there is no INs in hepatocytes.

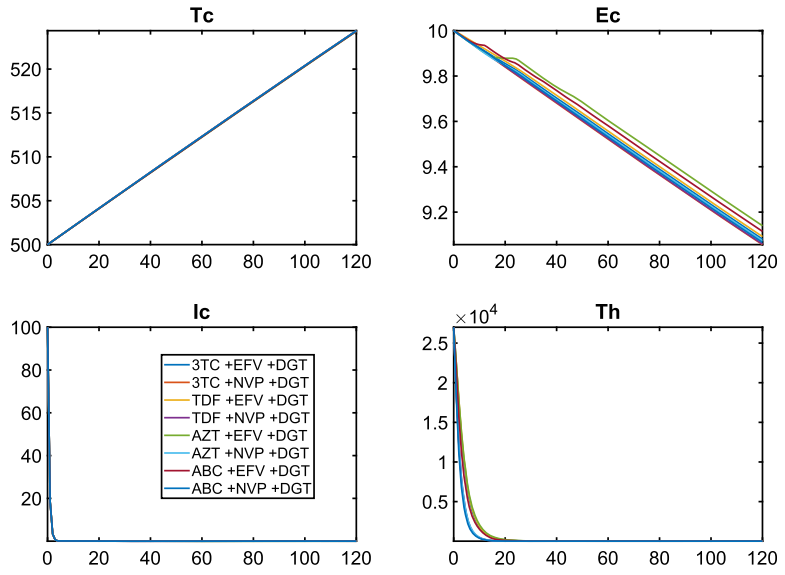

Figure 12 Dynamics of healthy, exposed and infectious CD4+ cells as well as healthy hepatocytes with first-line therapy efficacy and toxicity defined by PK parameters in equations (3.17)-(3.19) and Table 1. The horizontal axes represent time in hours

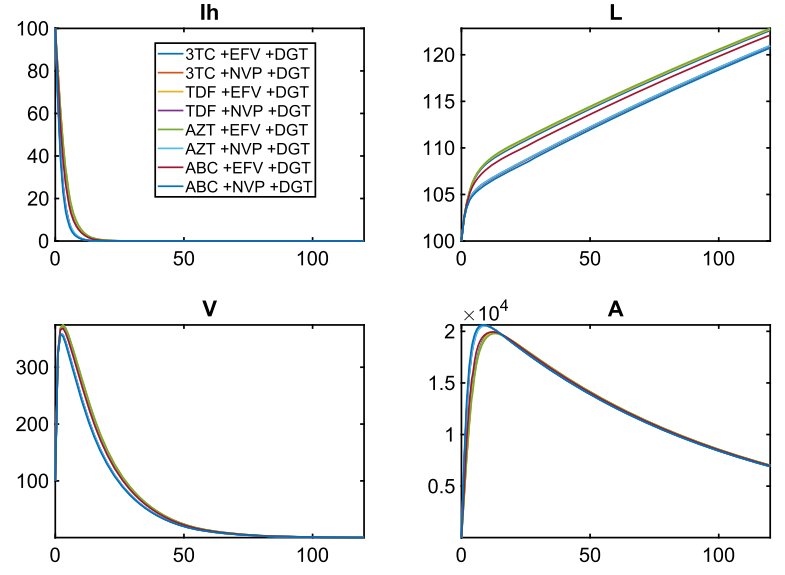

Figure 13 Dynamics of infectious hepatocytes, CTLs, viral load and ALT with first-line therapy efficacy and toxicity defined by PK parameters in equations (3.17)-(3.19) and Table 1. The horizontal axes represent time in hours

Hepatocytes decreases with medication due to hepatotoxicity. At initiation of therapy in all cases, the viral load first increases before it reduces on the effect of medication. Comparing Fig. 8 and Fig. 13, the increase in viral load is higher when PK parameters are included than the optimal values. According to [15], this behavior is mostly associated with entry inhibitors due to viral redistribution in plasma, where they artificially increase. This might also apply to enzyme inhibitors.

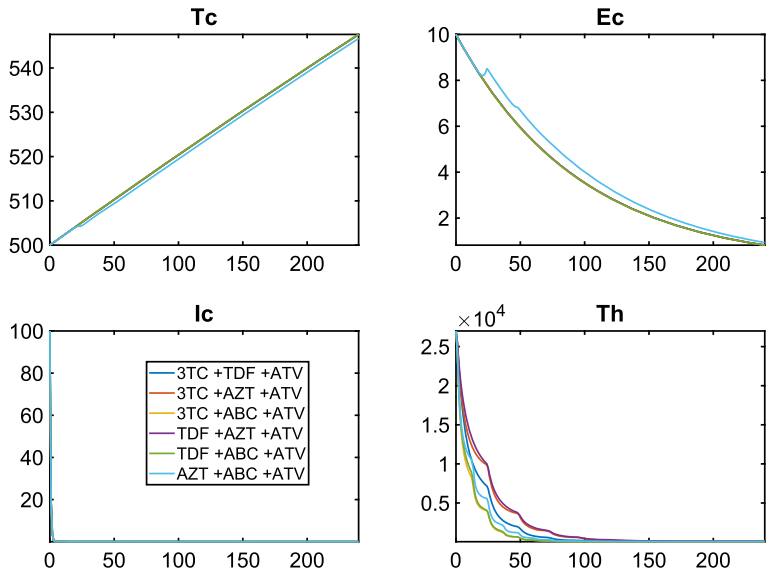

Figure 14 Dynamics of healthy, exposed and infectious CD4+ cells as well as healthy hepatocytes with second-line therapy efficacy and toxicity defined by PK parameters in equations (3.17)-(3.19) and Table 1. The horizontal axes represent time in hours

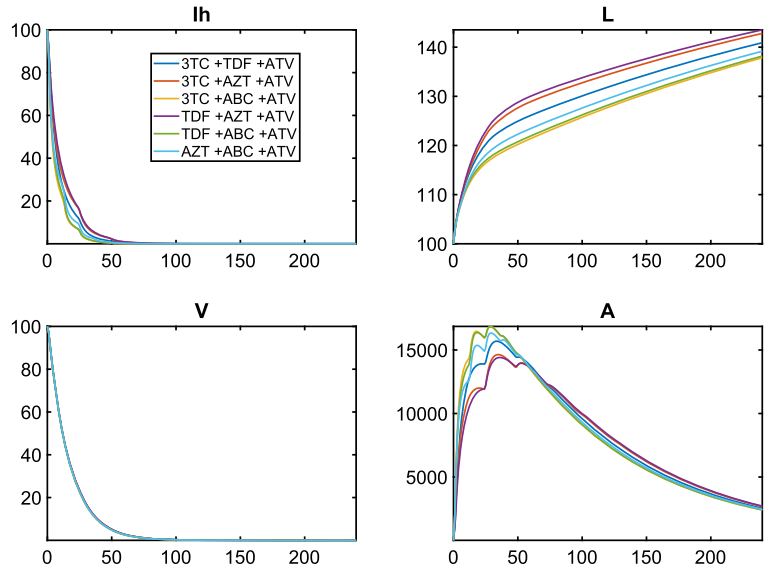

Figure 15 Dynamics of infectious hepatocytes, CTLs, viral load and ALT with second-line therapy efficacy and toxicity defined by PK parameters in equations (3.17)-(3.19) and Table 1. The horizontal axes represent time in hours

One observation with second-line medication is the comparable decline in viral load, though with much lower ALT as compared to first-line. This would suggest that, even though PIs are better than NRTIs in suppression of viral load, with NNRTI such as NVP, the combinations become comparable in viral suppression. When it comes to toxicity, nevirapine is highly toxic as compared to ATV, and that explains the much lower ALT levels in Fig. 15.

5 Discussion

We developed a mathematical model similar to our earlier work in [25], to define an optimal therapy that maximises DCD+ cells and hepatocytes in the liver while minimising HIV DNA copies, the level of transaminase in an HIV-infected patient as well as the systemic cost involved in treating the infection. Three controls, including, reverse transcriptase inhibitors, integrase inhibitors and protease inhibitors were used. The controls were implemented at different stages of viral replication. Pontryagin's maximum principle was used for analytical results and later Rounge Kutta forth-order method for numerical results. Two lines of HIV management were studied: (i) first-line regimen which includes one NRTI, one NNRTI and one IN. (ii) Second-line regimen that includes two NRTIs and one PI.

Simulation results show that both regimens are able to suppress viral DNA and consequently exposed and infectious cells increased. Therapy also led to the loss of hepatocytes and consequently increased alanine aminotransferase (ALT), an indicator of liver injury. Second-line medication suppressed more virus compared to first-line regimen.

First-line therapy minimises drug toxicity, viral load and cost, when both RTIs and INs exhibit close to 100% efficacy, regardless of the systemic cost. In second-line regimen, optimal control largely depends on the systemic cost of implementation. The higher the intervention systemic cost, the sooner a patient will get off the protease inhibitor but keeps on RTIs at 100% efficacy for the entire control period. This would imply that in addition to drug toxicity, there are other side effects that result from using this class of medication, whose cost is implied in the higher cost of implementation [5].

Pharmacokinetic parameters were used to define and analyse drug effectiveness and toxicity as used by [13]. Drugs considered include 3TC, TDF, AZT and ABC from the NRTIs, DGT as an IN, NVP and EFV as NNRTIs and ATV as a PI. With parameters from literature as shown in Table 1, all these drugs are highly efficacious and capable of suppressing HIV. NVP is the most efficacious and at the same time most toxic [22, 28]. INs are more efficacious than RTIs. NNRTIs are generally more toxic than any other class of medication [24, 28].

With optimal suppression of viral load and ALT attainable with highly efficacious controls, the inclusion of highly efficacious DGT and NVP in the first-line medication is recommendable. NVP-based treatments work best in suppressing viral load, however, patients on first-line regimen should be monitored for transaminase elevation. The study further recommends that all HIV management centers that have not yet been able to perform liver tests as part of their routine monitoring, should start doing so, alongside viral load tests. As shown in Fig. 2, Fig. 13 and Fig. 15, all studied drugs are highly efficacious to suppress HIV DNA, but all of them lead to high enzyme levels, indicating that there is no drug that is free of toxicity.

Finally, since optimal results are attained when medication is taken for 97.6% of the therapy period, then as the pharmacist ensure high efficacy, patients have to be encouraged to adhere to taking their medication.

Appendix A: Pontryagin's maximum principle

According to [30], the Lagrangian is defined as

$$L(T_c, T_h, V, A, \mu_{RT}, \mu_{IN}, \mu_{PI}) = T_c + T_h - (V + A + \frac{m_1\mu_{RT}^2}{2} + \frac{m_2\mu_{IN}^2}{2} + \frac{m_3\mu_{PI}^2}{2}) \quad \text{(A.1)}$$

From which we define the Hamilitonian as

$$
\begin{aligned}
H = {} & T_c + T_h - (V + A + (\frac{m_1\mu_{RT}(t)^2(t)}{2} + \frac{m_2\mu_{IN}^2(t)}{2} + \frac{m_3\mu_{PI}^2(t)}{2})) \\
& + \lambda_1\{\alpha_1 - (1-\mu_{RT}(t))(1-q)\beta_1 T_c V - d_1 T_c\} \\
& + \lambda_2\{\alpha_1 - (1-\mu_{RT}(t))(1-q)\beta_1 T_c V - (1-\mu_{IN}(t))\beta_2 E_c - d_2 E_c\} \\
& + \lambda_3\{(1-\mu_{IN}(t))\beta_2 E_c - k_1 I_c L - d_3 I_c\} \\
& + \lambda_4\{\alpha_2 - (1-\mu_{RT}(t))q\beta_3 T_h V - d_4 T_h - n_1\psi(t)T_h\} \\
& + \lambda_5\{(1-\mu_{RT}(t))q\beta_3 T_h V - k_2 I_h L - n_2\psi(t)I_h - d_5 I_h\} \\
& + \lambda_6\{x + k_3(I_c + I_h)L - d_6 L\} \\
& + \lambda_7\{(1-\mu_{PI}(t))s_1 I_C + (1-\mu_{PI}(t))s_2 I_h - d_7 V\} \\
& + \lambda_8\{r + k_4[(d_5 + n_2\psi(t) + k_2 L)I_h + n_1\psi(t)T_h] - d_8 A\} \\
& + w_{11}(t)(b_{11} - \mu_{RT}(t)) + w_{12}(t)(\mu_{RT}(t) - a_{11}) \\
& + w_{21}(t)(b_{22} - \mu_{IN}(t)) + w_{22}(t)(\mu_{IN}(t) - a_{22}) \\
& + w_{31}(t)(b_{33} - \mu_{PI}(t)) + w_{32}(t)(\mu_{PI}(t) - a_{33}),
\end{aligned} \tag{A.2}
$$

where λ_i for $i = 1, 2, \ldots, 8$ are the adjoint variables and $w_{ij} > 0$ for $i = 1, 2, 3$, $j = 1, 2$ are penalty multipliers satisfying $w_{11}(t)(b_{11} - \mu_{RT}(t)) = 0$ and $w_{12}(t)(\mu_{RT}(t) - a_{11}) = 0$ at optimal $\mu_{RT}(t)^*$, $w_{21}(t)(b_{22} - \mu_{IN}(t)) = 0$ and $w_{22}(t)(\mu_{IN}(t) - a_{22}) = 0$ at optimal $\mu_{IN}(t)^*$ and $w_{31}(t)(b_{33} - \mu_{RT}(t)) = 0$ and $w_{32}(t)(\mu_{RT}(t) - a_{33}) = 0$ at optimal μ_{PI}^*.

Theorem A.1 *Given optimal controls μ_{RT}^*, μ_{IN}^*, μ_{PI}^* with solutions T_c^*, E_c^*, I_c^*, T_h^*, I_h^*, L^*, V^*, A^* of model (3.1)-(3.8), there exist adjoint variables λ_i for $i = 1, 2, \ldots, 8$ satisfying*

$$
\begin{aligned}
\dot{\lambda_1} &= (1-\mu_{RT}^*)(1-q)\beta_1 V(\lambda_1 - \lambda_2) + d_1\lambda_1 - 1, \\
\dot{\lambda_2} &= (1-\mu_{IN}^*)\beta_2(\lambda_2 - \lambda_3) + d_2\lambda_2, \\
\dot{\lambda_3} &= \lambda_3(k_1 L + d_3) - k_3 L\lambda_6 - \lambda_7 s_1(1-\mu_{PI}^*), \\
\dot{\lambda_4} &= (1-\mu_{RT}^*)\beta_3 q V(\lambda_4 - \lambda_5) + n_1\psi(t)(\lambda_4 - k_4\lambda_8) + d_4\lambda_4 - 1, \\
\dot{\lambda_5} &= (k_2 L + d_5 + n_2\psi(t))(\lambda_5 - k_4\lambda_8) - k_3 L\lambda_6 - \lambda_7 s_2(1-\mu_{PI}^*), \\
\dot{\lambda_6} &= \lambda_3 I_c k_1 + k_2 I_h(\lambda_5 - k_4\lambda_8) + d_6\lambda_6 - \lambda_6 k_3(I_c + I_h), \\
\dot{\lambda_7} &= 1 + (1-\mu_{RT}^*)(1-q)\beta_1 T_c(\lambda_1 - \lambda_2) + (1-\mu_{RT}^*)\beta_3 T_h q(\lambda_4 - \lambda_5) + d_7\lambda_7, \\
\dot{\lambda_8} &= 1 + d_8\lambda_8.
\end{aligned} \tag{A.3}
$$

With transversality conditions $\lambda_i(T_f) = 0$ for $i = 1, 2, \ldots, 8$, then we have

$$
\mu_{RT}^* = min\{b_{11}, max\{a_{11}, \frac{M[\beta_1 T_c V(1-q)(\lambda_1 - \lambda_2) + \beta_3 T_h V q(\lambda_4 - \lambda_5)]}{m_1}\}\}, \tag{A.4}
$$

$$
\mu_{IN}^* = min\{b_{22}, max\{a_{22}, \frac{M\beta_2 E_c(\lambda_2 - \lambda_3)}{m_2}\}\}, \tag{A.5}
$$

$$
\mu_{PI}^* = min\{b_{33}, max\{a_{33}, \frac{-\lambda_7 M(s_1 I_c + I_h S_2)}{m_3}\}\}. \tag{A.6}
$$

Proof Pontryagin's maximum principle [17, 30] gives the existence of adjoint variables that are obtained by differentiating the Lagrangian (A.1) with respect to the state variables T_c, E_c, I_c, T_h, I_h, L, V, A. That is, $\frac{d\lambda_i}{dt} = -\frac{\partial H}{\partial f_i}$ for $i = 1, 2, \ldots, 8$. Thus,

$$\begin{aligned}
\dot{\lambda_1} &= (1-\mu_{RT})(1-q)\beta_1 V(\lambda_1-\lambda_2) + d_1\lambda_1 - 1,\\
\dot{\lambda_2} &= (1-\mu_{IN})\beta_2(\lambda_2-\lambda_3) + d_2\lambda_2,\\
\dot{\lambda_3} &= \lambda_3(k_1 L + d_3) - k_3 L\lambda_6 - \lambda_7 s_1(1-\mu_{PI}),\\
\dot{\lambda_4} &= (1-\mu_{RT})\beta_3 q V(\lambda_4-\lambda_5) + n_1\psi(t)(\lambda_4-k_4\lambda_8) + d_4\lambda_4 - 1,\\
\dot{\lambda_5} &= (k_2 L + d_5 + n_2\psi(t))(\lambda_5-k_4\lambda_8) - k_3 L\lambda_6 - \lambda_7 s_2(1-\mu_{PI}),\\
\dot{\lambda_6} &= \lambda_3 I_c k_1 + k_2 I_h(\lambda_5-k_4\lambda_8) + d_6\lambda_6 - \lambda_6 k_3(I_c+I_h),\\
\dot{\lambda_7} &= 1 + (1-\mu_{RT})(1-q)\beta_1 T_c(\lambda_1-\lambda_2) + (1-\mu_{RT})\beta_3 T_h q(\lambda_4-\lambda_5) + d_7\lambda_7,\\
\dot{\lambda_8} &= 1 + d_8\lambda_8,
\end{aligned} \tag{A.7}$$

where $\lambda_i(T_f) = 0$ give the transversality conditions.

Using Lagrangian maximization principle [17], the optimal controls are obtained when

$$\frac{\partial H}{\partial \mu_{RT}} = \frac{\partial H}{\partial \mu_{IN}} = \frac{\partial H}{\partial \mu_{PI}} = 0, \tag{A.8}$$

at μ^*_{RT}, μ^*_{IN}, μ^*_{PI}

Using $\frac{\partial H}{\partial \mu_{RT}} = 0$,

$$(1-q)\beta_1 T_c V(\lambda_2-\lambda_1) + q\beta_3 T_h V(\lambda_4-\lambda_5) - w_{11}(t) + w_{12}(t)) - \frac{m_1\mu_{RT}}{M} = 0.$$

Thus,

$$\frac{M}{m_1}[(1-q)\beta_1 T_c V(\lambda_2-\lambda_1) + q\beta_3 T_h V(\lambda_4-\lambda_5) - w_{11}(t) + w_{12}(t))] = \mu_{RT}. \tag{A.9}$$

On the set

$$\{t | a_{11} < \mu^*_{RT} < b_{11}\}$$

we have $w_{11}(t) = w_{12}(t) = 0$. Thus,

$$\mu_{RT} = \frac{M}{m_1}[(1-q)\beta_1 T_c V(\lambda_2-\lambda_1) + q\beta_3 T_h V(\lambda_4-\lambda_5)].$$

On the set

$$\{t | \mu^*_{RT} = a_{11}\},$$

$w_{11}(t) = 0$, then

$$\mu^*_{RT} = a_{11} = \frac{M}{m_1}[(1-q)\beta_1 T_c V(\lambda_2-\lambda_1) + q\beta_3 T_h V(\lambda_4-\lambda_5) + w_{12}(t)].$$

But since $w_{12} \geq 0$, we get

$$\frac{M}{m_1}[(1-q)\beta_1 T_c V(\lambda_2 - \lambda_1) + q\beta_3 T_h V(\lambda_4 - \lambda_5)] \leq a_{11}.$$

On the set

$$\{t|\mu^*_{RT} = b_{11}\},$$

$w_{12}(t) = 0$, thus,

$$\mu^*_{RT} = b_{11} = \frac{M}{m_1}[(1-q)\beta_1 T_c V(\lambda_2 - \lambda_1) + q\beta_3 T_h V(\lambda_4 - \lambda_5) - w_{11}(t).$$

Since

$$w_{11}(t) \geq 0,$$

we have

$$\frac{M}{m_1}[(1-q)\beta_1 T_c V(\lambda_2 - \lambda_1) + q\beta_3 T_h V(\lambda_4 - \lambda_5)] \geq b_{11}.$$

Combining all the three cases then we can conclude that

$$\mu^*_{RT} = \min\{\max\{a_{11}, \frac{M}{m_1}[(1-q)\beta_1 T_c V(\lambda_2 - \lambda_1) + q\beta_3 T_h V(\lambda_4 - \lambda_5)]\}, b_{11}\}. \tag{A.10}$$

Using the same approach, it can be shown that

$$\mu^*_{IN} = \min\{b_{22}, \max\{a_{22}, \frac{M\beta_2 E_c(\lambda_2 - \lambda_3)}{m_2}\}\}, \tag{A.11}$$

$$\mu^*_{PI} = \min\{b_{33}, \max\{a_{33}, \frac{-\lambda_7 M(s_1 I_c + I_h S_2)}{m_3}\}\}. \tag{A.12}$$

□

Appendix B: Optimality system

The optimality system that combines the state variables (3.1)-(3.8), costate variables (adjoint system) (A.7) and the optimal controls (A.10), (A.11) and (A.12), is:

$$\begin{aligned}
\dot{T}_c &= \alpha_1 - (1 - \eta_1(\min\{\max\{a_{11}, \frac{M}{m_1}[(1-q)\beta_1 T_c V(\lambda_2 - \lambda_1) && \text{(B.1)}\\
&\quad + q\beta_3 T_h V(\lambda_4 - \lambda_5)]\}, b_{11}\}))(1-q)\beta_1 T_c V - d_1 T_c,\\
\dot{E}_c &= (1 - \eta_1(\min\{\max\{a_{11}, \frac{M}{m_1}[(1-q)\beta_1 T_c V(\lambda_2 - \lambda_1) && \text{(B.2)}\\
&\quad + q\beta_3 T_h V(\lambda_4 - \lambda_5)]\}, b_{11}\}))(1-q)\beta_1 T_c V && \text{(B.3)}\\
&\quad - (1 - \eta_2(\min\{b_{22}, \max\{a_{22}, \frac{M\beta_2 E_c(\lambda_2 - \lambda_3)}{m_2}\}\}))\beta_2 E_c - d_2 E_c,\\
\dot{I}_c &= (1 - \eta_2(\min\{b_{22}, \max\{a_{22}, \frac{M\beta_2 E_c(\lambda_2 - \lambda_3)}{m_2}\}\}))\beta_2 E_c - k_1 I_c L - d_3 I_c,
\end{aligned}$$

$$\dot{T}_h = \alpha_2 - (1-\eta_1(\min\{\max\{a_{11}, \frac{M}{m_1}[(1-q)\beta_1 T_c V(\lambda_2-\lambda_1) \tag{B.4}$$
$$+ q\beta_3 T_h V(\lambda_4-\lambda_5)]\}, b_{11}\}))q\beta_3 T_h V - d_4 T_h - n_1\psi(t)T_h,$$

$$\dot{I}_h = (1-\eta_1(\min\{\max\{a_{11}, \frac{M}{m_1}[(1-q)\beta_1 T_c V(\lambda_2-\lambda_1) \tag{B.5}$$
$$+ q\beta_3 T_h V(\lambda_4-\lambda_5)]\}, b_{11}\}))q\beta_3 T_h V - k_2 I_h L - n_2\psi(t)I_h - d_5 I_h,$$

$$\dot{L} = x + k_3(I_c + I_h)L - d_6 L,$$

$$\dot{V} = (1-\eta_3(\min\{b_{33}, \max\{a_{33}, \frac{-\lambda_7 M(s_1 I_c + I_h S_2)}{m_3}\}\}))s_1 I_C \tag{B.6}$$
$$+ (1-\eta_3(\min\{b_{33}, \max\{a_{33}, \frac{-\lambda_7 M(s_1 I_c + I_h S_2)}{m_3}\}\}))s_2 I_h - d_7 V,$$

$$\dot{A} = r + k_4[(d_5 + n_2\psi(t) + k_2 L)I_h + n_1\psi(t)T_h] - d_8 A,$$

$$\dot{\lambda_1} = (1-\eta_1(\min\{\max\{a_{11}, \frac{M}{m_1}[(1-q)\beta_1 T_c V(\lambda_2-\lambda_1) \tag{B.7}$$
$$+ q\beta_3 T_h V(\lambda_4-\lambda_5)]\}, b_{11}\}))(1-q)\beta_1 V(\lambda_1-\lambda_2) + d_1\lambda_1 - 1,$$

$$\dot{\lambda_2} = (1-\eta_2(\min\{b_{22}, \max\{a_{22}, \frac{M\beta_2 E_c(\lambda_2-\lambda_3)}{m_2}\}\}))\beta_2(\lambda_2-\lambda_3) + d_2\lambda_2,$$

$$\dot{\lambda_3} = \lambda_3(k_1 L + d_3) - k_3 L\lambda_6 - \lambda_7 s_1(1-\eta_3(\min\{b_{33}, \max\{a_{33}, \frac{-\lambda_7 M(s_1 I_c + I_h S_2)}{m_3}\}\})),$$

$$\dot{\lambda_4} = (1-\eta_1(\min\{\max\{a_{11}, \frac{M}{m_1}[(1-q)\beta_1 T_c V(\lambda_2-\lambda_1) \tag{B.8}$$
$$+ q\beta_3 T_h V(\lambda_4-\lambda_5)]\}, b_{11}\}))\beta_3 qV(\lambda_4-\lambda_5) + n_1\psi(t)(\lambda_4 - k_4\lambda_8) + d_4\lambda_4 - 1,$$

$$\dot{\lambda_5} = (k_2 L + d_5 + n_2\psi(t))(\lambda_5 - k_4\lambda_8) - k_3 L\lambda_6$$
$$- \lambda_7 s_2(1-\eta_3(\min\{b_{33}, \max\{a_{33}, \frac{-\lambda_7 M(s_1 I_c + I_h S_2)}{m_3}\}\})),$$

$$\dot{\lambda_6} = \lambda_3 I_c k_1 + k_2 I_h(\lambda_5 - k_4\lambda_8) + d_6\lambda_6 - \lambda_6 k_3(I_c + I_h),$$

$$\dot{\lambda_7} = 1 + (1-\eta_1(\min\{\max\{a_{11}, \frac{M}{m_1}[(1-q)\beta_1 T_c V(\lambda_2-\lambda_1) \tag{B.9}$$
$$+ q\beta_3 T_h V(\lambda_4-\lambda_5)]\}, b_{11}\}))(1-q)\beta_1 T_c(\lambda_1-\lambda_2) \tag{B.10}$$
$$+ (1-\eta_1(\min\{\max\{a_{11}, \frac{M}{m_1}[(1-q)\beta_1 T_c V(\lambda_2-\lambda_1) \tag{B.11}$$
$$+ q\beta_3 T_h V(\lambda_4-\lambda_5)]\}, b_{11}\}))\beta_3 T_h q(\lambda_4-\lambda_5) + d_7\lambda_7,$$

$$\dot{\lambda_8} = 1 + d_8\lambda_8. \tag{B.12}$$

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Author contributions
HN has participated in formulating the research concept, designed the work, performed all the rigorous mathematical analysis, as well as interpreted the numerical results. MJS has implemented the model numerically and performed the simulation and participated in interpretation of results. MS has participated in research conception and has substantially revised the work. All authors read and approved the final manuscript.

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Data availability
No data has been used in this work.

Declarations

Competing interests
The authors are not aware of any competing interests.

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