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Research Article

Modelling Hepatotoxicity of Antiretroviral Therapy in the Liver during HIV Monoinfection

Hasifa Nampala,[1] Livingstone S. Luboobi,[2] Joseph Y. T. Mugisha,[2] and Celestino Obua[3]

[1] *Department of Mathematics, Faculty of Science Education, Busitema University, P.O. Box 236, Tororo, Uganda*
[2] *Department of Mathematics, School of Physical Sciences, College of Natural Sciences, Makerere University, P.O. Box 7062, Kampala, Uganda*
[3] *Department of Pharmacology and Therapeutics, College of Health Sciences, Makerere University, P.O. Box 7062, Kampala, Uganda*

Correspondence should be addressed to Hasifa Nampala; hnampala@yahoo.co.uk

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Liver related complications are currently the leading cause of morbidity and mortality among human immunodeficiency virus (HIV) infected individuals. In HIV monoinfected individuals on therapy, liver injury has been associated with the use of antiretroviral agents as most of them exhibit some degree of toxicity. In this study we proposed a mathematical model with the aim of investigating hepatotoxicity of combinational therapy of antiretroviral drugs. Therapy efficacy and toxicity were incorporated in the model as dose-response functions. With the parameter values used in the study, protease inhibitors-based regimens were found to be more toxic than nonnucleoside reverse transcriptase inhibitors-based regimens. In both regimens, the combination of stavudine and zidovudine was the most toxic baseline nucleoside reverse transcriptase inhibitors followed by didanosine with stavudine. However, the least toxic combinations were zidovudine and lamivudine followed by didanosine and lamivudine. The study proposed that, under the same second line regimens, the most toxic first line combination gives the highest viral load and vice versa.

1. Introduction

Among people infected with human immunodeficiency virus (HIV), liver related complications have become the leading causes of morbidity and mortality [1]. There are a number of factors identified that are known to contribute to liver related mortality in HIV infected people. These are, for instance, coinfections with viral hepatitis B (HBV) and hepatitis C (HCV) as well as the use of antiretroviral therapy (ART) [2–6]. Although liver disease can occur solely due to HIV infection [7–10], the use of ART is highly associated with end stage liver disease in HIV infected people [6, 11].

A human body identifies every substance it absorbs, including drugs as a foreign substance. All substances that are identified as foreign are subjected to chemical processes, [12], to make them suitable for elimination. Although all tissues in the body have some ability to metabolise, the liver is the central metabolic clearing organ of all chemicals from a human body. This process is carried out by metabolising enzymes cytochrome P450 which are found in hepatocytes [12]. The role played by hepatocytes in handling toxic drug substances makes them vulnerable to drug induced injury (hepatotoxicity) and, consequently, cell death [12–14]. Drug-induced liver injury is responsible for 5% of all hospital admissions and 50% of all acute liver failures [5].

According to [15], generally all antiretroviral drugs exhibit some level of toxicity to the liver. Hepatocytes that are responsible for metabolizing toxic antiretroviral drugs [12, 13] also support all stages of HIV infection and replication [9, 10, 16, 17]. This double distress to hepatocytes would possibly partly explain the progression of liver disease in HIV infected people on ART. Using ART in combination makes it even more complicated to assess which drug leads to higher levels of hepatotoxicity than the other [18].

According to [8, 10, 19], HIV can directly infect human hepatocytes. Considering HIV infection and replication in hepatocytes [16, 17, 20] and CD4+ cells [21–23] as well as macrophages, [11, 19], this study used a mathematical model

Table 1: Medication and corresponding parameter values. m and IC_{50} are from Supplementary Table 1 of [30].

Medication	d [μM]	m	IC_{50} [μM]	TD_{50} [μM]	Reference
Zidovudine (AZT)	37.4195	0.85	0.1823	127.7868	[32]
Didanosine (DDI)	28.2229	1.07	0.1794	275.3284	[32]
Lamivudine (3TC)	21.8103	1.15	0.0298	170.5277	[33]
Stavudine (d4T)	4.4603	1.13	0.552	431.6235	[32]
Efavirenz (EFV)	31.6776	1.67	0.0054	53.8520	[34]
Atazanavir (ATV)	7.0932	2.69	0.0136	85.1185	[32]
Nelfinavir (NFV)	62.81	1.81	0.1668	72.8875	[35]

to analyse therapeutic and toxic effects of HIV antiretroviral therapy. Defining hepatotoxicity generally as liver damage, there are a number of conditions that would fall under hepatotoxicity, and they include hepatitis, hepatic necrosis, and hepatic steatosis [24, 25]. This study considered only hepatic necrosis, which is the death of liver cells.

Drugs studied include zidovudine (AZT), emtricitabine (FTC), didanosine (DDI), lamivudine (3TC), stavudine (d4T), efavirenz (EFV), atazanavir (ATV), and nelfinavir (NFV). Various drug combinations as recommended by World Health Organisation were considered. The study accounted for therapeutic and toxic effects of all classes of ART in form of dose-response functions [26, 27].

2. Material and Methods

2.1. Mathematical Model Development. Recent study by [26] as well as [28] asserts that all classes of ART exhibit dose-response curves. Finding a dose that gives 50% of maximal response is one method of determining how effective the drug is; therefore, [26] recommends that it would be of great contribution if efficacy of ART would be modelled as dose-response.

Much as antiretroviral drugs are taken in doses at specific time intervals and the effectiveness and toxicity of the drug are largely dependent on the pharmacokinetics of the drug taken, our study preferred to use the Hill equation as recommended by [26], to model drug efficacy as opposed to Michaelis-Menten kinetics [29]. Reactions involving a single substrate are often assumed to follow Michaelis-Menten kinetics, irrespective of the model's underlying assumptions. Since we are dealing with possible multiple drug reactions, the use of Michaelis-Menten equation would thus be inappropriate. The study has also adopted the use of the Hill equation because we are investigating therapeutic and toxic effect of therapy at steady state.

Therapeutic response function is defined as a Hill equation (1) to describe the effectiveness of the drug [26]. Effectiveness of reverse transcriptase inhibitors (RTIs) and protease inhibitors (PIs) are represented, respectively, by drug efficacies ϕ_1 and ϕ_2, where $0 \le \phi_1, \phi_2 \le 1$. If the drug is 100% effective, then $\phi_1 = \phi_2 = 1$,

$$\phi_i = \frac{d^m}{d^m + \mathrm{IC}_{50}^m}, \quad i = 1, 2, \tag{1}$$

where d is the drug dose concentration, IC_{50} is the drug concentration that leads to 50% of the maximal viral inhibition, and m is the gradient of the dose-response curve. Response is the ability of the drug to inhibit viral replication [28]. Gradients for dose-response curves of HIV drugs are given by [30] and are shown in Table 1.

In the process of metabolising toxic ART, some healthy as well as HIV infected hepatocytes get injured/die [12–14]. The toxic effect of ART on hepatocytes is also assumed to be dose-dependent. Thus, infected and healthy hepatocytes are assumed to die during drug metabolism at a rate ψ for $0 \le \psi \le 1$ depending on the drug dose, [26], where ψ is defined as

$$\psi = \frac{d^m}{d^m + \mathrm{TD}_{50}^m}, \tag{2}$$

d is the drug dose, TD_{50} is the dose at which toxicity occurs in 50% of exposed cases, and m is the gradient of the dose-response curve. We assume that both toxic and therapeutic effects of antiretroviral drugs exhibit dose-response curves of relative gradients since both are dose-dependent [31]. Due to scarcity of literature regarding dose-response analysis of ART toxicity, we assume that all the gradients might not be the same but relative. This is based on the assumption that since nonnucleoside reverse transcriptase inhibitors (NNRTIs) and PIs are the most efficacious and have higher gradients than NRTIs, [28, 30], this is consistent with toxicity and hence relative gradients.

In model formulation, we define eight variables as follows: uninfected CD4+ cells (T_c), infectious CD4+ cells (I_c), uninfected hepatocytes (T_h), latently infected hepatocytes (I_{hl}), [9], productively infected hepatocytes (I_{ha}), HIV-specific cytotoxic T lymphocytes (L), viral load (V), and the level of enzyme alanine aminotransferase in blood (A).

Model parameters are as follows: CD4+ cells and hepatocytes are produced from within the body at rates λ_1 and λ_2 and die naturally at rates d_1 and d_3, respectively. We assume that, among all cells in the liver, HIV has high affinity for CD4+ cells and hepatocytes [20]. Thus, from the free viral population in the liver, if a virus is to infect a cell, there is a probability q that it will infect a hepatocyte at rate β_2 and a probability $1-q$ that it infects a CD4+ T cell at rate β_1. Infected CD4+cells die at rate d_2, where $d_2 > d_1$, and are cleared by HIV-specific cytotoxic T-lymphocytes (CTLs) at a rate k_1.

When a hepatocyte is infected, there is a probability p that it becomes productively infected (viral replication

will take place after successful reverse transcription) and probability $(1-p)$ that the cell will become latently infected, such that there is no viral production until cell activation. Decay rates for productive hepatocytes and latently infected hepatocytes are, respectively, d_5 and d_4, where $d_5 > d_4$ [36]. Productively infected hepatocytes are killed by HIV-specific CTLs at rate k_2 and until activated, latently infected hepatocytes will not trigger the action of CTLs. This study assumes that latently infected hepatocytes will either get activated to become infectious or die. There is no possibility that they will become uninfected again [37]. Latently infected hepatocytes are activated at rate μ, and it is assumed that this rate is reduced by the the efficacy of PIs. This is because our study assumed that reverse transcription has already taken place at this stage so reverse transcriptase inhibitors will have no effect.

With or without any pathogen in the body CTLs proliferate naturally at rate x and in the presence of HIV infection, they proliferate at rate k_3 and are cleared at rate d_6. Let s_1 and s_2 represent the rates of HIV production per infected CD4+ cells and productively infected hepatocytes, respectively. In addition to CD4+ cells and hepatocytes, HIV productively infects other cells and macrophages like Kupffer cells in the liver [11, 19, 45]. These cells produce virions at rate m. The study assumed that the effect of medication is translated generally into minimal viral load. Thus, viral production from macrophages is also inhibited by both RTIs and PIs. As in [46], we assumed a synergy additivity of PIs and RTIs as $\Phi = (1-\phi_1)(1-\phi_2)$ [39]. Virions die at a per capita rate d_7.

This study assumes that some infectious hepatocytes that die due to drug metabolism are able to release viral particles, provided that at the point of hepatocyte's death all the stages of viral production have been attained. N is the per capita rate of virions production by each infectious hepatocyte that dies due to drug metabolism. Viral production due to hepatotoxicity was inhibited by resultant efficacy of both RTIs and PIs.

Equation (10) defines the level of enzyme alanine aminotransferase (ALT) in the blood system. Among other enzymes, hepatocytes contain enzyme ALT, and when the cells die by any means, ALT leaks into the blood where it is clinically detected. According to [3], when there is no infection, the level of ALT in the blood system is generated from naturally dying hepatocytes at rate r. As described in [42], k_4 is the rate at which ALT is generated from hepatocytes that die due to HIV infection. $(d_5+\psi+k_2L)$ and $(d_4+\psi)$ are the total death rate of productively infected hepatocytes and latently infected hepatocytes, respectively, attributed to HIV infection. The contribution to ALT by healthy hepatocytes is only due to drug metabolism. ALT is cleared from the blood naturally at rate d_8.

From the assumptions and description above we have the following system of ordinary differential equations:

$$\frac{dT_c}{dt} = \lambda_1 - (1-\phi_1)(1-q)\beta_1 T_c V - d_1 T_c, \tag{3}$$

$$\frac{dI_c}{dt} = (1-\phi_1)(1-q)\beta_1 T_c V - d_2 I_c - k_1 I_c L, \tag{4}$$

$$\frac{dT_h}{dt} = \lambda_2 - (1-\phi_1) q\beta_2 T_h V - d_3 T_h - \psi T_h, \tag{5}$$

$$\begin{aligned}\frac{dI_{\mathrm{hl}}}{dt} &= (1-\phi_1)(1-p) q\beta_2 T_h V \\ &\quad - d_4 I_{\mathrm{hl}} - (1-\phi_2)\mu I_{\mathrm{hl}} - \psi I_{\mathrm{hl}},\end{aligned} \tag{6}$$

$$\begin{aligned}\frac{dI_{\mathrm{ha}}}{dt} &= (1-\phi_1)\, pq\beta_2 T_h V - d_5 I_{\mathrm{ha}} \\ &\quad - k_2 I_{\mathrm{ha}} L + (1-\phi_2)\mu I_{\mathrm{hl}} - \psi I_{\mathrm{ha}},\end{aligned} \tag{7}$$

$$\frac{dL}{dt} = x + k_3 (I_c + I_{\mathrm{ha}}) L - d_6 L, \tag{8}$$

$$\begin{aligned}\frac{dV}{dt} &= (1-\phi_2) s_1 I_c + (1-\phi_2) s_2 I_{\mathrm{ha}} \\ &\quad + \Phi m + N\psi I_{\mathrm{ha}} - d_7 V,\end{aligned} \tag{9}$$

$$\begin{aligned}\frac{dA}{dt} &= r + k_4 \left((d_5 + \psi + k_2 L) I_{\mathrm{ha}} + (d_4 + \psi) I_{\mathrm{hl}} + \psi T_h \right) \\ &\quad - d_8 A.\end{aligned} \tag{10}$$

2.2. Model Analysis

2.2.1. Positivity and Boundedness of Solutions. With initial conditions $T_{h0} > 0$, $I_{c0} > 0$, $T_{h0} > 0$, $I_{\mathrm{hl}0} \geq 0$, $I_{\mathrm{ha}0} \geq 0$, $L_0 > 0$, $V_0 > 0$, and $A_0 \geq 0$, the solutions for T_h, I_c, T_h, I_{hl}, I_{ha}, L, V, and A, respectively, remain positive and bounded provided $t > 0$.

We define N_c and N_h as the total number of CD4+ cells and hepatocytes, respectively, where

$$\begin{aligned}\frac{dN_c}{dt} &= \frac{dT_c}{dt} + \frac{dI_c}{dt}, \\ \frac{dN_h}{dt} &= \frac{dT_h}{dt} + \frac{dI_{\mathrm{ha}}}{dt} + \frac{dI_{\mathrm{hl}}}{dt}.\end{aligned} \tag{11}$$

Given that $d_2 > d_1$ and $d_5 > d_4 > d_3$ as in [36] and that all variables and parameters are positive (otherwise the model would not be biologically feasible) then

$$\begin{aligned}\frac{dN_h}{dt} &< \lambda_2 - (\psi + d_3) N_h - k_2 I_{\mathrm{ha}} L \\ &< \lambda_2 - (\psi + d_3) N_h.\end{aligned} \tag{12}$$

Thus

$$\frac{d}{dt}\left(N_h e^{(\psi+d_3)t} \right) < \lambda_2 e^{(\psi+d_3)t}. \tag{13}$$

Implying

$$N_h e^{(\psi+d_3)t} - \kappa < \frac{\lambda_2 e^{(\psi+d_3)}}{\psi + d_3} - \frac{\lambda_2}{\psi + d_3}, \tag{14}$$

hence

$$N_h < \frac{\lambda_2}{d_3 + \psi} + \left(\kappa - \frac{\lambda_2}{d_3 + \psi} \right) e^{-(d_3+\psi)t}, \tag{15}$$

where κ is the total number of hepatocytes at the time of infection. Equation (15) indicates that there are two cases to consider:

(1) consider

$$\kappa < \frac{\lambda_2}{\psi + d_3}, \tag{16}$$

the upper bound of N_h increases and approaches asymptotically the value $\lambda_2/(\psi + d_3)$;

(2) consider

$$\kappa > \frac{\lambda_2}{\psi + d_3}, \tag{17}$$

the upper bound of N_h decreases and approaches asymptotically the value $\lambda_2/(\psi + d_3)$.

In either case $N_h(t)$ remains bounded.

Similarly, it can also be shown that $N_c(t)$ is bounded by λ_1/d_1.

If the total number of CD4+ cells (N_c) and hepatocytes (N_h) are bounded by λ_1/d_1 and $\lambda_2/(d_3 + \psi)$, then the subclasses (I_c) and (I_{ha} and I_{hl}) respectively are bounded. Thus, letting $M_1 = \lambda_2/(d_3 + \psi)$ and $M_2 = \lambda_1/d_1$ then $T_c < M_2$, $I_c < M_2$, $T_h < M_1$, $I_{\text{hl}} < M_1$, and $I_{\text{ha}} < M_1$.

Using (9) and considering $I_c < M_2$ and $I_a < M_1$, then

$$\frac{dV}{dt} < (1 - \phi_2)\, s_1 M_2 + (1 - \phi_2)\, s_2 M_1 + (1 - \Phi)\, m - d_6 V. \tag{18}$$

Letting $Q = (1 - \phi_2)s_1M_2 + (1 - \phi_2)s_2M_1 + (1 - \Phi)m$, where $Q > 0$ since $0 \le \phi_1, \phi_2, \Phi \le 1$. Using the same method as in (15)

$$V < \frac{Q}{b_6} + \left(V_0 - \frac{Q}{d_6}\right) e^{-d_6 t}, \tag{19}$$

where V_0 is initial viral load.

Using the same argument as in (15), we can deduce that V is bounded by V_0.

Using (8) and taking only infection-dependent proliferation, on assumption that antigen-independent proliferation is naturally bounded, it can be shown that

$$\begin{aligned} \frac{dL}{dt} &< k_1 (M_1 + M_2)\, L - d_5 L, \\ L &< L_0 e^{st}, \end{aligned} \tag{20}$$

where $s = k_1(M_1 + M_2) - d_5$. Letting $M_4 = L_0 e^{k_1(M_1+M_2)-d_5}$, then $L < M_4$.

Equation (10) is defined by bounded functions; therefore, A is bounded by some M_5, where $M_5 = \max\{M_1, M_3, M_4\}$.

Suppose the feasible solution of CD4+ cells in the liver lies in the region Θ_c; then,

$$\Theta_c = \left\{ (T_c, I_c) \in \mathbb{R}^2 : N_c < \frac{\lambda_1}{d_1} \right\}. \tag{21}$$

Similarly, assuming the feasible solution of hepatocytes in the liver to lie in the region Θ_h, then

$$\Theta_h = \left\{ (T_h, I_{\text{hl}}, I_{\text{ha}}) \in \mathbb{R}^3 : N_h < \frac{\lambda_2}{(d_3 + \psi)} \right\}. \tag{22}$$

Letting $M_3 = Q/d_6$, it can be deduced that the feasible solution for the model (3)–(10) is

$$\begin{aligned} \Theta = \big\{ &(T_c, I_c, T_h, I_{\text{hl}}, I_{\text{ha}}, L, V, A) \in \mathbb{R}^8 : \\ &(T_c + I_c) < M_2, (T_h + I_{\text{hl}} + I_{\text{ha}}) < M_1, \\ &V < M_3, L < M_4, A < M_5 \big\}. \end{aligned} \tag{23}$$

2.2.2. The Basic Reproductive Number. When there is no HIV infection in the liver, the system of (3)–(10) settles to a disease-free equilibrium E_d defined by

$$\begin{aligned} E_d &= (T_c^o, I_c^o, T_h^o, I_{\text{hl}}^o, I_{\text{ha}}^o, L^o, V^o, A^o) \\ &= \left(\frac{\lambda_1}{d_1}, 0, \frac{\lambda_2}{d_3}, 0, 0, \frac{x}{d_6}, 0, \frac{r}{d_8} \right). \end{aligned} \tag{24}$$

Taking the system of (3)–(10) without medication, that is, $\phi_1 = \phi_2 = \psi = 0$, the basic reproductive number calculated using the next generation method as in [47] is given by

$$R_0 = \sqrt{R_{0\text{hl}} + R_{0\text{ha}} + R_{0c}}, \tag{25}$$

where

$$\begin{aligned} R_{0\text{hl}} &= \frac{(1 - p)\, s_2 \mu d_6 q \beta_2 \lambda_2}{d_3 d_7 (d_4 + \mu)(d_5 d_6 + k_2 x)}, \\ R_{0\text{ha}} &= \frac{s_2 d_6 p q \beta_2 \lambda_2}{d_3 d_7 (d_5 d_6 + k_2 x)}, \\ R_{0c} &= \frac{(1 - q)\, s_1 d_6 \beta_1 \lambda_1}{d_1 d_7 (d_2 d_6 + k_1 x)}. \end{aligned} \tag{26}$$

$R_{0\text{hl}}$ is the number of secondary infections in latently infected hepatocytes compartment. $R_{0\text{ha}}$ is the number of secondary infections in productively infected hepatocytes. R_{0c} is the number of secondary infections produced by one virus producing CD4+ cell. R_0 is the total number of secondary infections in the liver. The total number of secondary infections is directly proportional to the clearance rate of CTLs and inversely proportional to the clearance rate of virions. Generally, R_0 is dependent on antigen-independent CTLs proliferation rate (x) and independent of antigen-dependent proliferation rate (k_3). This indicates that if the CTLs are boosted prior to infection, then the body can handle infection better than when they (CTLs) proliferate in the presence of infection. High CTL clearance rate implies higher numbers of secondary infection. Probably, if many CTLs are cleared from the body by any means, then there are fewer cells left to fight the infection hence faster progression of the infection.

Using Theorem 2 of [47] we establish the following result that the disease-free equilibrium E_d is locally asymptotically stable when $R_0 < 1$ and unstable when $R_0 > 1$.

2.2.3. Effective Reproductive Number. Analysing the system of (3)–(10) with the medication ($\phi_1 = \phi_2 = \psi \neq 0$), we calculated the effective reproductive number (R_e) using the next generation method as in [47]. R_e is the actual average number of secondary cases per primary case that reflects the impact of therapy on infection. Technically, the number of secondary infections during therapy (R_e) should be less than those without therapy (R_0). R_e is defined as

$$R_e = \sqrt{R_{\text{ehl}} + R_{\text{eha}} + R_{ec}}, \tag{27}$$

where

$$\begin{aligned} R_{\text{ehl}} &= \left((1-p)(1-\phi_2)\left(N\Phi\psi + (1-\phi_2)s_2\right)\mu d_6 q\beta_2\lambda_2\right) \\ &\quad \times \left(d_3 d_7 \left(d_4 + \psi + \mu(1-\phi_2)\right)\right. \\ &\quad \left. \times \left(d_5 d_6 + k_2 x + \psi d_6\right)\right)^{-1}; \\ R_{\text{eha}} &= \frac{\left(N\Phi\psi + (1-\phi_2)s_2\right)(1-\phi_2)d_6 pq\beta_2\lambda_2}{d_3 d_7 \left(d_5 d_6 + k_2 x + \psi d_6\right)}, \\ R_{ec} &= \frac{(1-\phi_1)(1-\phi_2)(1-q)s_1 d_6\beta_1\lambda_1}{d_1 d_7 \left(d_2 d_6 + k_2 x\right)}, \end{aligned} \tag{28}$$

R_{ec}, R_{eha}, and R_{ehl} are defined the same way as R_{0c}, $R_{0\text{ha}}$, and $R_{0\text{hl}}$, respectively, in (25) except that the latter are functions of therapy efficacy and toxicity. Secondary infections in either type of cells largely depend on the drug efficacy. It can be seen that if the drug is 100% effective ($\phi_1 = \phi_2 = 1$), then there would be no secondary infections in either type of cell. However, if the drug is totally ineffective ($\phi_1 = \phi_2 = 0$), it would be expected that the number of secondary infections would be equivalent to those produced when no therapy is administered. This is however not the case, because whether the drug is effective or not, its toxicity will affect the cells involved in drug metabolism.

At present there is no HIV antiretroviral drug that is 100% effective, [48]; likewise, there is no HIV therapy that is free of toxicity [18]. When $\phi_1 = \phi_2 = 0$, it is not straightforward to deduce whether the number of secondary infections in hepatocytes during therapy is less or greater than the number of secondary infections when therapy is not administered. We therefore assess the toxic function that would result in the same number of secondary infections as those when no therapy is administered. We suppose that this is the critical toxic effect ψ_{crit} of the drug that should not be exceeded if the therapy should reduce the number of secondary infections in the liver. Since toxicity is a function of drug dose, the dose that corresponds to the critical toxic effect can consequently be computed. Using $R_{0\text{hl}} + R_{0\text{ha}} = R_{\text{ehl}} + R_{\text{eha}}$, the critical toxic effect which is a function of drug efficacy is then calculated and satisfies the equation

$$a_0\psi_{\text{crit}}^2 + a_1\psi_{\text{crit}} + a_2 = 0, \tag{29}$$

where

$$\begin{aligned} a_0 &= N\Phi p(1-\phi_1)\left(d_5 d_6 + k_2 x\right)\left(d_4 + \mu\right) - s_2 d_6\left(p d_4 + \mu\right), \\ a_1 &= (1-\phi_1)\left(d_5 d_6 + k_2 x\right) \\ &\quad \times \left[(1-\phi_2)s_2 p + N\Phi\left(p d_4 + \mu(1-\phi_2)\right)\left(d_4 + \mu\right)\right] \\ &\quad - s_2 p\left(d_4 + \mu\right)\left[\left(d_5 d_6 + k_2 x\right) + d_6\left(d_4 + \mu(1-\phi_2)\right)\right], \\ a_2 &= s_2\left(d_5 d_6 + k_2 x\right) \\ &\quad \times \left[\Phi\left(d_4 + \mu\right)\left(p d_4 + \mu(1-\phi_2)\right)\right. \\ &\quad \left. - \left(p d_4 + \mu\right)\left(d_4 + \mu(1-\phi_2)\right)\right]. \end{aligned} \tag{30}$$

It can be shown that $a_0 > 0$ and $a_2 < 0$ and in this case we have two possibilities for a positive ψ_{crit}.

Case 1. When $a_1 > 0$, that is,

$$\begin{aligned} &(1-\phi_1)\left(d_5 d_6 + k_2 x\right) \\ &\quad \times \left[(1-\phi_2)s_2 p + N\Phi\left(p d_4 + \mu(1-\phi_2)\right)\left(d_4 + \mu\right)\right] \\ &> s_2 p\left(d_4 + \mu\right)\left[\left(d_5 d_6 + k_2 x\right) + d_6\left(d_4 + \mu(1-\phi_2)\right)\right], \end{aligned} \tag{31}$$

then

$$\psi_{\text{crit}_1} = \frac{-a_1 + \sqrt{a_1^2 + 4a_0 a_2}}{2a_0}. \tag{32}$$

Case 2. When $a_1 < 0$, that is,

$$\begin{aligned} &(1-\phi_1)\left(d_5 d_6 + k_2 x\right) \\ &\quad \times \left[(1-\phi_2)s_2 p + N\Phi\left(p d_4 + \mu(1-\phi_2)\right)\left(d_4 + \mu\right)\right] \\ &< s_2 p\left(d_4 + \mu\right)\left[\left(d_5 d_6 + k_2 x\right) + d_6\left(d_4 + \mu(1-\phi_2)\right)\right], \end{aligned} \tag{33}$$

then

$$\psi_{\text{crit}_2} = \frac{a_1 + \sqrt{a_1^2 + 4a_0 a_2}}{2a_0}. \tag{34}$$

Comparing the two scenarios, we take $\max\{\psi_{\text{crit}_1}, \psi_{\text{crit}_2}\}$ and hence deduce the critical drug toxicity that should not be exceeded by HIV medication if it should help in reducing the number of secondary infections, given the appropriate choice of parameters, as

$$\psi_{\text{crit}} = \frac{a_1 + \sqrt{a_1^2 + 4a_0 a_2}}{2a_0}. \tag{35}$$

2.2.4. Sensitivity Analysis. We carried out sensitivity analysis of the toxic function in the effective reproductive number of the hepatocytes. The study ignored CD4+ cells component of the basic reproductive number in toxic analysis, on

assumption that toxic effect of the medication does not have direct effect on CD4+ cells. Following [49], we determined the effect of ψ on R_e first by calculating the difference between R_{0h} and R_{eh} as Δ. If $\Delta > 0$ then the toxic effect will slow down the progress of the infection; otherwise it will speed it up:

$$\begin{aligned}\Delta = R_{0h} - R_{eh} = &-d_6 q\beta_2\lambda_2\left(\mu + d_4\right)\\ &\times \left(pd_4 + p\psi + \mu\left(1 - p\phi_2\right)\right)\left(d_6d_5 + k_2x\right)\Lambda\\ &+ d_6q\beta_2\lambda_2\left(\mu + pd_4\right)\left(d_4 + \psi + \mu\left(1 - \phi_2\right)\right)\\ &\times \left(d_6\left(d_5 + \psi\right) + k_2x\right),\end{aligned} \tag{36}$$

where $\Lambda = (1 - \phi_2)(N\psi\Phi + s_2(1 - \phi_2))$.

Since $0 \le p \le 1$, the right hand side of (36) is greater than the left hand side provided $(N\psi\Phi + s_2(1 - \phi_2)) < 1$. This is not likely because of the values of N and s_2 (100 and 1000, resp.). Therefore $\Delta < 0$; this would imply that $R_{0h} < R_{eh}$, hence indicating that the toxic effect of medication speeds up the progression of infection.

Differentiating R_{eh} with respect to ψ

$$\begin{aligned}\frac{\partial R_{eh}}{\partial\psi} = &\left(\left(C + p\psi\right)\left(G + d_6\psi\right)\left(AE - FB\right)\right.\\ &\left.+ \left(E + F\psi\right)\left(A\psi + B\right)\left(pG - d_6C\right)\right)\\ &\times \left(\left(E + F\psi\right)^2\left(G + d_6\psi\right)^2\right)^{-1},\end{aligned} \tag{37}$$

where

$$\begin{aligned}A &= d_6q\beta_2\lambda_2\left(1 - \phi_2\right)N\Phi, \qquad B = \left(1 - \phi_2\right)s_2,\\ C &= \mu + pd_4 - p\mu\phi_2, \qquad E = d_3d_7\left(d_4 + \mu\left(1 - \phi_2\right)\right),\\ F &= d_3d_7, \qquad G = d_5d_6 + k_2x.\end{aligned} \tag{38}$$

From (37), if $(AE - FB) > 0$ and $(pG - d_6C) > 0$, that is,

$$\begin{aligned}\phi_2 &> \frac{d_6\left(\mu + pd_4\right) - p\left(d_5d_6 + k_2x\right)}{p\mu d_6},\\ \phi_1 &< 1 - \frac{1}{d_6q\beta_2\lambda_2N\left(1 - \phi_2\right)^2\left(d_4 + \mu\left(1 - \phi_2\right)\right)},\end{aligned} \tag{39}$$

then

$$\frac{\partial R_{eh}}{\partial\psi} > 0. \tag{40}$$

According to [49], in order to slow down the infection rate of the virus when treatment is implemented, the conditions $\Delta > 0$ and $\partial R_{eh}/\partial\psi < 0$ should be satisfied. Based on the condition derived from (36), the effective reproductive number of hepatocytes is an increasing function of the toxic effect of therapy ψ. This implies that increase in toxicity of medication leads to increase in secondary infections in the liver, provided the relationship between drug efficacies as stated in conditions (39) is fulfilled.

Carrying out sensitivity analysis on the drug efficacies ϕ_1 and ϕ_2, we considered the effective reproductive number R_e of both CD4+ cells and hepatocytes. Starting with reverse transcriptase inhibitors (RTIs),

$$\frac{\partial R_e}{\partial\phi_1} = \frac{-Y - R}{Z}, \tag{41}$$

where

$$\begin{aligned}Y &= d_1d_6\beta_2\lambda_2\left(1 - \phi_2\right)^2N\\ &\quad\times\left(\mu + pd_4 - p\mu\phi_2 + p\psi\right)\left(d_2d_6 + k_1x\right),\\ R &= \left(1 - \phi_2\right)\left(1 - q\right)\left(d_4 + \mu\left(1 - \phi_2\right) + \psi\right)\\ &\quad\times\left(d_5d_6 + k_2x + \psi d_6\right)s_1\beta_1\lambda_1d_3d_7,\\ Z &= d_1d_3d_7\left(d_2d_6 + k_1x\right)\left(d_4 + \mu\left(1 - \phi_2\right) + \psi\right)\\ &\quad\times\left(d_5d_6 + k_2x + \psi d_6\right).\end{aligned} \tag{42}$$

Since $R, Y, Z > 0$, then $\partial R_e/\partial\phi_1 < 0$ indicating that R_e is a decreasing function of RTIs. Thus, increase in efficacy of RTIs implies a reduction in secondary infection.

With protease inhibitors (PIs), we have

$$\begin{aligned}\frac{\partial R_e}{\partial\phi_2} = &\left(a_1\left(1 - \phi_2\right)^2p\mu\left(a_4 + \mu\left(1 - \phi_2\right)\right)\right.\\ &\left.- a_3\left(a_4 - \mu\left(1 - \phi_2\right)\right)^2\right)\\ &\times\left(a_5\left(a_4 + \mu(1 - \phi_2)\right)\right)^{-1}\\ &- \left(a_1\left(1 - \phi_2\right)\left(a_2 - p\mu\phi_2\right)\right.\\ &\left.\times\left(\mu\left(1 - \phi_2\right) + 2a_4\right)\right)\\ &\times\left(a_5\left(a_4 + \mu\left(1 - \phi_2\right)\right)\right)^{-1},\end{aligned} \tag{43}$$

where

$$\begin{aligned}a_1 &= d_1d_3d_6\beta_2\lambda_2\left(N\left(1 - \phi_1\right) + s_2\right)\left(d_2d_6 + k_1x\right),\\ a_2 &= \mu + pd_4 + p\psi,\\ a_3 &= s_1\beta_1\lambda_1d_3d_7\left(1 - \phi_1\right)\left(1 - q\right)\left(d_5d_6 + k_2x + \psi d_6\right),\\ a_4 &= d_4 + \psi,\\ a_5 &= d_1d_3d_7\left(d_2d_6 + k_1x\right)\left(d_5d_6 + k_2x + \psi d_6\right).\end{aligned} \tag{44}$$

It can be shown that $\partial R_e/\partial\phi_2 < 0$. We can therefore conclude that R_e is a decreasing function of ϕ_1 and ϕ_2 as shown in Figure 1. Increasing the drug efficacy will result in a decrease in secondary infections. Referring to (1), increasing efficacy would necessitate increasing drug dose concentration so that it is much greater than its IC_{50}.

2.2.5. Endemic Equilibrium. Due to the complexity of the model, mathematical analysis is rather cumbersome. We therefore assume a free virus spread of infection and no

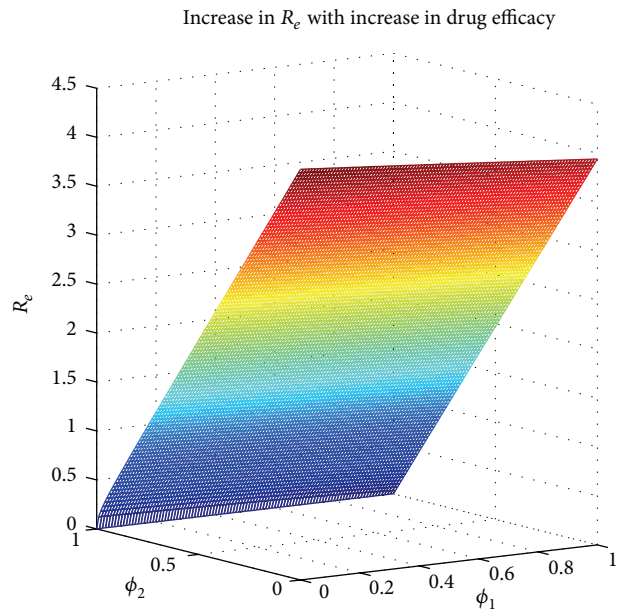

FIGURE 1: Increase in effective reproductive number with increase in drug efficacy with $\psi = 0.5$. Horizontal axes represent time in days and parameter values are as shown in Table 2.

cell-to-cell transfer of HIV, [50], ruling out the interaction between CD4+ cells and hepatocytes. We therefore split the model into two subpopulations of either cell. We further consider virions produced from either type of cells as the viral production in that subpopulation. We assume a fraction ρ of the total viral population from macrophages to contribute to the viral population in hepatocytes subpopulation while the remainder would contribute to the viral population in CD4+ cells subpopulation. We subdivide the system of (3)–(10) into the following.

CD4+ cells subpopulation infection dynamics:

$$\begin{aligned}
\frac{dT_c}{dt} &= \lambda_1 - (1-\phi_1)(1-q)\beta_1 T_c V - d_1 T_c,\\
\frac{dI_c}{dt} &= (1-\phi_1)(1-q)\beta_1 T_c V - d_2 I_c - k_1 I_c L,\\
\frac{dL}{dt} &= x + k_3 I_c L - d_6 L,\\
\frac{dV}{dt} &= (1-\phi_2) s_1 I_c + \Phi(1-\rho) m - d_7 V.
\end{aligned} \tag{45}$$

Hepatocytes subpopulation infection dynamics:

$$\begin{aligned}
\frac{dT_h}{dt} &= \lambda_2 - (1-\phi_1) q\beta_2 T_h V - d_3 T_h - \psi T_h,\\
\frac{dI_{\mathrm{hl}}}{dt} &= (1-\phi_1)(1-p) q\beta_2 T_h V\\
&\quad - d_4 I_{\mathrm{hl}} - (1-\phi_2)\mu I_{\mathrm{hl}} - \psi I_{\mathrm{hl}},\\
\frac{dI_{\mathrm{ha}}}{dt} &= (1-\phi_1) pq\beta_2 T_h V - d_5 I_{\mathrm{ha}}\\
&\quad - k_2 I_{\mathrm{ha}} L + (1-\phi_2)\mu I_{\mathrm{hl}} - \psi I_{\mathrm{ha}},\\
\frac{dL}{dt} &= x + k_3 I_{\mathrm{ha}} L - d_6 L,\\
\frac{dV}{dt} &= (1-\phi_2) s_2 I_{\mathrm{ha}} + \Phi\rho m + N\psi I_{\mathrm{ha}} - d_7 V,\\
\frac{dA}{dt} &= r + k_4\left(\left(d_4 + \psi + k_2 L\right) I_{\mathrm{ha}} + \left(d_5 + \psi\right) I_{\mathrm{hl}} + \psi T_h\right)\\
&\quad - d_8 A.
\end{aligned} \tag{46}$$

We derive the endemic equilibrium state as

$$\begin{aligned}
T_c^* &= (\lambda_1 d_7)\\
&\quad \times \left((1-q)(1-\phi_1)(1-\phi_2) s_1 \beta_1 I_c^*\right.\\
&\quad \left. + (1-q)(1-\phi_1)\beta_1 \Phi(1-\rho) m + d_1 d_7\right)^{-1},\\
T_h^* &= (\lambda_1 d_7)\\
&\quad \times \left((1-\phi_1)(1-\phi_2) s_2 q\beta_2 I_{\mathrm{ha}}^*\right.\\
&\quad \left. + (1-q)(1-\phi_1)\beta_1 \Phi\rho m + d_7\left(d_3 + \psi\right)\right)^{-1},\\
L^* &= \max\left\{\frac{x}{d_6 - k_3 I_c^*}, \frac{x}{d_6 - k_3 I_{\mathrm{ha}}^*}\right\},\\
I_{\mathrm{hl}}^* &= \left((1-\phi_1)(1-p)(1-\phi_2) s_2 q\beta_2 \lambda_2 d_7 I_{\mathrm{ha}}^*\right.\\
&\quad \left. + (1-\phi_1)(1-p) q\beta_2 \lambda_2 d_7 \Phi\rho m\right)\\
&\quad \times (\Gamma + \Lambda)^{-1},\\
V^* &= \frac{(1-\phi_2) s_2 I_{\mathrm{ha}}^* + \Phi\rho m + (1-\phi_2) s_1 I_c^* + \Phi(1-\rho) m}{d_7},\\
A^* &= \frac{r + k_4\left(\left(d_4 + \psi + k_2 L^*\right) I_{\mathrm{ha}}^* + \left(d_5 + \psi\right) I_{\mathrm{hl}}^* + \psi T_h^*\right)}{d_8},
\end{aligned} \tag{47}$$

where

$$\begin{aligned}
\Gamma &= d_7\left(d_4 + (1-\phi_2)\mu + \psi\right)\left((1-\phi_1) q\beta_2 \Phi\rho m\right),\\
\Lambda &= d_7\left(d_3 + \psi\right) + d_7\left(d_4 + (1-\phi_2)\mu + \psi\right)\\
&\quad \times (1-\phi_1) q\beta_2 (1-\phi_2) s_2 I_{\mathrm{ha}}^*,
\end{aligned} \tag{48}$$

and I_c^* and I_{ha}^* are given by the following equations:

$$w_0 I_c^{*3} - w_1 I_c^{*2} - w_2 I_c^* - w_3 = 0, \tag{49}$$

$$b_0 I_{\mathrm{ha}}^{*4} + b_1 I_{\mathrm{ha}}^{*3} + b_2 I_{\mathrm{ha}}^{*2} + b_3 I_{\mathrm{ha}}^* + b_4 = 0, \tag{50}$$

in which

$$
\begin{aligned}
w_0 &= d_2 d_7 k_3 (1-q)(1-\phi_1)(1-\phi_2) s_1 \beta_1,\\
w_1 &= d_7 (1-q)(1-\phi_1)(1-\phi_2)\\
&\quad \times s_1 \beta_1 (d_2 d_6 + k_1 x + \lambda_1 k_3)\\
&\quad - d_2 k_3 d_7 (d_1 d_7 + \rho \Phi m \beta_1 (1-\phi_1)(1-q)),\\
w_2 &= d_7 (((1-q)(1-\phi_1)\beta_1 \rho \Phi m + d_1 d_7)\\
&\quad \times (d_2 d_6 + k_1 x))\\
&\quad + k_3 d_7 \lambda_1 \rho \Phi m (1-q)(1-\phi_1)\\
&\quad - d_6 d_7 \lambda_1 \beta_1 s_1 (1-q)(1-\phi_1)(1-\phi_2),\\
w_3 &= d_6 d_7 \lambda_1 \rho \Phi m \beta_1 (1-q)(1-\phi_1),\\
b_0 &= d_7^2 k_3 (1-\phi_1)^2 (1-\phi_2)^2 q^2 \beta_2^2 s_2^2,\\
b_1 &= d_7^2 \Phi q \beta_2 \mu (d_4 + (1-\phi_2)\mu + \psi)\\
&\quad \times [k_3 (d_3 + \psi)\\
&\quad \times ((1-\phi_1) q \beta_2 (1-\rho) \Phi m + d_7 (d_3 + \psi))]\\
&\quad - d_7^2 \Phi q \beta_2 \mu (d_4 + (1-\phi_2)\mu + \psi)\\
&\quad \times \Phi q \beta_2 \mu (k_2 x + d_6 (d_3 + \psi)),\\
b_2 &= d_7^2 k_3 (d_4 + (1-\phi_2)\mu + \psi)\\
&\quad \times ((1-\phi_1) q \beta_2 (1-\rho) \Phi m + d_7 (d_3 + \psi))^2 (d_5 + \psi)\\
&\quad - d_7^2 (d_4 + \psi + (1-\phi_2)\mu)(1-\phi_1) q \beta_2\\
&\quad \times (1-\phi_2) s_2 ((1-\phi_1) q \beta_2 (1-\rho) \phi m + d_7 (d_3 + \psi))\\
&\quad \times (k_2 x + d_6 (d_5 + \psi))\\
&\quad - (k_3 (1-\phi) q \beta_2 \lambda_2 d_7 (1-\phi_2) s_2)\\
&\quad \times (p + (1-\phi_2)\mu (1-p)),\\
b_3 &= (1-\phi_2)(1-\phi_1) q \beta_2 \lambda_2 d_7 \mu\\
&\quad \times (d_6 p + (1-p)(1-\phi_2) s_2)\\
&\quad - d_7^2 (d_4 + \psi + (1-\phi_2)\mu)\\
&\quad \times ((1-\phi_1) q \beta_2 (1-\rho) \Phi m + d_7 (d_3 + \psi))^2\\
&\quad \times (k_2 x + d_6 (d_5 + \psi))\\
&\quad - k_3 (1-\phi) q \beta_2 \lambda_2 d_7 (1-\rho) \Phi m\\
&\quad \times (p + \mu (1-p)(1-\phi_2)),\\
b_4 &= d_6 (1-\phi_1)(1-\rho) q \beta_2 \lambda_2 d_7 \Phi m\\
&\quad \times (p + (1-\phi_2)\mu (1-p)).
\end{aligned}
\tag{51}
$$

Differentiating (49) with respect to I_c to obtain the steady states values of I_c, it can be shown that given

$$
\begin{aligned}
&d_7 (((1-q)(1-\phi_1)\beta_1 \rho \Phi m + d_1 d_7)(d_2 d_6 + k_1 x))\\
&\quad + k_3 d_7 \lambda_1 \rho \Phi m (1-q)(1-\phi_1)\\
&> d_6 d_7 \lambda_1 \beta_1 s_1 (1-q)(1-\phi_1)(1-\phi_2),
\end{aligned}
\tag{52}
$$

then there would be two equilibrium values of I_c. Otherwise CD4+ cells would have one positive endemic equilibrium point given by

$$
I_c^* = \frac{w_1 + \sqrt{w_1^2 + 3 w_0 w_2}}{3 w_0},
\tag{53}
$$

provided the relationship between the two drug efficacies was given by

$$
\begin{aligned}
&\frac{1}{(1-\phi_2)}\\
&< \frac{(1-\phi_1)^2 \beta_1 \rho m (1-q)(d_2 d_6 + k_1 x)}{d_1 d_7 (d_2 d_6 + k_1 x)}\\
&\quad + \frac{(1-\phi_1)(k_3 \lambda_1 \rho m (1-q)(1-\phi_1) - \lambda_1 \beta_1 s_1 (1-q))}{d_1 d_7 (d_2 d_6 + k_1 x)\, 1-\phi_1}.
\end{aligned}
\tag{54}
$$

With hepatocytes subpopulation, however, there was no finite number of equilibrium states but rather a rage of values. Therefore, using Descartes rule of signs [51], (50) had at most one positive endemic equilibrium everywhere except in the region θ satisfied by $\theta = \{b_1 < 0, b_2 > 0, b_3 < 0\}$.

2.2.6. Reduced Model. We reduce the model for further analysis with assumption that RTIs and PIs have an overall drug efficacy given by Φ, where $\Phi = 1 - (1-\phi_1)(1-\phi_2)$ [52]. The combined efficacy Φ reduces the rate at which the virus infects CD4+ cells (β_1) and hepatocytes (β_2). We further assumed that much as macrophages act as reserve source for HIV production throughout HIV infection [53], the level of replication is low as compared to other cells. We therefore revised the model to exclude viral production from macrophages and subdivided it into CD4+ cells and hepatocytes subpopulation. The objective was to investigate the critical combined efficacy of antiretroviral therapy above which the infection would be managed as well as the optimal toxicity below which alanine aminotransferase level in the blood would be negligible.

CD4+ cells subpopulation:

$$
\begin{aligned}
\frac{dT_c}{dt} &= \lambda_1 - (1-\Phi)(1-q)\beta_1 T_c V - d_1 T_c,\\
\frac{dI_c}{dt} &= (1-\Phi)(1-q)\beta_1 T_c V - d_2 I_c - k_1 I_c L,\\
\frac{dL}{dt} &= x + k_3 I_c L - d_6 L,\\
\frac{dV}{dt} &= s_1 I_c - d_7 V.
\end{aligned}
\tag{55}
$$

Hepatocytes subpopulation:

$$\begin{aligned}
\frac{dT_h}{dt} &= \lambda_2 - (1-\Phi)\, q\beta_2 T_h V - d_3 T_h - \psi T_h,\\
\frac{dI_{\mathrm{hl}}}{dt} &= (1-\Phi)(1-p)\, q\beta_2 T_h V - d_4 I_{\mathrm{hl}} - \mu I_{\mathrm{hl}} - \psi I_{\mathrm{hl}},\\
\frac{dI_{\mathrm{ha}}}{dt} &= (1-\Phi)\, pq\beta_2 T_h V - d_5 I_{\mathrm{ha}} - k_2 I_{\mathrm{ha}} L + \mu I_{\mathrm{hl}} - \psi I_{\mathrm{ha}},\\
\frac{dL}{dt} &= x + k_3 I_{\mathrm{ha}} L - d_6 L,\\
\frac{dV}{dt} &= s_2 I_{\mathrm{ha}} - d_7 V,\\
\frac{dA}{dt} &= r + k_4\left(\left(d_4 + \psi + k_2 L\right) I_{\mathrm{ha}} + \left(d_5 + \psi\right) I_{\mathrm{hl}} + \psi T_h\right)\\
&\quad - d_8 A.
\end{aligned} \tag{56}$$

The corresponding endemic equilibrium values for the variables in CD4+ cells subpopulation are

$$\begin{aligned}
T_c^+ &= \frac{\lambda_1 d_7}{(1-\Phi)(1-q)\,\beta_1 s_1 I_c^+ + d_1 d_7},\\
V^+ &= \frac{s_1 I_c^+}{d_7},\\
L^+ &= \frac{x}{d_6 - k_3 I_c^+},
\end{aligned} \tag{57}$$

in which

$$c_2 {I_c^+}^2 + c_1 I_c^+ + c_0 = 0, \tag{58}$$

where

$$\begin{aligned}
c_2 &= (1-\Phi)(1-q)\,\beta_1 s_1 d_2 k_3,\\
c_1 &= d_1 d_7 d_2 k_2 + (1-\Phi)(1-q)\left(d_2 d_6 + k_1 x\right)\beta_1 s_1\\
&\quad + k_3 (1-\Phi)(1-q)\,\beta_1 \lambda_1 d_7 s_1,\\
c_0 &= d_1 d_7 \left(d_2 d_6 + k_1 x\right) - (1-\Phi)(1-q)\,\beta_1 \lambda_1 s_1 d_6.
\end{aligned} \tag{59}$$

It is clear that $c_2 > 0$ and $c_1 > 0$. Comparing with (28), (considering $1-\Phi = (1-\phi_1)(1-\phi_2)$) and assuming the effective reproductive number of CD4+ cells to be above unity in HIV infection during therapy, it can be shown that $c_0 < 0$. Therefore, (58) has one positive root given by

$$I_c^+ = \frac{-c_1 + \sqrt{c_1^2 - 4c_2 c_0}}{2c_2} \tag{60}$$

To find the critical combined efficacy of antiretroviral therapy, we assume this happens when $V^+ = 0$. Since all parameters are nonnegative, then V^+ can only be zero if $I_c^+ = 0$. Thus, the critical efficacy of ART in CD4+ cells above which the infection would be managed would be given by

$$\Phi_{\mathrm{critical}} = 1 - \frac{d_1 d_7 \left(d_2 d_6 + k_1 x\right)}{(1-q)\,\beta_1 \lambda_1 s_1 d_6} = 1 - \frac{1}{R_{0c}}. \tag{61}$$

If $\Phi > \Phi_{\mathrm{critical}}$ then the medication will be able to keep the virus in a controlled state even if the infection remains endemic; that is, the disease-free state and the endemic steady state coexist [54].

In the same way we investigated the optimal toxicity of ART that would not elevate liver enzymes in the blood system even if HIV infection remained endemic. This was assumed to happen when $A^+ = 0$; we thus established the endemic equilibrium point in the hepatocyte subpopulation as

$$\begin{aligned}
T_h^+ &= \frac{\lambda_2 d_6}{(1-\Phi)\, q\beta_2 s_2 I_{\mathrm{ha}}^+ + d_3 d_6 + \psi d_6},\\
L^+ &= \frac{x}{d_6 - k_3 I_{\mathrm{ha}}},\\
V^+ &= \frac{s_2 I_{\mathrm{ha}}^+}{d_6},\\
I_{\mathrm{hl}}^+ &= \left(\frac{(1-\Phi)(1-p)\, q\beta_2 s_2 I_{\mathrm{ha}}}{d_6\left(d_4 + \mu + \psi\right)}\right) T_h,\\
A^+ &= \frac{r + k_4\left[\left(d_4 + \psi + k_2 L\right) I_{\mathrm{ha}} + \left(d_5 + \psi\right) I_{\mathrm{hl}} + \psi T_h\right]}{d_8},
\end{aligned} \tag{62}$$

in which

$$y_3 I_{\mathrm{ha}}^3 + y_2 I_{\mathrm{ha}}^2 + y_1 I_{\mathrm{ha}} + y_0 = 0, \tag{63}$$

where

$$\begin{aligned}
y_0 &= (1-\Phi)(1-p)\left(d_4 + \Psi\right) q\beta_2 s_2 \lambda_2 d_6^2,\\
y_1 &= (1-\Phi)(1-p)\left(d_4 + \Psi\right) q\beta_2 s_2 \lambda_2 d_6\\
&\quad + d_6^2\left(d_4 + \mu + \psi\right)\left(d_3 + \psi\right)\left(k_1 x + d_5 d_6 + d_6 \psi\right),\\
y_2 &= d_6\left(d_4 + \mu + \psi\right)\\
&\quad \times \left(d_6 k_3\left(d_3 + \psi\right)\left(d_5 + \psi\right)\right.\\
&\quad \left. - \left(k_1 x + d_5 d_6 + d_6 \psi\right)(1-\Phi)\, q\beta_2 s_2\right),\\
y_3 &= \left(d_4 + \mu + \psi\right)\left(d_3 + \psi\right)(1-\Phi)\, d_3 d_6 q\beta_2 s_2.
\end{aligned} \tag{64}$$

We previously analysed the critical toxicity that would result in the same level of ALT in the blood as when no therapy is administered and found that this was a function of therapy efficacy. Our aim now is to identify the optimal toxic value ψ_{opt} of medication that would not lead to elevated alanine aminotransferase in the blood even if HIV remains endemic in the liver. We therefore compute ψ_{opt} as

$$\begin{aligned}
&d_6\left(d_4 + \mu + \psi_{\mathrm{opt}}\right)\left((1-\Phi)\, q\beta_2 s_2 I_{\mathrm{ha}}^+ + d_6 d_3 + \psi d_6\right)\\
&\quad \times \left(\left(d_4 + \psi_{\mathrm{opt}}\right)\left(d_6 - k_3 I_{\mathrm{ha}}^+\right) + k_2 x\right)\\
&\quad + \left(d_5 + \psi_{\mathrm{opt}}\right)\left(d_6 - k_3 I_{\mathrm{ha}}^+\right)(1-p)\\
&\quad \times (1-\Phi)\, q\beta_2 \lambda_2 d_6 s_2 I_{\mathrm{ha}}^+\\
&\quad + \left(d_6 - k_3 I_{\mathrm{ha}}^+\right)\left(d_4 + \mu + \psi_{\mathrm{opt}}\right)\lambda_2 d_6^2 \psi_c = 0.
\end{aligned} \tag{65}$$

Like our previous findings, system (65) also shows that the toxicity is a function of efficacy. Analytical solution of ψ_{opt} from (65) could not be easily obtained since it is also a function of I_{ha}^{+}. We therefore investigated for $A^{+} = 0$ when $I_{ha}^{+} = 0$. When $I_{ha}^{+} = 0$ then $d_6\psi_{opt}(d_4 + \mu)(d_4 + \mu + \psi_{opt}) = 0$. Since $(d_4 + \mu + \psi_{opt}) \neq 0$ and $(d_4 + \mu) \neq 0$ then the only possibility of having no elevated alanine aminotransferase in the blood when HIV is endemic in the liver and the infectious hepatocytes have been reduced to zero is when the medication is not toxic at all. This concurs with various researches that report high levels of liver enzyme in the blood due to toxic nature of all classes of antiretroviral drugs [11, 13–15].

3. Results

3.1. Numerical Simulation. In this section we present the numerical simulations of the model while both the therapeutic and toxic effects of the drugs are incorporated. Medications used in this study are listed in Table 1, while parameter values used in simulations are in Table 2. Parameter values used in calculation of therapeutic and toxic functions in (1) and (2) are shown in Table 1.

Simulating the dynamics of HIV in the liver, three cases were considered: (1) no treatment, (2) with treatment but without toxic effect of the drugs, and (3) with treatment plus toxic effect. Figure 2 depicts the results. Clearly, therapy reduced viral load resulting in fewer number of latent and infectious cells. In case of CD4+ cells, the medication consequently resulted into increased number of uninfected cells. Healthy CD4+ cells were many when the toxic therapy was administered as opposed to when it was not used. However, the dynamics were different in hepatocytes. When the toxic medication was administered, the number of uninfected cells was much less than when medication was not applied at all. This suggested that much as HIV infects hepatocytes, the rate of progression is slower in these types of cells as compared to CD4+ cells [20]. However, hepatocytes seemed to be more affected by toxicity than HIV infection. This was consequently seen in the level of enzymes in the blood that was a lot higher in the case of drug toxicity included than when it was not considered. However, these findings are subject to parameter values and our results are based on parameters in Tables 1 and 2.

The World Health Organisation recommends that antiretroviral therapy be used in combination of NRTIs together with NNRTIs or PIs [55]. This study considered three drugs from NRTIs, one drug from NNRTIs and two drugs from PIs. All combinations from the sample drugs were studied. It is further recommended that atazanavir (ATV) should be used with another PI in a PI-based regimen [55], so it was combined with nelfinavir (NFV). Therapeutic effect of the drugs was modeled using a Hill function as shown in (1). In NNRTI-based regimen, Figure 3 shows that 3TC + DDI + EFV gave the minimal viral load while AZT + d4T + EFV gave the maximal viral load. In PI-based combinations, Figure 4 shows that DDI + 3TC + ATV + NFV gave the least viral load and AZT + d4T + ATV + NFV gave the most. This would suggest that, within the parameter values in Table 2, among

Table 2: Parameters used in simulations.

Par.	Description	Value	Source
λ_1	Rate of creation of CD4+ cells from within the body	10 $(mL)^{-1}$	[36]
d_1	Natural death rate of uninfected CD4+ cells	0.01	[37]
q	Probability that HIV infects hepatocytes	0.2	Estimate
p	Probability that hepatocyte becomes productively infected	0.3	Estimate
μ	Rate at which latently infected hepatocytes become productive	0.006	Estimate
β_1	Rate of transmission of HIV in CD4+ cells	0.00015 $(mL)^{-1}$	[36]
x	Antigen-independent CTLs proliferation rate	20	[23]
k_1	Rate at which CTLs kill infectious CD4+ cells	50	[38]
k_2	Rate at which CTLs kill infectious hepatocytes	1	[21]
k_3	Antigen-dependent proliferation rate of CTLs	0.2	[39]
d_2	Death rate of infected CD4+ due to infection	0.5	[40]
λ_2	Rate of creation of hepatocytes from within the body	27200	[41]
d_3	Natural death rate of hepatocytes	0.002	[42]
β_2	Rate of transmission of HIV in hepatocytes	0.000015	Estimate
d_4	Death rate of latently infected hepatocytes	0.01	Estimate
d_5	Death rate of infectious hepatocytes	0.5	Estimate
d_6	Rate of clearance of CTLS by all means	0.15	[21]
s_1	Average rate of production of virions by an infected CD4+ cells	50,000	[43]
s_2	Average rate of production of virions by an infected hepatocyte	1000	Estimate
d_7	Death rate of HIV	2	[40]
m	Rate of production of virions from macrophages	5	[23]
N	Virions produced due to drug metabolism	100	Estimate
r	Natural enzyme elevation	14	[44]
d_8	Rate of clearance of ALT from blood system	0.25	[42]
k_4	Rate of generation of liver enzyme in the blood	2000	[42]

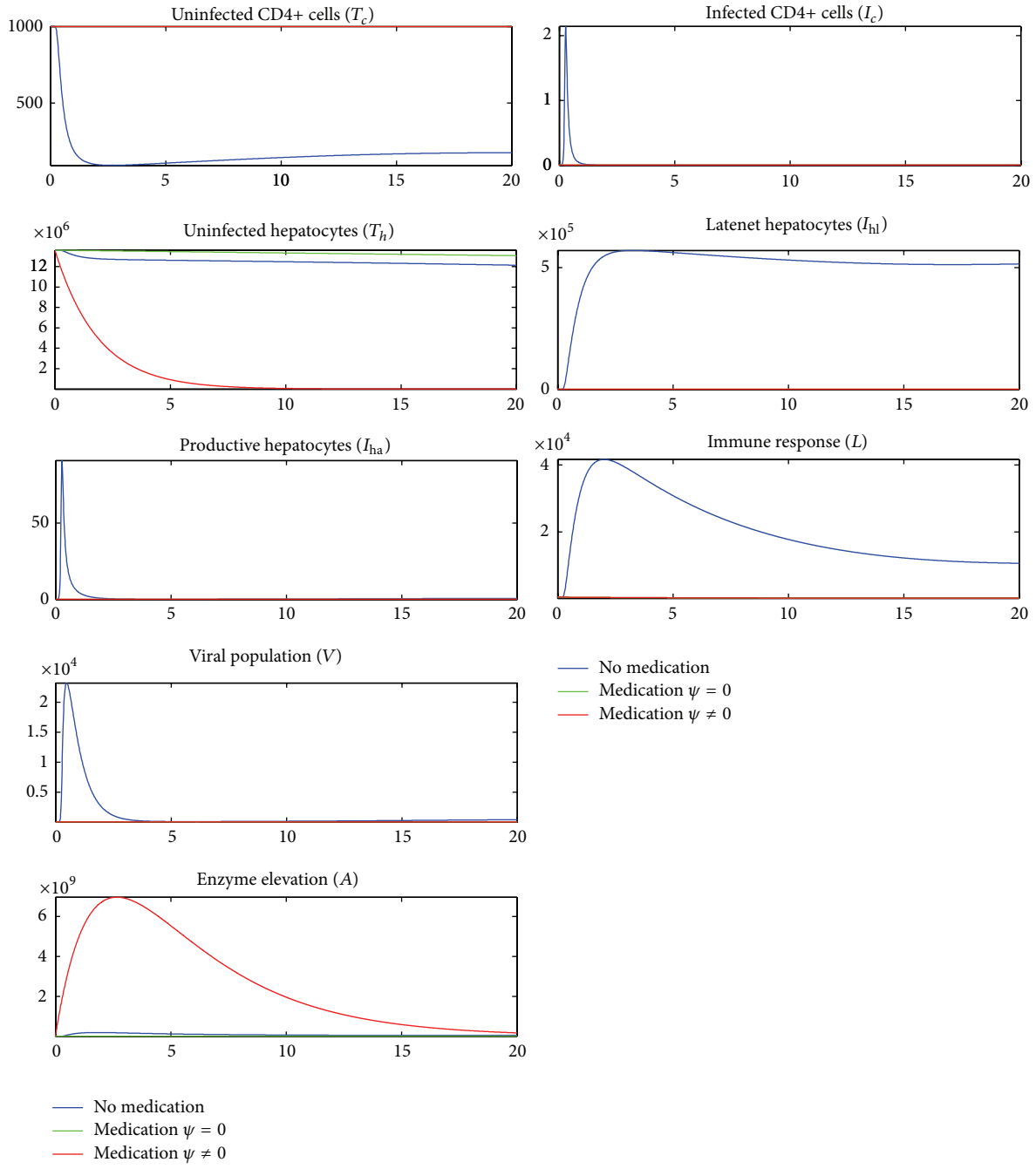

FIGURE 2: HIV infection dynamics with and without medication and with and without drug toxic effect. Horizontal axes represent time in days and parameter values are as shown in Table 2.

the baseline NRTIs studied, DDI + 3TC is the most efficacious and AZT + d4T is the least.

We compared Figures 2, 3, and 4 and established that the level of ALT in the blood when no medication was used was higher than the level of ALT when medication was used. This was contradicting with a number of researches [2–6], indicating that the use of ART increases the level of ALT in the blood stream.

All antiretrovirals are associated with some level of toxicity [5, 56]. During drug metabolism, the toxic nature of ART causes liver cells stress and consequently cell death. This study assumes that the lower the ALT level in the blood the less toxic the therapy. With toxic effect (2) incorporated in the model, simulation results are shown in Figure 5 for NNRTI-based regimen and Figure 6 for PI-based regimen.

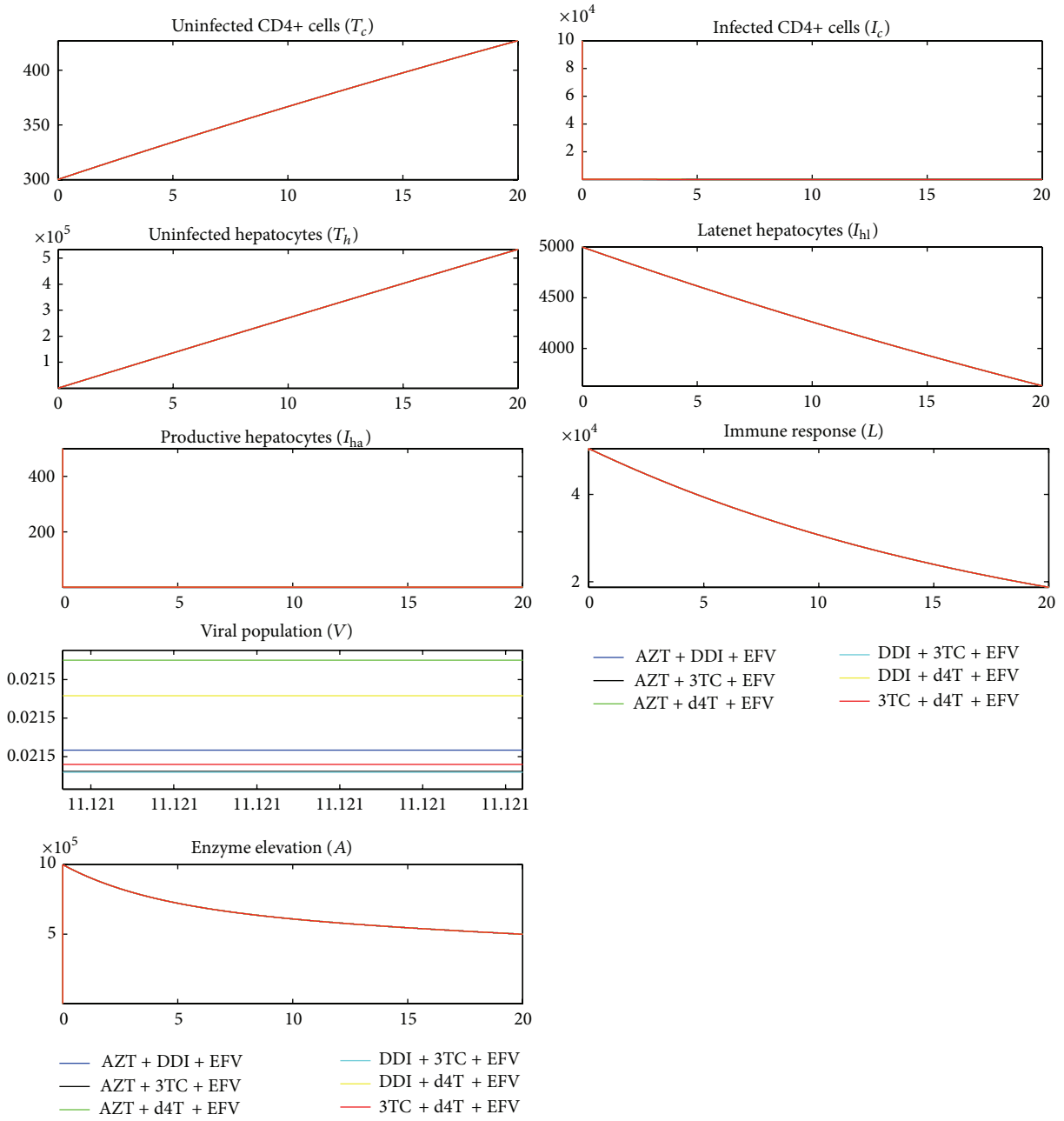

FIGURE 3: HIV infection dynamics when NNRTI-based regimen is administered without considering the toxic effect of the therapy. Horizontal axes represent time in days and parameter values are as shown in Table 2.

Comparing Figures 5 and 6 and their corresponding dynamics in toxic-free cases in Figures 3 and 4, respectively, it is noted that the level of ALT is highest in the former. It can also be noted that PI-based regimens are more toxic than NNRTI-based regimens among the studied drugs. In NNRT-based regimen, the least toxic combination was 3TC + DDI + EFV while AZT + d4T + EFV was the most toxic. In PI-based regimen, 3TC + DDI + ATV + NFV and AZT + d4T + ATV + NFV were the least and most toxic combinations, respectively. Combinations that contained 3TC were least toxic while combining d4T with either AZT or DDI made the combination toxic. This is consistent with a number of researches that assert that 3TC is the least toxic NRTI while d4T is the most toxic [18, 25, 48, 55, 57].

4. Discussion

Much as liver injury can occur solely due to HIV infection [7–10], liver related mortality and morbidity are being associated with the use of antiretroviral therapy, [2–6], because all antiretroviral therapy has some degree of toxicity, [15]. This study used a mathematical model with therapy efficacy as

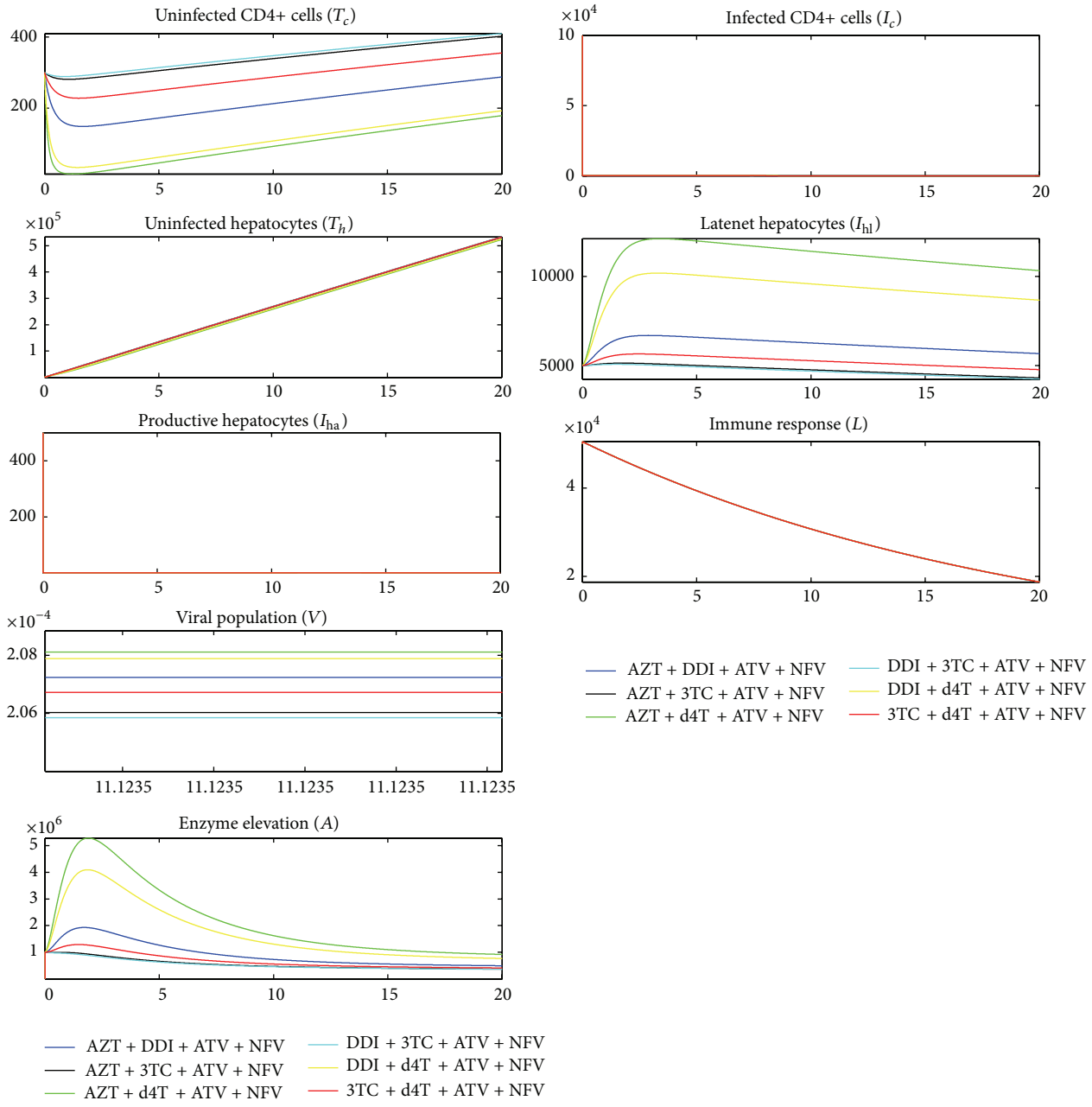

FIGURE 4: HIV infection dynamics when PI-based regimen is administered without considering the toxic function of the therapy. Horizontal axes represent time in days and parameter values are as shown in Table 2.

well as toxicity incorporated, to study various types of HIV drugs.

The study investigated for toxicity threshold between 0 and 1 inclusive, below which HIV infection in the liver can be controlled. Mathematical analysis showed that the critical toxicity threshold was a function of drug efficacy. The dependency of toxicity on efficacy would be due to the fact that both are dose-dependent [26, 28].

With parameter values as given in Table 2, without including the toxic effect of medication, in NNRTI-based regimen, the combination of DDI + 3TC that contained EFV gave the minimal viral load while the combination of AZT + d4T gave the maximum. In PI-based regimen, the combination of ATV + NFV + DDI + 3TC gave the least viral load while ATV + NFV + AZT + d4T gave the highest.

With toxicity incorporated and parameter values as in Table 2, in NNRTIs-based combinations, DDI + EFV + 3TC produced the minimal level of ALT, while including d4T + EFV + AZT gave maximal ALT level in the blood system. In PI-based regimen the most toxic combination was d4T + ATV + NFV + AZT while the least toxic was DDI + ATV + NFV + 3TC. Our findings are consistent with [24, 58],

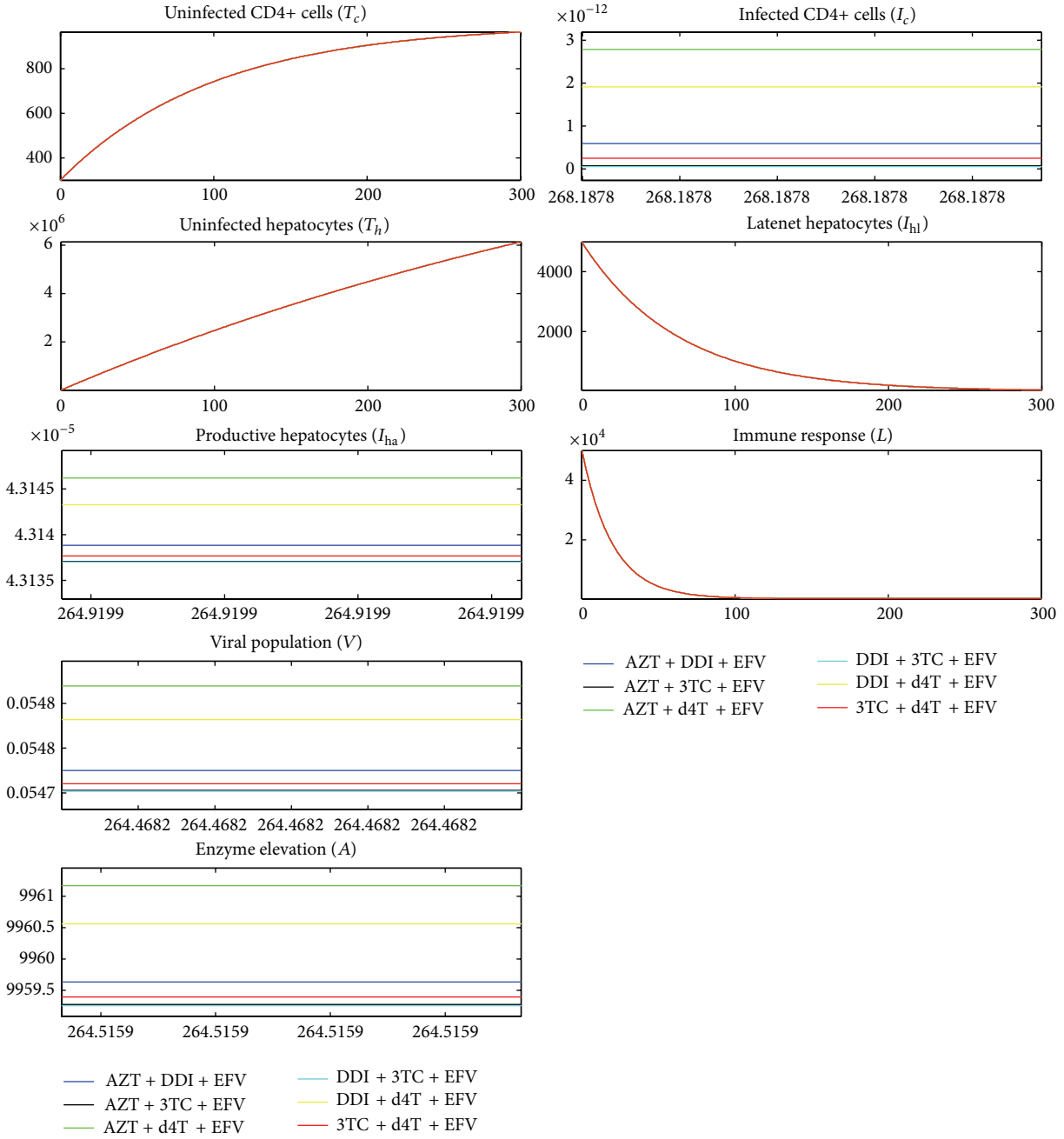

FIGURE 5: HIV infection dynamics when NNRTI-based regimen is administered with the toxic function of the therapy considered. Horizontal axes represent time in days and parameter values are as shown in Table 2.

who recommend that d4T should not be combined with AZT because the combination is highly toxic. PI-based regimens were found to be the most toxic and at the same time the best in reducing viral load in the liver as compared to NNRTI-based regimens [24, 25, 58].

5. Conclusion

The findings regarding toxic and therapeutic effects of NRTI drugs were consistent with the already existing literature. We therefore deduce that, with the drugs studied and parameter values used, the most toxic combination gave the highest viral load in the liver and vice versa. It is important to note that there was no variability in NNRTIs and PIs as a single drug from NNRTIs and same combination from PIs was used. The same method could possibly be used with various drugs in NNRI-based and PI-based regimens to explore the most therapeutic and toxic combinations in HIV therapy.

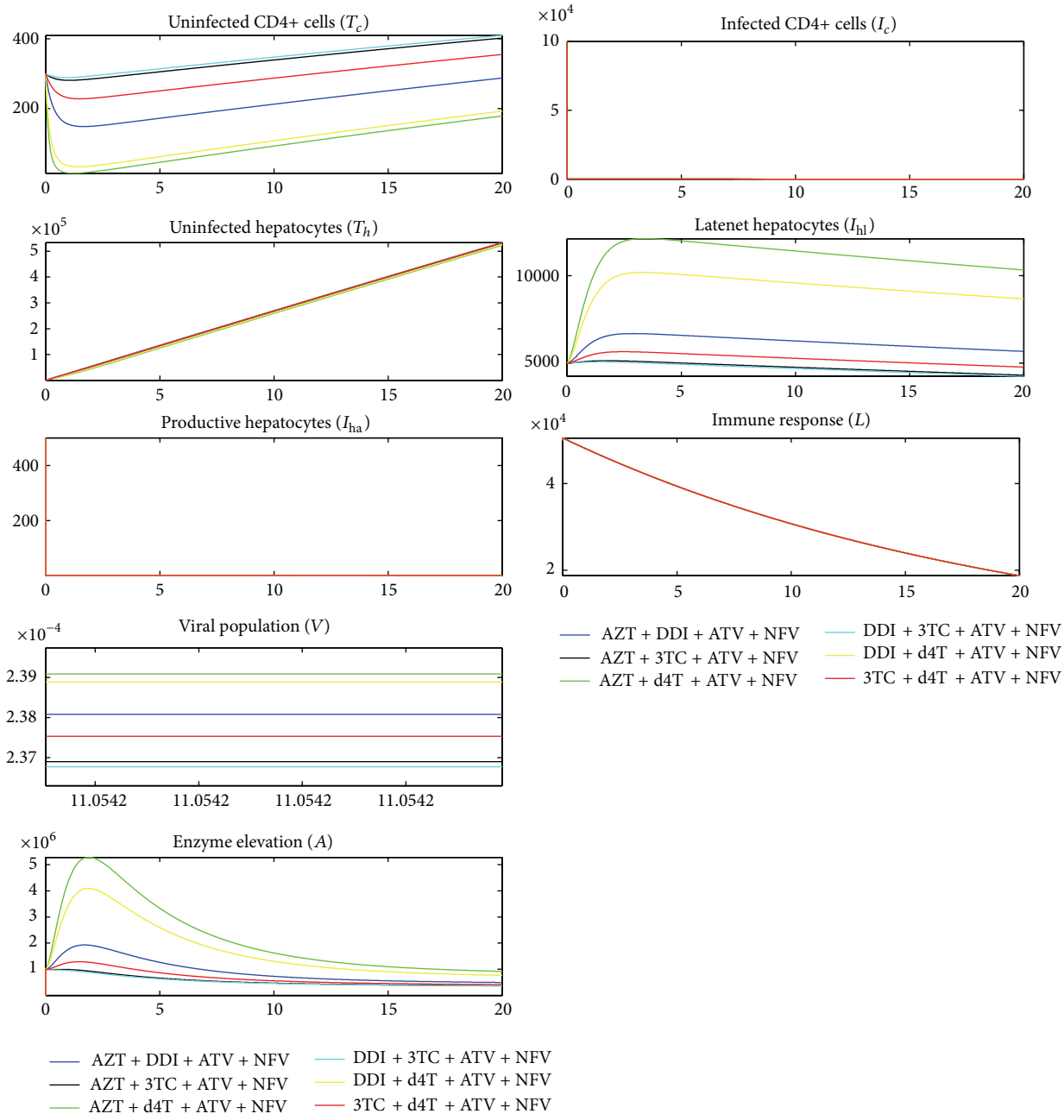

FIGURE 6: HIV infection dynamics when PI-based regimen is administered with the toxic function of the therapy considered. Horizontal axes represent time in days and parameter values are as shown in Table 2.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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