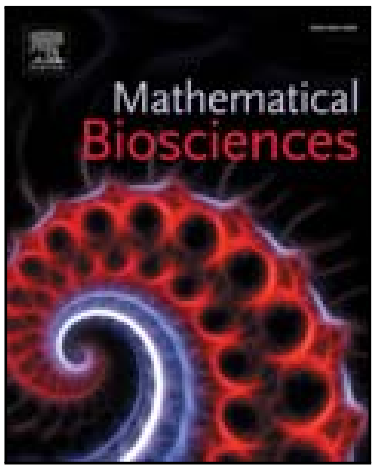

Modelling Hepatotoxicity and Antiretroviral Therapeutic effect in HIV/HBV Coinfection

Hasifa Nampala, Livingstone S. Luboobi, Joseph Y.T. Mugisha, Celestino Obua, Matylda Jablonska-Sabuka

PII: S0025-5564(17)30408-X
DOI: 10.1016/j.mbs.2018.05.012
Reference: MBS 8082

To appear in: *Mathematical Biosciences*

Received date: 24 July 2017
Revised date: 16 May 2018
Accepted date: 21 May 2018

Please cite this article as: Hasifa Nampala, Livingstone S. Luboobi, Joseph Y.T. Mugisha, Celestino Obua, Matylda Jablonska-Sabuka, Modelling Hepatotoxicity and Antiretroviral Therapeutic effect in HIV/HBV Coinfection, *Mathematical Biosciences* (2018), doi: 10.1016/j.mbs.2018.05.012

Highlights

- Emtricitabine, tenofovir and atazanavir is the most effective yet most toxic combination in treating HIV/HBV coinfection.
- Emtricitabine, tenofovir and lopinavir is least effective while lamivudine, tenofovir and lopinavir is least toxic
- Nevirapine is highly toxic yet less effective compared to efavirenz
- Optimal combination that balances toxicity and efficacy emtricitabine, tenofovir and efavirenz

Modelling Hepatotoxicity and Antiretroviral Therapeutic effect in HIV/HBV Coinfection

Hasifa Nampala[1a], Livingstone S. Luboobi[b], Joseph Y.T. Mugisha[b], Celestino Obua[c], Matylda Jablonska-Sabuka[d]

[a]*Department of Mathematics, Kyambogo University, p.o box 1 Kampala, Uganda*

[b]*Department of Mathematics, Makerere University, p.o box 7062 Kampala, Uganda*

[c]*Department of Pharmacology and Therapeutics, Makerere University, p.o box 7062, Kampala, Uganda*

[d]*Department of Mathematics and Physics, Lappeenranta University of Technology, Finland*

Abstract

Enzyme alanine aminotransferase (ALT) elevation which reflects hepatocellular injury is a current challenge in people infected with human immunodeficiency virus (HIV) on antiretroviral therapy (ART). One of the factors that enhance the risk of hepatotoxicity is underlying diseases such as hepatitis caused by hepatitis B virus (HBV). HIV/HBV coinfected patients stand a greater risk of hepatotoxicity because all ART are toxic and liver cells (hepatocytes) that are responsible for metabolising the toxic ART, support all stages of HIV and HBV viral production. Mathematical models coupled with numerical simulations are used in this study with the aim of investigating the optimal combination of ART in HIV/HBV coinfection. Emtricitabine, tenofovir and efavirenz is the optimal combination that maximises the therapeutic effect of therapy and minimises the toxic response to medication in HIV/HBV coinfection.

[1]corresponding author: hnampala@yahoo.co.uk

Keywords: HIV/HBV coinfection, hepatocytes, antiretroviral therapy, Liver enzyme elevation

1. Introduction

Worldwide, close to 10% of all people infected with Human Immunodeficiency Virus (HIV) are also chronically coinfected with hepatitis B virus (HBV) [1, 2, 3]. HBV alone is the leading cause of chronic liver disease and also the leading cause of death as it accounts for up to half of all cases of cirrhosis and hepatocellular carcinoma [4].

HBV and HIV have common routes of transmission and endemic areas, though HBV is about 100 times more infectious than HIV [3, 5]. HIV/HBV coinfection increases the morbidity and mortality beyond those caused by either infection alone [4]. Coinfection with HIV totaly changes the natural history of HBV infection with higher serum HBV DNA and higher rates of cirrhosis, especially in those with low CD4+ T cell counts [6].

There are few studies that have examined the interaction between HIV and HBV *in vitro*. However, it is assumed that HIV infection of human hepatocytes has contribution towards HBV viral life cycle [7]. In countries where antiretroviral therapy (ART) is now available, liver failure has emerged as a major cause of death in HIV-infected individuals [1].

Although, liver disease can occur solely due to HIV infection [8, 9, 10, 11], the use of ART has been highly associated with end stage liver disease in HIV/HBV coinfected people [12, 13]. According to Wit *et al.* [14], virtually every licensed antiretroviral drug has been associated with liver enzyme elevation. The complexity among HBV/HIV coinfected patients is enhanced by the choice of drugs, [3, 15], because the drug should have a dual antiviral activity towards both viruses.

Hepatocytes that are responsible for drug metabolism [16], support all stages of HIV and HBV production [10, 11, 17]. The role played by hepatocytes in handling toxic drug substances, makes them vulnerable to drug induced liver injury (hepatotoxicity) and consequently, cell death [16, 18, 19]. In their study, Powderly *et al.* [15] analyse a number of drugs used as therapy for HIV/HBV coinfection, including, Lamivudine and Tenofovir. They suggest that, since patients do not receive individual drugs but combinations, more attention needs to be paid to whether certain combinations carry a greater risk of liver toxicity, especially in HIV/HBV coinfected people.

Mathematical models have been used over the years, to inform medical epidemiologists and pubic health, of the interplay between variables that determine the course of the infection and the variables that control the pattern of infection, within an individual or communities of people. Stochastic and deterministic mathematical models such as Anderson *et al.* [20], Wodarz and Nowak, [21], Nowak and Bangham, [22], Perelson *et al.* [23], Nampala *et al.* [8], Gumel *et al.* [24], Nampala *et al.* [25], have been used to understand the dynamics of HIV and the immune system.

In order to understand the dynamics of HBV in the liver, the basic virus infection model (BVIM) of HBV, which considers mass action cell infection of the virus as well as constant recruitment of hepatocytes, was develpoed by Nowak *et al.* [17]. This model has been improved by a number of studies such as Su *et al.* [26], Ciupe *et al.* [27], Hattaf *et al.* [28], Colombatto *et al.* [29], Long *et al.* [30], Hews *et al.* [31], to either replace the constant recruitment by a logistic term or the mass action by standard incidence rate.

Much as HIV and HBV share the same means of transmission [3], and their co-existence is a current global burden, especially, with the use of ART [2], the immune dynamics of the coexistence has not yet attracted much attention from mathematical modellers. Although, Bowong *et al.* [32] studies

HIV/HBV dynamics on a population level, there is need to study the immunodynamics of the coinfection, since it has been and is still a challenge, especially after initiation of therapy.

In this study therefore, we develop a mathematical model and use numerical simulations to study the therapeutic as well as toxic effect of the currently used HIV/HBV therapy, and consequently derive an optimal combination in treating the coinfection. Hepatic necrosis (death of hepatocytes due to use of ART) is considered. Drugs under study include Emtricitabine (FTC), lamivudine (3TC) and tenofovir (TDF), as backbone of necleoside reverse transcriptase inhibitors (NRTI) [3]. These are combined with either efavirenz (EFV)/nevirapine (NVP) in non-necleoside reverse transcriptase inhibitors (NNRTI)-based regimen or with atazanavir (ATV)/lopinavir (LPV) in PI-based regimen.

2. Model development

The study assumes that at the instant of infection, a healthy cell cannot get simultaneously infected by both viruses. It gets infected with one virus at a time before it gets infected with the other. We further assume that much as the cytotoxic T lymphocytes (CTLs) are able to cure HBV in HBV-monoinfection, this does not happen in HIV/HBV coinfected cells. CTLs are considered to be multispecific, that is, they are able to attack cells infected by either virus [3]. When hepatocytes are destroyed by HIV, HBV or CTLs, enzyme alanine aminotransferase (ALT) is detected in the blood of HIV/HBV infected people. The value of ALT in the blood stream is generally taken to be an indicator of the liver cell damage [30]. We assume that the higher the ALT levels, the faster the progression of liver disease [33]. We also assume no latent infection in either type of cells due to the fact that coinfection changes the dynamics of either infection alone [3, 6, 34]. Apart from hepatocytes,

HIV production from all other liver cells and macrophages [35] are assumed to contribute least to the viral population [36], hence, they are ignored.

In the model formulation, we define ten variables as shown in Table 1.

Table 1: Variables for the HIV/HBV model.

Variable	Description
T_c	Activated CD4+ cells
I_c	Infectious CD4+ cells
T_h	Uninfected hepatocytes
I_{hH}	Hepatocytes infected by HIV
I_{hB}	Hepatocytes infected by HBV
I_{hBH}	Hepatocytes infected by both HIV and HBV
L	Cytotoxic T lymphocytes
V_H	HIV viral population
V_B	HBV viral population
A	Level of enzyme alanine aminotransferase (ALT) in the blood

The interaction between the variables in Table 1 is shown in the compartmental diagram in Figure 1.

Uninfected CD4+ cells are produced from within the bone marrow at rate λ_1 and are infected by HIV at an average rate β_{H1}. When HIV infects the liver, there is a probability (p) that it infects a hepatocyte and a probability $1-p$ that it infects a CD4+ cell. All CD4+ cells (healthy and infected) die naturally at rate d_1, infectious CD4+ cells die due to infection at rate d_2, where $d_2 > d_1$ and are killed by CTLs at rate k_1. Uninfected hepatocytes are produced from within the body at rate λ_2 and are infected by HIV and HBV at a rate β_{H2} and β_B respectively. All hepatocytes (healthy and infected) die naturally at a rate d_3. Hepatocytes infected by HBV are cured by CTLs at

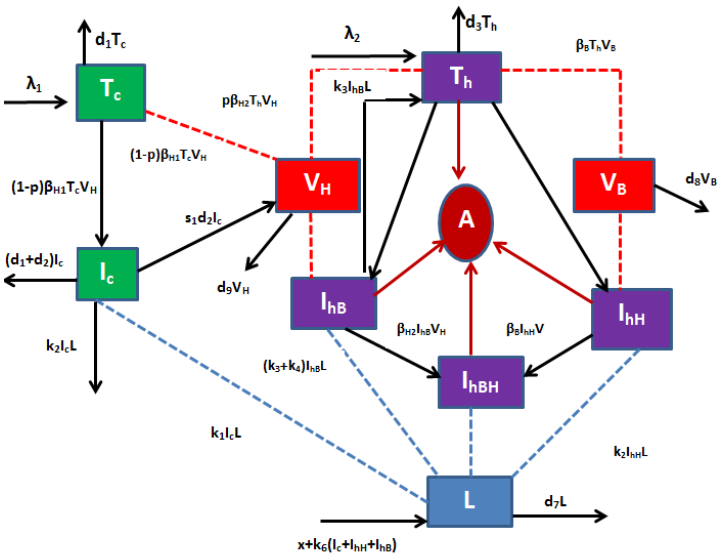

Figure 1: Compartmental diagram for within-host dynamics of HIV/HBV.

a rate k_3. Hepatocytes infected by only HIV die due to infection at a rate d_4, are killed by CTLs at a rate k_2 and are infected by HBV at a rate β_B. Hepatocytes infected by HBV are infected by HIV at rate β_{H2}, are killed by CTLs at rate k_4 and die due to infection at rate d_5. Hepatocytes dually infected by both HIV and HBV (I_{hBH}) die due to either infection at rate d_6 and are killed by CTLs at a rate k_5. The death rate of all infectious cells is the sum of natural and infection related death rates.

The interaction of CTLs (L) with infected cells is considered linear as in [22]. It is assumed that a fraction γ of the dually infected hepatocytes die due to HBV. CTLs proliferate naturally at rate x and due to infectious cells at rate k_6 and are cleared from the body at rate d_7. n_1 and n_2 are the number of hepatitis B virions produced by a single dying HBV monoinfected and HBV/HIV coinfected cells respectively. HBV is cleared from the body at rate d_8. Both hepatocytes and CD4+ cells support the last stage of HIV

production. Thus, HIV is produced from both HIV-infected hepatocytes and infected CD4+ cells. s_1, s_2 and s_3 are the numbers of HIV virions produced by a single dying HIV infected CD4+ cells, HIV monoinfected hepatocyte and HIV/HBV coinfected hepatocyte respectively. HIV virions are cleared naturally from the body at rate d_9. ALT (A) in the blood is contributed by infection-induced death of hepatocytes. k_7 is the average amount of ALT per hepatocyte and ALT is cleared from the blood naturally at rate d_{10}. We therefore have the following system of ordinary differential equations:

$$\frac{dT_c}{dt} = \lambda_1 - (1-p)\beta_{H1}T_cV_H - d_1T_c, \tag{2.1}$$

$$\frac{dI_c}{dt} = (1-p)\beta_{H1}T_cV_H - (d_1+d_2)I_c - k_1I_cL, \tag{2.2}$$

$$\frac{dT_h}{dt} = \lambda_2 - p\beta_{H2}T_hV_H - \beta_BT_hV_B - d_3T_h + k_3I_{hB}L, \tag{2.3}$$

$$\frac{dI_{hH}}{dt} = p\beta_{H2}T_hV_H - (d_3+d_4)I_{hH} - k_2I_{hH}L - \beta_BI_{hH}V_B, \tag{2.4}$$

$$\frac{dI_{hB}}{dt} = \beta_BT_hV_B - (d_3+d_5)I_{hB} - (k_3+k_4)I_{hB}L - \beta_{H2}I_{hB}V_H, \tag{2.5}$$

$$\frac{dI_{hBH}}{dt} = \beta_{H2}I_{hB}V_H + \beta_BI_{hH}V_B - (d_3+d_6)I_{hBH} - k_5I_{hBH}L, \tag{2.6}$$

$$\frac{dL}{dt} = x + k_6(I_c + I_{hH} + I_{hB} + I_{hBH})L - d_7L, \tag{2.7}$$

$$\frac{dV_B}{dt} = n_1d_5I_{hB} + n_2\gamma d_6I_{hBH} - d_8V_B, \tag{2.8}$$

$$\frac{dV_H}{dt} = s_1d_2I_c + s_2d_4I_{hH} + s_3(1-\gamma)d_6I_{hBH} - d_9V_H, \tag{2.9}$$

$$\frac{dA}{dt} = k_7(d_5I_{hB} + k_4I_{hB}L + d_6I_{hBH} + d_4I_{hH} + k_2I_{hH}L) - d_{10}A \tag{2.10}$$

Table 2: **Parameters values.**

Par	Description	Value	Source
λ_1	rate of creation of CD4+ from within the body	$10(ml)^{-1}$	[37]
p	probability that hepatocyte becomes productively infected	0.3	Estimate
β_{H1}	rate of transmission of HIV in CD4+	$0.00015(ml)^{-1}$	[37]
d_1	natural death rate of uninfected CD4+	$0.01(ml)^{-1}$	[38]
d_2	death rate of infected CD4+ due to HIV infection	$0.5(ml)^{-1}$	[21]
k_1	rate at which CTLs kill infectious CD4+	$50(ml)^{-1}$	[39]
λ_2	rate of creation of hepatocytes from within the body	$27200(ml)^{-1}$	[27]
β_{H2}	rate of transmission of HIV in hepatocytes	$1.0x10^{-8}(ml)^{-1}$	Estimate
β_B	rate of transmission of HBV in hepatocytes	$0.005(ml)^{-1}$	[30]
d_3	natural death rate of hepatocytes	$0.002(ml)^{-1}$	[30]
k_3	rate at which hepatocytes are cured of HBV by CTLs	$6000(ml)^{-1}$	[30]
d_4	death rate of hepatocytes due to HIV infection	$0.5(ml)^{-1}$	estimate
k_2	rate at which CTLs kill infectious hepatocytes	$50(ml)^{-1}$	estimate
d_5	death rate of hepatocytes due to HBV infection	$0.5(ml)^{-1}$	estimate
k_4	rate at which hepatocytes are killed by CTLs	$20(ml)^{-1}$	[30]
d_6	death rate of hepatocytes due to HIV/HBV coinfection	$0.15(ml)^{-1}$	estimate
k_5	rate at which coinfected hepatocytes are killed by CTLs	$10(ml)^{-1}$	estimate
x	antigen-independent CTLs proliferation rate	$10(ml)^{-1}$	[24]
k_6	antigen-dependent proliferation rate of CTLs	$0.25(ml)^{-1}$	[40]
d_7	rate of clearance of CTLS by all means	$0.05(ml)^{-1}$	[41]
n_1	average number HBV produced by a dying HBV infected hepatocyte	$204(ml)^{-1}$	[27]
n_2	average number HBV produced by a dying HIV/HBV infected hepatocyte	50	estimate
d_8	clearance rate of HBV	$0.67(ml)^{-1}$	[27]
s_1	average rate of production of virions by an infected CD4+	$50000(ml)^{-1}$	[42]
s_2	average rate of production of virions by an infected hepatocyte	$5000(ml)^{-1}$	Estimate
γ	fraction of HIB/HBV infected hepatocytes that die due to HBV	0.3	Estimate
d_9	death rate of HIV	$2(ml)^{-1}$	[21]
k_7	Average amount of ALT per hepatocyte	$2000(ml)^{-1}$	[30]
d_{10}	rate of clearance of ALT from blood system	$0.25(ml)^{-1}$	[30]

3. Model Analysis

3.1. Positivity and boundedness of solutions of HIV/HBV model

With initial conditions $T_{c0} > 0$, $I_{c0} > 0$, $T_{h0} > 0$, $I_{hH0} > 0$, $I_{hB0} > 0$, $I_{hBH0} > 0$ $L_0 > 0$, $V_{B0} > 0$, V_{H0} and $A_0 > 0$, the solutions for T_h, I_c, T_h, I_{hH}, I_{hB}, I_{hBH}, L, V_B, V_H and A respectively, remain positive and bounded provided $t > 0$. Take the total number of CD4+ cells be N_C and that of hepatocytes be N_H then

$$\frac{dN_C}{dt} = \frac{dT_c}{dt} + \frac{dI_c}{dt}$$

Thus

$$\begin{aligned} \frac{dN_C}{dt} &= \lambda_1 - d_1 N_C - k_1 I_c L - d_2 I_c - k_1 I_C L \\ &\leq \lambda_1 - d_1 N_C \end{aligned}$$

Since all parameters are considered positive, then

$$N_C < \frac{\lambda_1}{d_1} + (N_{C0} - \frac{\lambda_1}{d_1}) e^{-d_1 t}$$

Where N_{C0} is the number of CD4+ cells at the point of infection. When $N_{C0} > \frac{\lambda_1}{d_1}$ then as $t \to \infty$ then $N_C \to (\frac{\lambda_1}{d_1})^+$ and vice versa. Calculating the total number of hepatocytes (N_H)in the same way, it can be shown that

$$N_H < \frac{\lambda_2}{d_3} + (N_{H0} - \frac{\lambda_2}{d_3}) e^{-d_3 t}$$

where N_{H0} is the total number of hepatocytes at the time of infection.

Considering the number of CTLs,

$$\frac{dL}{dt} = x + k_6(I_c + I_{hH} + I_{hB} + I_{hBH})L - d_7 L$$

Assuming that $\frac{\lambda_1}{d_1} = \vartheta_1$ and $\frac{\lambda_2}{d_3} = \vartheta_2$, then hepatocytes are bounded by ϑ_2 and CD4+ cells are bounded by ϑ_1. Thus

$$\begin{aligned}
\frac{dL}{dt} &< x + k_6(\vartheta_1 + \vartheta_2)L - d_7 L \\
&< x - (d_7 - k_6\vartheta)L \\
L &< \frac{x}{d_7 - k_6\vartheta} + (L_0 - \frac{x}{d_7 - k_6\vartheta})e^{-(d_7 - k_6\vartheta)t}
\end{aligned}$$

given that $\vartheta = \vartheta_1 + \vartheta_2$. Where L_0 is the number of cytotoxic T lymphocytes when there is no infection in the liver. CTLs are bounded given that $d_7 > k_6\vartheta$

$$\begin{aligned}
\frac{dV_B}{dt} &= n_1 d_5 I_{hB} + n_2\gamma d_6 I_{hBH} - d_8 V_B \\
\frac{dV_B}{dt} &< n_1 d_5 \vartheta_2 + n_2\gamma d_6 \vartheta_2 - d_8 V_B \\
\frac{dV_B}{dt} &< (n_1 d_5 + n_2\gamma d_6)\vartheta_2 - d_8 V_B \\
\frac{dV_B}{dt} &< \eta - d_8 V_B \\
V_B &< \frac{\eta}{d_8} - (V_{B0} - \frac{\eta}{d_8})e^{-d_8 t}
\end{aligned}$$

where $\eta = (n_1 d_5 + n_2\gamma d_6)\vartheta_2$. Therefore V_B is bounded.

$$\begin{aligned}
\frac{dV_H}{dt} &= s_1 d_2 I_c + s_2 d_4 I_{hH} + s_3(1-\gamma)d_6 I_{hBH} - d_9 V_H \\
\frac{dV_H}{dt} &< s_1 d_2 \vartheta_1 + s_2 d_4 \vartheta_2 + s_3(1-\gamma)d_6\vartheta_2 - d_9 V_H \\
\frac{dV_H}{dt} &< \pi - d_9 V_H \\
V_H &< \frac{\pi}{d_9} - (V_{H0} - \frac{\pi}{d_9})e^{-d_9 t}
\end{aligned}$$

where $\pi = s_1 d_2 \vartheta_1 + s_2 d_4 \vartheta_2 + s_3(1-\gamma)d_6\vartheta_2$.

$$\frac{dA}{dt} = k_7(d_5 I_{hB} + k_4 I_{hB} L + d_6 I_{hBH} + d_4 I_{hH} + k_2 I_{hH} L) - d_{10} A$$

A is defined by bounded variables I_{hB}, L, I_{hBH} and I_{hH}, we can therefore deduce that it is also bounded by some ϑ_3 where $\vartheta_3 = max\{\vartheta_1, \vartheta_2, \vartheta\}$

We can therefore deduce that the feasible solutions of HIV/HBV model starting in the region Θ, stay and remain in the region, where

$$\begin{aligned}\Theta \;=\; & (T_c, I_c, T_h, I_{hH}, I_{hB}, I_{hBH}, L, V_B, V_H, A) \in R^{10} \\ & (T_c + I_c) < \frac{\lambda_1}{d_1}, (T_h + I_{hH} + I_{hB} + I_{hBH}) < \frac{\lambda_2}{d_2} \\ & L < \vartheta, V_B < \frac{\eta}{d_8}, V_H < \frac{\pi}{d_9}, A < \vartheta_3\}.\end{aligned}$$

3.2. Existence and stability analysis of disease-free equilibrium of HIV/HBV model

It is possible that both viruses may not exist in the liver ($V_B = V_H = 0$). In this case the model represented by a system of equations (A.7) - (A.13) to have a disease-free equilibrium (D_f) given by

$$D_f = (T_c, I_c, T_h, I_{hH}, I_{hB}, I_{hBH}, L, V_B, V_H, A) = (\lambda_1/d_1, 0, \lambda_2/d_3, 0, 0, 0, x/d_7, 0, 0, 0) \tag{3.1}$$

The basic reproductive number (R_0), can be calculated using the next generation method (Appendix A) as by [43] and is given as

$$R_0 = max\{R_0^H, R_0^B\}. \tag{3.2}$$

where $R_0^H = R_{0h}^H + R_{0c}^H$ and

$$\begin{aligned}R_0^B =& \frac{d_7\lambda_2\beta_B n_1 d_5}{d_3 d_8(d_3 d_7 + d_5 d_7 + k_4 x + k_3 x)}. \\ R_{0h}^H =& \frac{(1-p)d_7\lambda_2\beta_{H2}s_2 d_4}{d_3 d_9(d_3 d_7 + d_4 d_7 + k_2 x)} \\ R_{0c}^H =& \frac{p d_7\lambda_1\beta_{H1}s_1 d_2}{d_1 d_9(d_2 d_7 + d_1 d_7 + k_1 x)}\end{aligned}$$

R_0^B and R_0^H are basic reproduction numbers of HBV monoinfection and HIV monoinfection respectively. The basic reproduction number is the expected

number of secondary infections produced by one infected individual cell in a totally activated cell population. R_0 as computed using the next generation method is defined as the spectral radius of the next generation matrix. HIV and HBV infect cells independent of the existence of the other infection. Thus each virus has its own number of secondary infections. Considering that R_0 is a spectral radius and a threshold parameter, the highest number of secondary infections among the two has to be considered. Thus, during coinfection, the number of secondary infections of an infectious cell in a purely activated cell population, is equivalent to the number of secondary infections arising from the dominant virus, if it were to infect the cell in the absence of the second virus.

Clinically in any multiple infections, the predominant virus is the one that is symptomatically seen. Test results will show the coexisting infections, though the symptoms will not be visible. Thus the maximum effect observed is not the sum of the two or more infections but the one that predominates in its expression is the one that will be seen clinically.

Using Theorem 2 of van den Driessche and Watmough [43], we establish the following result

Theorem 1. *The disease-free equilibrium D_f is locally asymptotically stable when $R_0 < 1$ and unstable when $R_0 > 1$.*

3.3. Global stability of disease-free equilibrium of HIV/HBV coinfection.

To study the global behavior of system (A.7)-(A.13) we use a Theorem by [44] as shown in Appendix B.

Rewriting system (A.7)-(A.13) in the form of equation (B.1) we have

$$\begin{aligned} X &= (T_c, T_h, L, A), \\ Z &= (I_c, I_{hH}, I_{hB}, I_{hBH}, V_B, V_H), \end{aligned}$$

and

$$F(X,0) = \begin{bmatrix} \lambda_1 - d_1 T_c \\ \lambda_2 - d_3 T_h \\ x - d_7 L \\ -d_{10} A \end{bmatrix} \tag{3.3}$$

$M = D_Z G(X^*, 0)$ is given by

$$M = \begin{bmatrix} c_1 & 0 & 0 & 0 & 0 & \frac{(1-p)\beta_{H1}\lambda_1}{d_1} \\ 0 & c_2 & 0 & 0 & 0 & \frac{p\beta_{H2}\lambda_2}{d_3} \\ 0 & 0 & c_3 & 0 & \frac{\beta_B \lambda_2}{d_3} & 0 \\ 0 & 0 & 0 & c_4 & 0 & 0 \\ 0 & 0 & n_1 d_5 & n_2 \gamma d_6 & -d_8 & 0 \\ s_1 d_2 & s_2 d_4 & 0 & s_3(1-\gamma) d_6 & 0 & -d_9 \end{bmatrix}, \tag{3.4}$$

where
$c_1 = -d_1 - d_2 - \frac{k_1 x}{d_7}$, $c_2 = -d_3 - d_4 - \frac{k_2 x}{d_7}$, $c_3 = -d_3 - d_5 - \frac{(k_3+k_4)x}{d_7}$ and $c_4 = -d_3 - d_6 - \frac{k_5 x}{d_7}$.

$\hat{G}(X,Z)$ defined as $\hat{G}(X,Z) = MZ - G(X,Z)$ is given by

$$\hat{G}(X,Z) = \begin{bmatrix} \hat{G}_1(X,Z) \\ \hat{G}_2(X,Z) \\ \hat{G}_3(X,Z) \\ \hat{G}_4(X,Z) \\ \hat{G}_5(X,Z) \\ \hat{G}_6(X,Z) \end{bmatrix} = \begin{bmatrix} 0 \\ \beta_B I_{hH} V_B \\ \beta_{H2} I_{hB} V_H \\ -k_5 x I_{hBH} - \beta_{H2} I_{hB} V_H - \beta_B I_{hB} V_B \\ 0 \\ 0 \end{bmatrix}. \tag{3.5}$$

It can be seen that since $\hat{G}_4(X, Z) < 0$ then, $\hat{G}(X, Z) < 0$ and according to the second condition H(2) in Theorem B, the disease-free equilibrium may not be globally asymptotically stable.

However, if the system (A.7)-(A.13) is revised to exclude the coinfected hepatocytes (I_{hBH}), then we obtain

$$Z = (I_c, I_{hH}, I_{hB}, V_B, V_H)$$

from which we obtain the corresponding matrix A (X remains as above) and hence calculate $\hat{G}(X, Z)$ as

$$\hat{G}(X, Z) = \begin{bmatrix} 0 \\ \beta_B I_{hH} V_B \\ \beta_{H2} I_{hB} V_H \\ 0 \\ 0 \end{bmatrix}. \tag{3.6}$$

For this case $\hat{G}(X, Z) \geq 0$ hence we derive the following result

Theorem 2. *If there are no hepatocytes that are infected by both HIV and HBV at the same time, then the disease-free equilibrium of HIV/HBV coinfection is globally asymptotically stable.*

4. Sensitivity Analysis

According to Chitnis *et al.* [45], the transmission of a virus is directly related to the basic reproductive number. In order to ascertain the importance of each parameter to the basic reproductive number, we compute sensitivity indices of all the parameters in the model. Sensitivity indices will show how important each parameter is, in transmitting the viruses. A highly sensitive parameter should be carefully estimated because a small variation in that

parameter will lead to large quantitative changes and may even produce qualitatively different results. An insensitive parameter, on the other hand, does not require as much effort to estimate as a small variation in that parameter will not produce large changes to the quantity of interest. The normalized forward sensitivity index of a variable to a parameter is the ratio of the relative change in the variable to the relative change in the parameter [45]. That is,

$$\Upsilon_p^V = \frac{\partial V}{\partial p} \cdot \frac{p}{V} \tag{4.1}$$

where V is the variable and p is the parameter.

We derive the values of the sensitivity of R_0 to each of the 30 parameters in the model,using partial derivatives as in equation 4.1. Sensitivity indices are shown in Table 2. The parameters of interest will largely depend on the dominant virus. For example, if HIV is the dominant virus in the liver, then the parameters to be controlled will be those that will have large magnitudes in R_0^H [46].

From Table 3 it can be seen that if R_0 is dominated by HIV infection (R_0^H), the most sensitive parameters are the rate of hepatocytes cells recruitment (λ_2), the burst size of HIV-infected hepatocytes (s_2), the rate at which HIV infect hepatocytes cells (β_{H2}), the death rate of hepatocytes due to infection (d_4) and rate of clearance of CTLs (d_7), rate at which CTLs kill HIV infected hepatocytes (k_2), antigen-independent proliferation rate (x), natural death rate of hepatocytes (d_3). For example, increasing or decreasing λ_2 by 10% would result in a 9.997% increase or decrease in R_0. For parameters that have negative indices, it implies that R_0 decreases with increase in those parameters. Basing on negative indices in Table 3, it implies that, much as HIV infects both hepatocytes and CD4+ cells, during coinfection with HBV, the rate of progression of the disease largely depends on HIV dynamics in hepatocytes. This could possibly be due to the fact that both HIV and HBV

Table 3: Sensitivity indices of R_0^H and R_0^B to parameters of HIV/HBV model evaluated at parameter values given in Table 2.

Parameter (p)	$\Upsilon_p^{R_0^H}$	$\Upsilon_p^{R_0^B}$	Parameter (p)	$\Upsilon_p^{R_0^H}$	$\Upsilon_p^{R_0^B}$
λ_1	$3.1503 \cdot 10^{-4}$	0	x	-1	-0.001
p	-0.4281	0	k_6	0	0
β_{H1}	$3.1503 \cdot 10^{-4}$	0	d_7	0.9997	1
d_1	$-3.1503 \cdot 10^{-4}$	0	n_1	0	1
d_2	$3.1503 \cdot 10^{-4}$	0	n_2	0	0
k_1	$-3.1503 \cdot 10^{-4}$	0	d_8	0	-1
λ_2	0.9997	1	s_1	$3.1503 \cdot 10^{-4}$	0
β_{H2}	0.9997	0	s_2	0.9997	0
β_B	0	1	d_9	-1	0
d_3	-0.9997	-1	k_7	0	0
k_3	0	-0.9967	d_{10}	0	0
d_4	0.9996	0	s_3	0	0
k_4	0	-0.0033	k_2	-0.9996	0
d_6	0	0	d_5	0	1
k_5	0	0	γ	0	0

infect hepatocytes [9, 31]. If HIV progresses very fast in hepatocytes then the coinfection is enhanced, since there is enough evidence that HIV has a great impact on HBV progression [34].

However, if R_0 is dominated by HBV infection (R_0^B) then the most sensitive parameters include: rate of HBV infection (β_B), recruitment rate of hepatocytes (λ_2), the death rate of hepatocytes due to HBV infection (d_5), the burst size of hepatocyte due to HBV infection (n_1) and clearance rate of CTLs (d_7), the clearance rate of HBV (d_8), natural death rate of hepatocytes (d_3) and

the rate at which CTLs cure HBV-infected hepatocytes (k_3).

It can be seen that some parameters have no significance in reducing the basic reproductive number, regardless of whether it is dominated by either infection, these include antigen-dependent proliferation rate of CTLs (k_6), the number of HBV virions produced by an HIV/HBV coinfected hepatocyte (n_2), death rate of hepatocytes due to HIV/HBV coinfection (d_6), rate at which CTLs kill HIV/HBV coinfected hepatocytes (k_5), rate of generation of ALT from infected hepatocytes (k_7), rate of clearance of ALT (d_{10}), number of HIV virions produced by a single HIV/HBV coinfected hepatocytes (s_3) and the fraction of HIV/HBV coinfected hepatocytes that produce HBV virions (γ).

5. HIV/HBV coinfection model with antiretroviral therapy

The WHO [3], recommended drugs for first line regimens include 2NRTI + 1NNRT or 2NRTI +1PI, though the former is preferred . NRTI component include tenofovir (TDF) plus lamivudine (3TC) or emtricitabine (FTC), the NNRTI component include efavirenz (EFV) or nevirapine (NVP) and the PI component include atazanavir (ATV) or lopinavir (LPV).

TDF (combined with 3TC or FTC) is the most preferred drug since it is active against both HBV and HIV [3]. Wit *et al.* [14], recommend that as new antiretroviral agents become available, there is need for studies that compare the hepatotoxicity of antiretroviral agents, since the consequences are life-threatening. We therefore rewrite the system of equations (A.7)-(A.13) to include therapeutic and toxic effects of therapy.

The therapeutic function as given in Nampala *et al.* [25], is defined by

$$\phi = \frac{d^m}{d^m + IC_{50}^m} \tag{5.1}$$

where ϕ is the drug efficacy fraction, 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.

The toxic function as in Nampala *et al.* [47], is defined as

$$\psi = \frac{d^m}{d^m + TD_{50}^m} \tag{5.2}$$

ψ is the drug toxicity fraction, d is the drug dose in mg/kg, TD_{50} is the dose at which toxicity occurs in 50% of exposed cases and m is the gradient of the dose-response curve. Effectiveness of reverse transcriptase inhibitors and protease inhibitors are represented by drug efficacies ϕ_1 and ϕ_2 respectively.

With therapeutic and toxic functions as defined above and all the assumptions stated, we arrive at the following system of differential equations

$$\begin{aligned}
\frac{dT_c}{dt} &= \lambda_1 - (1-\phi_1)(1-p)\beta_{H1}T_cV_H - d_1T_c,\\
\frac{dI_c}{dt} &= (1-\phi_1)(1-p)\beta_{H1}T_cV_H - (d_1+d_2)I_c - k_1I_cL,\\
\frac{dT_h}{dt} &= \lambda_2 - (1-\phi_1)p\beta_{H2}T_hV_H - (1-\phi_1)\beta_BT_hV_B - d_3T_h + k_3I_{hB}L - \psi T_h,\\
\frac{dI_{hH}}{dt} &= (1-\phi_1)p\beta_{H2}T_hV_h - (d_3+d_4)I_{hH} - k_2I_{hH}L - (1-\phi_1)\beta_BI_{hH}V_B - \psi I_{hH},\\
\frac{dI_{hB}}{dt} &= (1-\phi_1)\beta_BT_hV_B - (d_3+d_5)I_{hB} - (k_3+k_4)I_{hB}L - (1-\phi_1)\beta_{H2}I_{hB}V_H - \psi I_{hB},\\
\frac{dI_{hBH}}{dt} &= (1-\phi_1)\beta_{H2}I_{hB}V_H + (1-\phi_1)\beta_BI_{hH}V_B - d_3I_{hBH} - \psi I_{hBH},\\
\frac{dL}{dt} &= x + k_6(I_c + I_{hH} + I_{hB})L - d_7L,\\
\frac{dV_B}{dt} &= (1-\phi_2)n_1d_5I_{hB} - d_8V_B,\\
\frac{dV_H}{dt} &= (1-\phi_2)s_1d_2I_c + (1-\phi_2)s_2d_4I_{hH} - d_9V_H,\\
\frac{dA}{dt} &= k_7(d_5I_{hB} + k_4I_{hB}L + +d_4I_{hH} + k_2I_{hH}L + \psi(T_h + I_{hH} + I_{hB} + I_{hBH})) - d_{10}A.
\end{aligned}$$

6. Numerical simulations of HIV/HBV coinfection

Numerical simulations are used to assess the dynamics of the coinfection and parameter values used are as shown in Tables 2, 4, 5 and 6

Table 4: Dosage of ART in micro moles and mg/kg as used in efficacy and toxic equations respectively.

Medication	d [μ M]	dose [mg/kg]	Reference
Lamivudine (3TC)	21.8105	5	[48], [49]
Emtricitabine (FTC)	13.347	3.3333	[48],[50]
Tenofovir (TDF)	7.8676	5	[48],[51]
Efavirenz (EFV)	31.67767	10	[48],[52]
Nevirapine (NVP)	12.5171	3.3333	[48],[53]
Atazanavir (ATV)	7.0932	5	[48],[54]
Lopinavir (LPV)	10.496	6.6667	[48],[55]

Table 5: Gradient (m) and IC_{50} as used in efficacy and toxic equations.

Medication	m	IC_{50} [μM]	Reference
Lamivudine (3TC)	1.15	0.1823	[56]
Emtricitabine (FTC)	1.18	0.0074	[56]
Tenofovir (TDF)	0.97	0.1684	[56]
Efavirenz (EFV)	1.69	0.0054	[56]
Nevirapine (NVP)	1.55	0.0814	[56]
Atazanavir (ATV)	2.69	0.0136	[56]
Lopinavir (LPV)	2.05	0.0358	[56]

Figure 2 shows the impact of coinfection on the dynamics of the immune response and the level of ALT in the blood system. During coinfection, there

Table 6: TD_{50} as used in toxic equation.

Medication	TD_{50} [mg/kg]	Reference
Lamivudine (3TC)	39.102	[57],[58]
Emtricitabine (FTC)	65.04	[59],[58]
Tenofovir (TDF)	25	[60],[58]
Efavirenz (EFV)	17	[61],[58]
Nevirapine (NVP)	30.4878	[62],[58]
Atazanavir (ATV)	60	[63],[58]
Lopinavir (LPV)	33.333	[64],[58]

is high demand for immune activity, thus, there is higher proliferation rate of CTLs than during monoinfection. With monoinfection, as shown in Figure 2, there are more immune cells during HBV infection than HIV infection. This confirms that HBV stimulates immune response more than HIV, because HBV is more infectious than HIV [5].

Figure 2 also shows that during monoinfection, the level of ALT is higher during HIV than HBV infection. HIV infects both hepatocytes and CD4+ cells [11] unlike HBV that infects only hepatocytes [65]. This results in higher HIV load and consequently more infected hepatocytes, hence higher ALT. During coinfection however, the level of ALT is higher than either monoinfection throughout the infection period.

We assume that when HIV/HBV medication is used in combination, the additive drug interaction yield a synergetic efficacy [66]. Steady state conditions are considered.

Wit *et, al* [14], state that 3TC and FTC have the same efficacy, yet [67] argue that 3TC + FTC have low additive antiviral activity, thus, they should not be used together. However, we still analysed the combination on the assumption

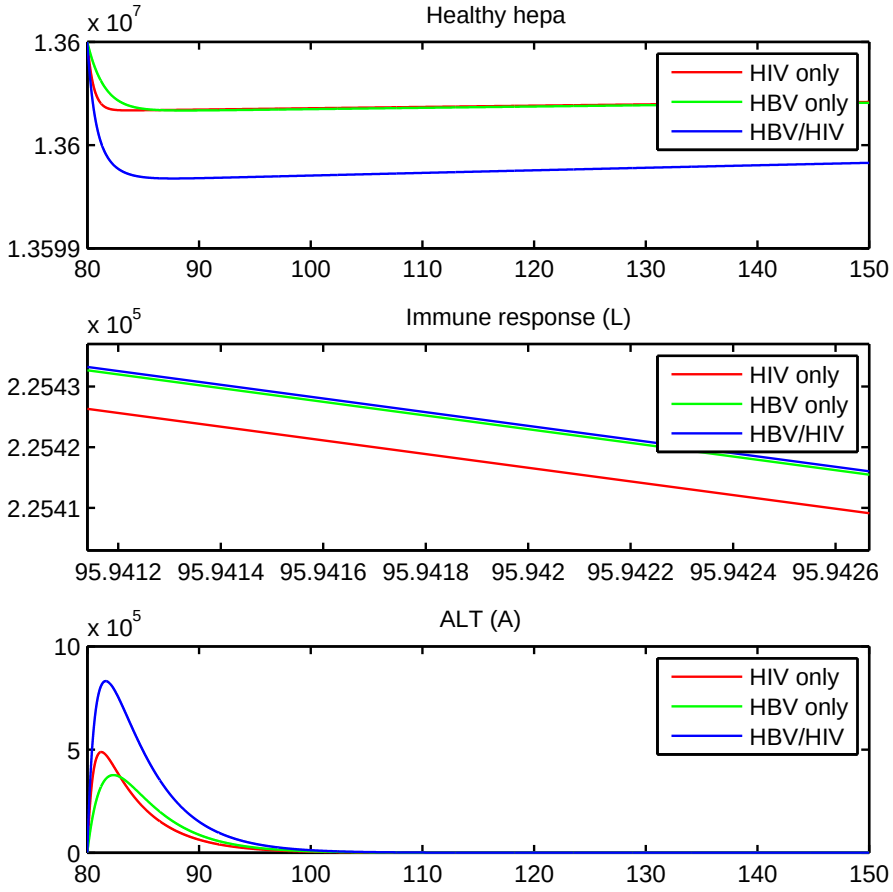

Figure 2: Impact of coinfection on immune system and ALT level in the absence of therapy. Vertical axes represent variables while the horizontal ones represent time in days. Parameter values are as shown in Table 2

that their additive toxicity might not be equally low or high.

In PI-based regimen, simulation results in Figures 4 show that the combination of 3TC and FTC together with either ATV or LPV indeed have nearly the same effect in controlling HBV load, however, it is not same for HIV

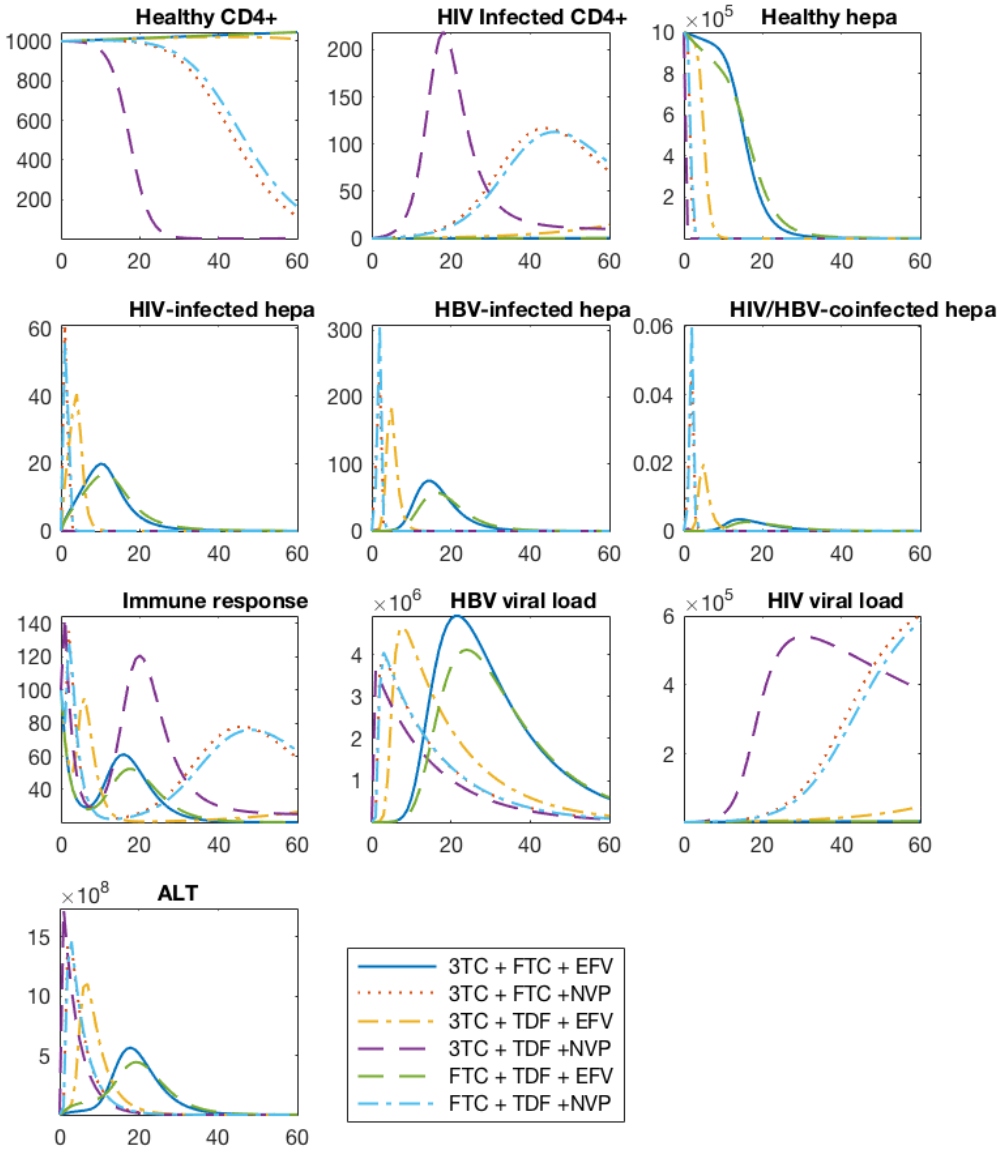

Figure 3: HIV/HBV coinfection dynamics when NNRTI-based regimen is administered with toxic effect of the therapy incorporated. Parameter values are as shown in Table 2.

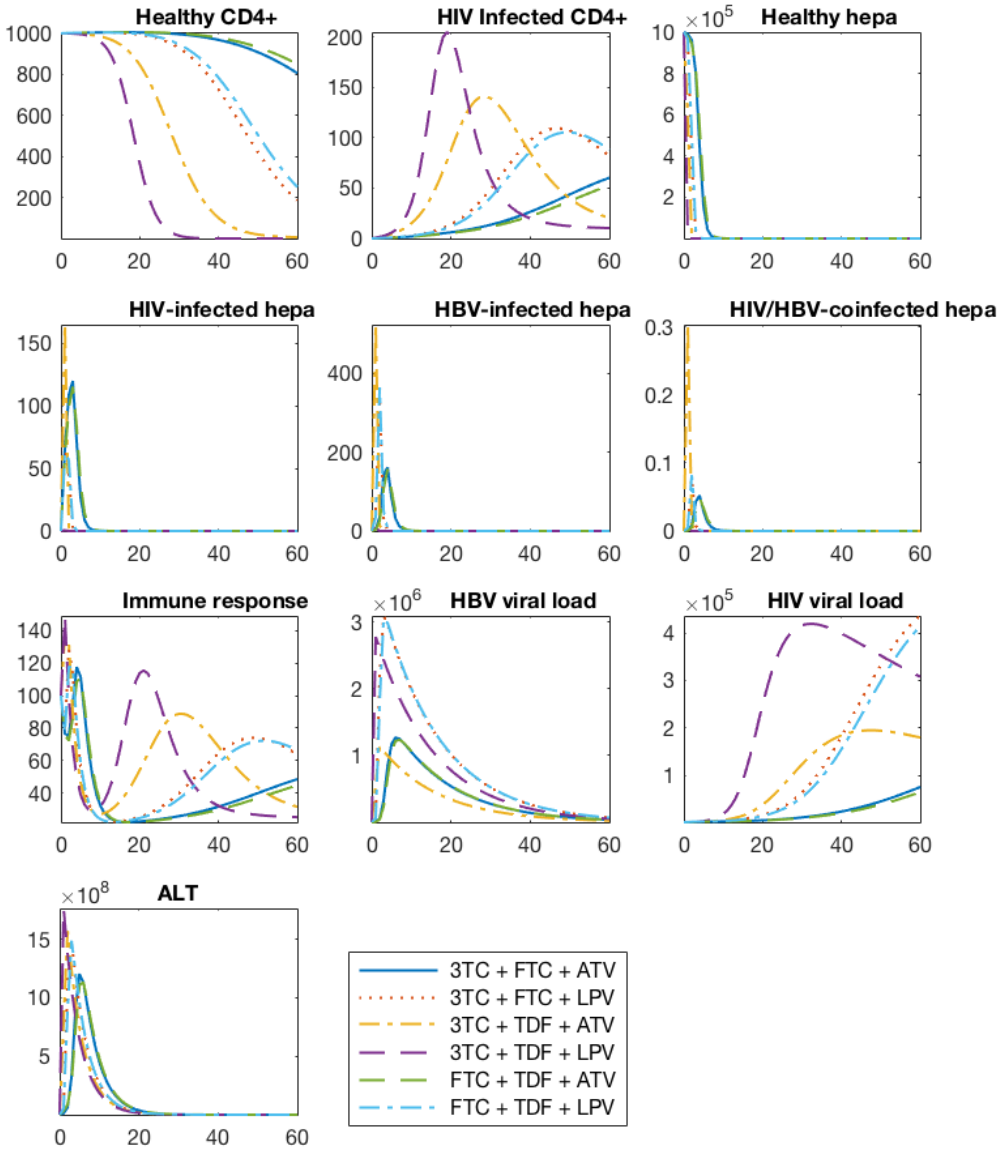

Figure 4: HIV/HBV coinfection dynamics when PI-based regimen is administered with toxic effect of the therapy incorporated. Parameter values are as shown in Table 2.

load. On the other hand, combining the two lead to a higher HBV load (due to low antiviral activity, [67]), though, this is not the case for HIV load.

If we consider that FTC and 3TC should not be combined, the combination of TDF and ATV is best in reducing the viral load, though 3TC works better for HBV while FTC is good for HIV. The combination that gives low HIV levels also results in low HIV infected hepatocytes and consequently higher uninfected CD4+ cells, though, it does not give the lowest infected CD4+ cells. However in HBV, the combination that gives the lowest HBV load does not give the lowest HBV infected hepatocytes or highest healthy hepatocytes. This would be due to the fact that the existence of HIV changes the dynamics of HBV [14]. For either virus, ATV has better efficacy than LPV when combined with the same NRTIs. Despite the low additive efficacy of 3TC combined with FTC, if combined with ATV, the efficacy is stronger than other NRTIs combined with LPV. The most effective combination in reducing HIV viral load is FTC + TDF + ATV, while 3TC+ FTC + ATV is best for HBV viral load.

The level of toxicity of various ART combinations were assessed by the level of enzyme alanine aminotransferase in the blood system [68]. Much as 3TC and FTC have the same antiviral activity, their toxic effects are not so close. Simulation results also indicate that the combination of FTC + TDF + ATV is the most toxic while 3TC + TDF + LPV is the least toxic in PI-based regimen.

In NNRTI-based regimens, simulation results in Figure 3 (zoomed), show that NVP is more effective than EFV in reducing HBV while the reverse is true for HIV. 3TV+TDF+NVP is the most effective in reducing HBV load while FTC+TDF+EFV is best in reducing HIV load. The most toxic combination is FTC+TDF+EFV.

The combination that gives high HBV load consequently lead to high HBV infected hepatocytes, however, the same combination gives the highest healthy heaptocytes. On the other hand the combination that gives the highest HIV load, does not give the highest number of HIV infected CD4+ cells or HIV infected hepatocytes, neither does it give the lowest healthy CD4+ cells. This is an indication that there is no straightforward approach to obtaining the best combination that will give the least viral load and consequently the improved number of healthy cell. We thus investigate the optimal solution that will give a reduction in the number of infected cells while reducing on the level of alanine aminotransferase.

7. Optimisation

We investigate the optimal combination that will maximize the the improvement that medication brings to the users while side effects (hepatotoxicity) are considered. Numerical simulations have shown that the level of ALT in the blood during medication is less than the level of ALT when no medication is used. This is due to the reduction in the number of cells that die due to infection.

The optimal goal is to maximize the percentage reduction in the number of HIV-infected hepatocytes, HBV-infected hepatocytes and the level of ALT in the blood, as a result of using ART. CD4+ cells are ignored because they have no direct contribution to the level of ALT in the blood. We suppose that

$$\begin{aligned} I_{hH}(imprv) &= \left|\frac{I_{hH}(tr) - I_{hH}(Notr)}{I_{hH}(Notr)}\right|, \\ I_{hB}(imprv) &= \left|\frac{I_{hB}(tr) - I_{hB}(Notr)}{I_{hB}(Notr)}\right|, \\ A(imprv) &= \left|\frac{A(tr) - A(Notr)}{A(Notr)}\right|. \end{aligned}$$

Optimal Goal

$$\max\{I_{hH}(imprv) + I_{hB}(imprv) + A(imprv)\},$$

where $I_{hH}(imprv)$, $I_{hB}(imprv)$ and $A(imprv)$ are percentage reduction in HIV-infected hepatocytes, HBV-infected hepatocytes and ALT respectively, due to the use of therapy. $I_{hH}(tr)$, $I_{hB}(tr)$ and $A(tr)$ are the numbers of HIV-infected hepatocytes, HBV-infected hepatocytes and the level of ALT respectively, when therapy is used. $I_{hH}(Notr)$, $I_{hB}(Notr)$ and $A(Notr)$ are the numbers of HIV-infected hepatocytes, HBV-infected hepatocytes and the level of ALT respectively, when therapy is not used.

Steady state conditions were obtained after 30 days of therapy. The optimal combination that gives the maximum improvement in the liver in 30 days of using therapy is shown in Table 7.

From Table 7, it can be seen that the most optimal combination that gives the highest percentage improvement in liver cells due to use of therapy is FTC+TDF+EFV. This can also be verified in Figure 5, which shows the improvement ratio achieved by a particular combination over time (computed for the period 60-365 days marked on the x-axis). It is seen that if we assume 3TC and FTC should not be combined [69], then FTC +TDF +EFV gives the best percentage improvement in the NNRTI regimen while FTC+TDF+ATV is the best in PIs regimen.

8. Discussion

The aim of this study was to find the most toxic and least toxic combination among HIV/HBV coinfection medication and consequently, investigate the optimal combination in treating the coinfection.

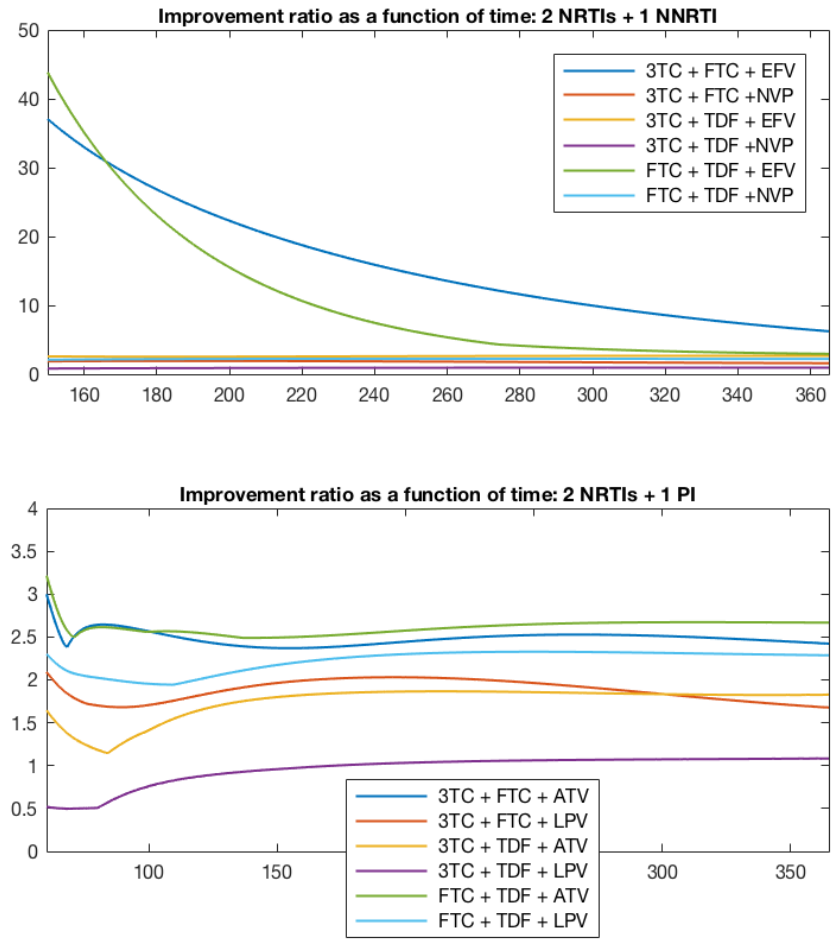

Figure 5: Improvement ratio achieved by all the combinations over time, with NNRTI-based regimen (top panel) and PI-based regimen (bottom panel). The x-axis denotes days.

Table 7: Percentage improvement in infectious hepatocytes and level of ALT due to the use of therapy.

Combination	Percentage improvement
3TC+FTC+EFV	6.6997
3TC+FTC+NVP	5.4054
3TC+TDF+EFV	4.0214
3TC+TDF+NVP	5.6728
FTC+TDF+EFV	18.0286
FTC+TDF+NVP	2.5096
3TC+FTC+ATV	2.7236
3TC+FTC+LPV	2.6489
3TC+TDF+ATV	6.8050
3TC+TDF+LPV	2.7417
FTC+TDF+ATV	2.7086
FTC+TDF+LPV	2.7279

Disease-free equilibrium of the HIV/HBV model was locally asymptotically stable when the basic reproduction number was below unity and unstable when above unity. However, the disease-free equilibrium was globally asymptotically stable only if there are no hepatocytes that are coinfected with both viruses at the same time. Global stability depends on the number of cells that were infected by the first virus before the second would infect them.

After inclusion of therapy, our findings to some extent concur with [67] generally, that 3TC+FTC have a low additive efficacy as their combination gives the highest HBV load. 3TC + FTC + NVP gives the highest HIV viral load in NNRTI-based regime. In PI-based regimen 3TC+FTC+LPV give the highest HIV and HBV viral load. 3TC+FTC is much better when combined with ATV than with LPV. Much as the combination has a low additive

efficacy, it is less toxic than most other combinations.

The combinations that are most effective in reducing HBV load are not equally good in reducing HIV load. This implies that both virus respond differently to different antiretroviral drugs. At the same time, the low viral load does not consequently result in the low number of infected cells as well as higher healthy cells. It further suggests that the existence of two virus in the liver changes the pathogenesis of either virus. The least effective combination does not also imply high toxicities, in other words the level of ALT in the blood is not inversely proportional to effectiveness of the drug. Thus different drugs carry different toxicities regardless of their effectiveness.

The simulations were also rerun with the most sensitive estimate parameters to verify their influence on the model. It turns out that it influenced the speed of infection in various ways but did not change the order of the combinations' performance.

9. Conclusion

With HIV/HBV/ART co-existence, the study shows that 3TC +TDF is the best baseline NRTI for HBV while FTC+TDF is best for HIV in either regimen. The combination that is most effective in reducing HIV load is at the same time the most toxic in either regimen. PIs are more effective in reducing HIV and HBV load in the liver. Generally, NVP was highly toxic while EFV was highly efficacious in reducing HIV/HBV load in the liver. The therapy that is so good in reducing HIV load is the one that is most toxic. The drug combination that optimizes efficacy and toxicity in HIV/HBV coinfection was FTC+ TDF + EFV.

References

[1] G. Matthews, E. Seaberg, G. Dore, S. Bowden, S. Lewin, J. Sasadeusz, P. Marks, Z. Goodman, F. Philp, Y. Tang, L. Stephen, C. Thio, Combination HBV therapy is linked to greater HBV DNA suppression in a cohort of lamivudine-experienced HIV/HBV coinfected individuals., *NIH Public Access* 23 (13) (2009) 1707–1715.

[2] AIDSinfo, Side effects of anti-HIV medication: Health information for patients; US department of health and human services., *http://aidsinfo.nih.gov/ContentFiles/SideEffectAnitHIVMeds_cbrochure_en.pdf.*

[3] WHO, Management of hepatitis b and hiv coinfection., *Clinical Protocol for the WHO European Region* 7.

[4] A. Kourtis, M. Bulterys, D. Hu, D. Jamieson, HIV-HBV coinfection - A global challenge, *The New England Journal of Medicine* 366 (19).

[5] M. Puoti, D. Manno, P. Nasta, G. Carosi, Hepatitis B virus and HIV coinfection in low-income countries: Unmet needs, *Clinical Infectious Diseases* 46 (2008) 367–369.

[6] S. Lewin, R. Ribeiro, A. Avihingsanon, S. Bowden, G. Matthews, P. Marks, S. Locarnini, K. Ruxrungtham, A. Perelson, G. Dore, Viral dynamics of hepatitis B virus (HBV) DNA in HIV-1-HBV coinfected individuals: similar effectiveness of lamivudine, tenofovir or combination therapy, *Clinical Infectious Diseases* 46 (2008) 367–369.

[7] D. Iser, N. Warner, P. Revill, A. Solomon, F. Wightman, S. Saleh, M. Crane, P. Cameron, S. Bowden, T. Nguyen, C. Pereira, P. Desmond, S. Locarnini, S. Lewin, Coinfection of hepatic cell lines with human immunodeficiency virus and hepatitis B virus leads to an increase in

intracellular hepatitis B surface antigen, *Journal of Virology* 84 (12) (2010) 5860–5867.

[8] H. Nampala, L. Luboobi, J. Mugisha, C. Obua, Mathematical modeling of liver enzyme elevation in HIV mono-infection., *Mathematical Biosciences* 242 (2013) 77–85.

[9] P. Xiao, O. Usamia, Y. Suzuki, H. Ling, N. Shimizu, H. Hoshino, M. Zhuang, Y. Ashino, H. Gu, T. Hattori, Characterization of a CD4-independent clinical HIV-1 that can efficiently infect human hepatocytes through chemokine (C-X-C motif) receptor 4., *AIDS* 22 (2008) 1749–1757.

[10] J. Blackard, K. Sherman, HCV/HIV co-infection: Time to re-evaluate the role of HIV in the liver?, *Journal of Viral Hepatitis* 15 (2008) 323–330.

[11] M. Crane, K. Visvanathan, S. Lewin, HIV Infection and TLR Signalling in the liver., *Gastroenterology Research and Practice* 2012.

[12] M. Landrum, A. Fieberg, H. Chun, N. Crum-Cianflone, V. Marconi, A. Weintrob, A. Ganesan, R. Barthel, G. Wortmann, , B. Agan, The effect of Human Immunodeficiency Virus on Hepatitis B Virus Serologic Status in Co-Infected Adults., *PLoS ONE* 5 (1).

[13] A. Balagopal, S. Ray, R. De Oca, C. Sutcliffe, P. Vivekanandan, Y. Higgins, S. Mehta, R. Moore, M. Sulkowski, D. Thomas, M. Torbenson, Kupffer cells are depleted with HIV immunodeficiency and partially recovered with antiretroviral immunereconstitution:, *AIDS* 23 (18) (2009) 2397–2404.

[14] F. Wit, G. Weverling, J. Weel, S. Jurriaans, J. Lange, Incidence of and risk factors for severe hepatotoxicity associated with antiretroviral

combination therapy, *The Journal of Infectious Diseases* 186 (2002) 23–31.

[15] W. Powderly, Antiretroviral Therapy in Patients with Hepatitis and HIV: Weighing Risks and Benefits., *Clinical Infectious Diseases* 38 (2) (2004) 109–113.

[16] C. Liddle, C. Stedman, Hepatic metabolism of drugs, Wiley-Blackwell and GastroHep.com, 2007, pp. 241–249.

[17] M. Nowak, S. Bonhoeffer, M. Hill, R. Boehme, H. Thomas, Viral dynamics in hepatitis b virus infection., *Proceedings of the National Academy of Sciences of the United States of America* 93 (1996) 4398–4402.

[18] N. Hewitt, Primary hepatocytes: current understanding of the regulation of metabolic enzymes and transporter proteins, and pharmaceutical practice for the use of hepatocytes in metabolism, enzyme induction, transporter, clearance, and hepatotoxicity studies., *Drug Metabolism Reviews* 39 (2007) 159–234.

[19] H. Malhi, M. Guicciardi, G. Gores, Hepatocyte death: A clear and present danger., *Physiology Review* 90 (2010) 1165–1194.

[20] B. Anderson, J. Jackson, M. Sitharam, Descartes's Rule of Signs Revisited., *American Mathematical Monthly* 105 (5) (1998) 447–451.

[21] D. Wodarz, M. Nowak, Immune responses and viral phenotype: Do replication rate and cytopathogenicity influence virus load?, *Journal of Theorerical Medicine* 2 (1999) 113–127.

[22] M. Nowak, C. Bangham, Population Dynamics of Immune Responses to Persistent Viruses., *Science* 272 (5258) (1996) 74–79.

[23] A. Perelson, D. Kischner, R. de Boer, Dynamics of HIV infections of CD4 T cells., *Mathematical Biosciences* 114 (1993) 81–125.

[24] A. Gumel, X.-W. Zhang, P. Shivakumar, M. Garba, B. Shai, A New Mathematical Model for Assessing Therapeutic Strategies for HIV Infection, *Journal of Theoretical Medicine* 4 (2) (2002) 147–155.

[25] H. Nampala, L. Luboobi, J. Mugisha, C. Obua, Modelling effective antiretroviral therapy that inhibits hiv production in the liver, *Antivirals and Antiretrovirals* 7 (2) (2015) 43–51.

[26] Y. Su, Y. Wen, L. Min, Analysis of HBV infection models with ALT., *IEEE 6th International Conference on Systems Biology, Xi'an, China* August 18-20 (2012) 97–100.

[27] S. Ciupe, R. Ribeiro, P. Nelson, A. Perelson, Modeling the mechanisms of acute hepatitis B virus infection., *Journal of Theoretical Biology* 247 (2007) 23–35.

[28] K. Hattaf, N. Yousfi, Hepatitis B virus infection model with logistic hepatocyte growth and cure rate., *Journal of Mathematical Biology* 5 (47) (2011) 2327–2335.

[29] P. Colombatto, L. Civitano, R. Bizzarri, F. Oliveri, S. Choudhury, R. Gieschke, F. Bonino, M. Brunetto, A multiphase model of the dynamics of HBV infection in HBeAg-negative patients during pegylated interferon-α2a, lamivudine and combination therapy., *Antiviral Therapy* 11 (2006) 197–212.

[30] C. Long, H. Qi, S. Huang, Mathematical modeling of cytotoxic lympocyte-mediated immune response to hepatitis B virus infection., *Journal of Biomedicine and Biotechnology* 2008 (2008) 1–9.

[31] S. Hews, S. Eikenberry, J. Nagy, Y. Kuang, Rich dynamics of a hepatitis B viral infection model with logistic hepatocyte growth., *Journal of Mathematical Biology* 60 (4) (2010) 573–590.

[32] S. Bowong, J. Kamganga, J. Tewa, B. Tsanou, Modelling and analysis of hepatitis b and hiv co-infections., *Proceedings of the* 10^{th} *African Conference on Research in Computer Science and Applied Mathematics.* (2010) 109–116.

[33] A. Alberti, N. Clumeck, S. Collins, W. Gerlich, J. Lundgren, G. Palu, P. Reiss, R. Thiebaut, O. Weiland, Y. Yazdanpanah, S. Zeuzem, Short statement of the first european consensus conference on the treatment of chronic hepatitis B and C in HIV co-infected patients., *Journal of Hepatology* 42 (2005) 615–624.

[34] K. Fix, S. Locarnini, M. Peters, Virology and clinical management of hepatitis B and HIV coinfection., *The PRN notebook* 11 (4).

[35] M. Crane, D. Iser, S. Lewin, Human immunodeficiency virus infection and the liver., *World Journal of Hepatology* 4 (3) (2012) 91–98.

[36] N. Nasr, S. Maddocks, S. Turvile, A. Harman, N. Woolger, K. Helbig, J. Wilkinson, C. Bye, T. Wright, D. Rambukwelle, H. Donaghy, M. Beard, A. Cunningham, HIV-1 infection of human macrophages directly induces viperin which inhibits viral production., *Immunobiology* 120 (2012) 778–788.

[37] M. Nowak, S. Bonhoeffer, G. Shaw, R. May, Anti-viral drug treatment: Dynamics of resistance in free virus and infected cell populations., *Journal of Theoretical Biology* 184 (1996) 203–217.

[38] P. Srivastava, P. Chandara, Modeling the dynamics of HIV and CD4+

T cells during primary infection., *Nonlinear Analysis: Real World Applications* 11 (2) (2008) 612–618.

[39] R. Smith, E. Schwartz, Predicting the potential impact of a cytotoxic T-lymphocyte HIV vaccine: How often should you vaccinate and how strong should the vaccine be?, *Mathematical Biosciences* 212 (2008) 180–187.

[40] L. Rong, M. Gilchrist, Z. Feng, A. Perelson, Modeling within-host HIV-1 dynamics and the evolution of drug resistance: Trade-offs between viral enzyme function and drug susceptibility., *Journal of Theoretical Biology* 247 (2007) 804–818.

[41] R. Arnaout, M. Nowak, D. Wodarz, HIV-1 dynamics revisited: Biphasic decay by cytotoxic T-lymphocyte killing?, *PLoS ONE* 267 (2000) 1347–1354.

[42] R. de Boer, R. Ribeiro, A. Perelson, Current estimates for HIV-1 production imply rapid viral clearance in lymphoid tissues., *Computational Biology* 6 (9) (2010) 1–9.

[43] P. van den Driessche, J. Watmough, Reproduction numbers and subthreshold endemic equilbria for compartmental models of disease transmission., *Mathematical Biosciences* 180 (2002) 29–48.

[44] C. Castillo-Chavez, Z. Feng, W. Huang, On the computation of r_0 and its role on global stability., https://math.la.asu.edu/ chavez/CCCPUB/On the computation of R0 and its role in global stability.pdf 47.

[45] N. Chitnis, J. Hyman, J. Cushing, Determining important parameters in the spread of malaria through the sensitivity analysis of a mathematical model., *Bulletin of Mathematical Biology* 70 (2008) 1272–1296.

[46] A. Mikucki, Sensitivity analysis of the basic reproduction number and other quantities for infectious disease models., *Colorado State University.*

[47] H. Nampala, L. Luboobi, J. Mugisha, C. Obua, Modelling hepatotoxicity of antiretroviral therapy in the liver during hiv monoinfection, *International Journal of Computational Mathematics* (2014) 1–18Http://dx.doi.org/10.1155/2014/659675.

[48] Drugs.com, *http://www.drugs.com, Downloaded on 3.06.2013.*

[49] Liverpool, Lamivudine pk fact sheet, Univeristy of Liverpool, *www.hiv-druginteractions.org* Downloaded 09/04/2014.

[50] Liverpool, Emtricitabine PK Fact Sheet, Univeristy of Liverpool, *www.hiv-druginteractions.org, Downloaded 02/04/2013* .

[51] Liverpool, Tenofovir PK Fact Sheet, Univeristy of Liverpool, *www.hiv-druginteractions.org, Downloaded 02/04/2013.*

[52] Liverpool, Efavirenz PK Fact Sheet, Univeristy of Liverpool, *www.hiv-druginteractions.org, Downloaded 21/03/2013.*

[53] Liverpool, Nevirapine PK Fact Sheet, Univeristy of Liverpool, *www.hiv-druginteractions.org, Downloaded 09/04/2013.*

[54] Liverpool, Atazanavir PK Fact Sheet, Univeristy of Liverpool, *www.hiv-druginteractions.org, Downloaded 21/03/2013.*

[55] Liverpool, Lopinavir PK Fact Sheet, University of Liverpool, *www.hiv-druginteractions.org, Downloaded 02/04/2014.*

[56] L. Shen, S. Peterson, A. Sedaghat, M. McMahon, M. Callender, H. Zhang, Y. Zhou, E. Pitt, K. Anderson, E. Acosta, R. Siliciano, Supplementary information: Dose-response curve slope sets class-specific

limits on inhibitory potential of anti-HIV drugs., *Nature Medicine.* 14 (7) (2008) 762–766.

[57] L. Bisset, H. Lutz, J. Boni, R. Hofmann-Lehmann, R. Luthy, J. Schupbach, Combined effect of zidovudine (ZDV), lamivudine (3TC) and abacavir (ABC) antiretroviral therapy in suppressing in vitro FIV replication, *Antiviral Research* 53 (2002) 35–45.

[58] CDER, Guidance for industry, estimating the maximum safe starting dose in initial clinical trials for therapeutics in adult healthy volunteers. U.S. department of health and human services food and drug administration center for drug evaluation and research, *http://www.fda.gov/cder/guidance/index.htm.*

[59] AIDSinfo, AIDSinfo drug database, *http://aidsinfo.nih.gov/drugs/424/atripla/0/professional.*

[60] Bristol-Myers, The electronic Medicine Compendium (eMC): Bristol-Myers Squibb Phamaceuticals Limited., *http://www.medicines.org.uk/emc/medicine/20505/SPC/Atripla+600+mg+200+mg+245+mg+film+coated+tablets/#PRECLINICAL_SAFETY.*

[61] Bristol-Myers, Product Monograph: Atripla(efavirenz/emtricitabine/tenofovir disoproxil fumarate tablets) 600 mg/200 mg/300 mg Antiretroviral agent, *www.gilead.ca.*

[62] Bristol-Myers, The electronic medicines compendium (eMC), Bristol-Myers Squibb Pharmaceutical Limited, *http://www.medicines.org.uk/emc/medicine/28232/SPC/Nevirapine+200+mg+tablets/.*

[63] Bristol-Myers, The electronic medicine compendium(eMC),

Bristol-Myers Squibb Pharmaceutical Limited, *http://www.medicines.org.uk/emc/default.aspx*.

[64] AIDSinfo, AIDSinfo Drug Database, *http://aidsinfo.nih.gov/drugs/316/lopinavir—ritonavir/0/professional*.

[65] X. Lu, T. Block, Study of the early steps of the hepatitis B virus life cycle., *International Journal of Medical Sciences* 1 (1) (2004) 21–33.

[66] R. King, R. Klabe, C. Reid, S. Erickson-Viitanen, Potency of nonnucleoside reverse transcriptase inhibitors (NNRTIs) used in combination with other human immunodeficiency virus NNRTIs, NRTIs, or Protease Inhibitors., *Antimicrobial agents and chemotherapy* (2002) 1640–1646.

[67] T. Campbell, L. Smeaton, N. Kumarasamy, T. Flanigan, K. Klingman, C. Firnhaber, B. Grinsztejn, M. Hosseinipour, J. Kumwenda, U. Lalloo, C. Riviere, J. Sanchez, M. Melo, K. Supparatpinyo, S. Tripathy, A. Martinez, A. Nair, A. Walawander, L. Moran, Y. Chen, W. Snowden, J. Rooney, J. Uy, R. Schooley, V. De Gruttola, J. Hakim, Efficacy and safety of three antiretroviral regimens for initial treatment of HIV-1: A randomized clinical trial in diverse multinational settings, *PLOS Medicine* 9 (8).

[68] M. Nunez, Clinical Syndromes and Consequences of Antiretroviral-Related Hepatotoxicity., *Hepatology* 52 (3) (2010) 1143–1155.

[69] AIDSinfo, Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents., *Department of Health and Human Services. http://aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf*.

Appendices

A. Basic Reproduction number

In the model equation (A.7)-(A.13), if we consider a case where the cells are only infected with HBV, that is, $V_H = 0 = I_C$, then the system reduces to an HBV-only model of the form

$$\frac{dT_h}{dt} = \lambda_2 - \beta_B T_h V_B - d_3 T_h + k_3 I_{hB} L, \tag{A.1}$$

$$\frac{dI_{hB}}{dt} = \beta_B T_h V_B - (d_3 + d_5) I_{hB} - (k_3 + k_4) I_{hB} L, \tag{A.2}$$

$$\frac{dL}{dt} = x + k_6 I_{hB} L - d_7 L, \tag{A.3}$$

$$\frac{dV_B}{dt} = n_1 d_5 I_{hB} - d_8 V_B, \tag{A.4}$$

$$\frac{dA}{dt} = k_7(d_5 I_{hB} + k_4 I_{hB} L) - d_{10} A. \tag{A.5}$$

The basic reproductive number (R_0^B) of the system (A.1)-(A.5), is calculated using the next generation method [43] as

$$R_0^B = \frac{d_7 \lambda_2 \beta_B n_1 d_5}{d_3 d_8 (d_3 d_7 + d_5 d_7 + k_4 x + k_3 x)}. \tag{A.6}$$

Considering a scenario where $I_{hB} = I_{hBH} = V_B = 0$ in the system (A.7) - (A.13) then we have an HIV-only infection. The HIV-only model becomes

$$\begin{aligned}
\frac{dT_c}{dt} &= \lambda_1 - (1-p)\beta_{H1}T_cV_H - d_1T_c, && \text{(A.7)}\\
\frac{dI_c}{dt} &= (1-p)\beta_{H1}T_cV_H - (d_1+d_2)I_c - k_1I_cL, && \text{(A.8)}\\
\frac{dT_h}{dt} &= \lambda_2 - p\beta_{H2}T_hV_H - d_3T_h, && \text{(A.9)}\\
\frac{dI_{hH}}{dt} &= p\beta_{H2}T_hV_H - (d_3+d_4)I_{hH} - k_2I_{hH}L-, && \text{(A.10)}\\
\frac{dL}{dt} &= x + k_6(I_c+I_{hH})L - d_7L, && \text{(A.11)}\\
\frac{dV_H}{dt} &= s_1d_2I_c + s_2d_4I_{hH} - d_9V_H, && \text{(A.12)}\\
\frac{dA}{dt} &= k_7(d_4I_{hH} + k_2I_{hH}L) - d_{10}A. && \text{(A.13)}
\end{aligned}$$

Calculating the basic reproductive number (R_0^H) as the average number of secondary infections caused by an HIV infectious cell in an HIV only case of model (A.7) - (A.13), we get

$$R_0^H = R_{0h}^H + R_{0c}^H \tag{A.14}$$

where

$$R_{0h}^H = \frac{(1-p)d_7\lambda_2\beta_{H2}s_2d_4}{d_3d_9(d_3d_7 + d_4d_7 + k_2x)}, \tag{A.15}$$

$$R_{0c}^H = \frac{pd_7\lambda_1\beta_{H1}s_1d_2}{d_1d_9(d_2d_7 + d_1d_7 + k_1x)}. \tag{A.16}$$

Since HIV infects both hepatocytes and CD4+ cells, R_{0h}^H is the number of secondary infections due to HIV in hepatocytes while R_{0c}^H are HIV secondary infections in CD4+ cells.

The basic reproductive number (R_0), can be calculated using the next generation method as by [43]. Let the Jacobian of the matrices that represents the

rate of appearance of new infections into a compartment and the difference between the rate of transfer of individual cells out of a compartment at D_f be $\mathfrak{F}$ and ν respectively. We have

$$\mathfrak{F} = \begin{bmatrix} 0 & 0 & 0 & 0 & 0 & (1-p)\beta_{H1}\lambda_1/d_1 \\ 0 & 0 & 0 & 0 & 0 & p\beta_{H2}\lambda_2/d_3 \\ 0 & 0 & 0 & 0 & \beta_B\lambda_2/d_3 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & n_1d_5 & d_2\gamma d_6 & 0 & 0 \\ s_1d_2 & s_2d_4 & 0 & s_3(1-\gamma)d_6 & 0 & 0 \end{bmatrix} \tag{A.17}$$

and

$$\nu = \begin{bmatrix} \frac{(d_2d_7+d_1d_7+k_1x)}{d_7} & 0 & 0 & 0 & 0 & 0 \\ 0 & \frac{(d_3d_7+d_4d_7+k_2x+k_4x)}{d_7} & 0 & 0 & 0 & 0 \\ 0 & 0 & \frac{(d_3d_7+d_5d_7+k_3x+k_4x)}{d_7} & 0 & 0 & 0 \\ 0 & 0 & 0 & \frac{(d_3d_7+d_6d_7+k_5x)}{d_7} & 0 & 0 \\ 0 & 0 & 0 & 0 & d_8 & 0 \\ 0 & 0 & 0 & 0 & 0 & d_9 \end{bmatrix}. \tag{A.18}$$

The eigenvalues of $\mathfrak{F}\nu^{-1}$ are given as

$$e_1 = e_2 = 0 \tag{A.19}$$

$$e_3 = \sqrt{\left(\frac{d_7\lambda_2\beta_B n_1 d_5}{d_3d_8(d_3d_7+d_5d_7+k_4x+k_3x)}\right)} \tag{A.20}$$

$$e_4 = -\sqrt{\left(\frac{d_7\lambda_2\beta_B n_1 d_5}{d_3d_8(d_3d_7+d_5d_7+k_4x+k_3x)}\right)} \tag{A.21}$$

$$e_5 = \sqrt{\left(\frac{(1-p)d_7\lambda_2\beta_{H2}s_2d_4}{d_3d_9(d_3d_7+d_4d_7+k_2x)} + \frac{pd_7\lambda_1\beta_{H1}s_1d_2}{d_1d_9(d_2d_7+d_1d_7+k_1x)}\right)} \tag{A.22}$$

$$e_6 = -\sqrt{\left(\frac{(1-p)d_7\lambda_2\beta_{H2}s_2d_4}{d_3d_9(d_3d_7+d_4d_7+k_2x)} + \frac{pd_7\lambda_1\beta_{H1}s_1d_2}{d_1d_9(d_2d_7+d_1d_7+k_1x)}\right)} \tag{A.23}$$

R_0 is defined as the spectral radius of $\mathfrak{F}\nu^{-1}$. Thus

$$R_0 = max\{e_3, e_5\}. \tag{A.24}$$

It can be seen from equation (A.6) that e_3 is the basic reproduction number R_0^B of the HBV model and that $e_5 = R_0^H$ from equation (A.14). We can therefore deduce that

$$R_0 = max\{R_0^H, R_0^B\}, \tag{A.25}$$

B. Castillo-Chavez Theorem

Theorem 3. *Castillo-Chavez et al. [44].*
For a system

$$\begin{cases} \frac{dX}{dt} = F(X, Z), \\ \frac{dZ}{dt} = G(X, Z), G(X, 0) = 0, \end{cases} \tag{B.1}$$

where the components of the column-vector $X \in R^m$ denotes the number of uninfected individuals and the components of vector $Z \in R^n$ denotes the number of infected individuals. Let $\bigcup_0 = (X^*, 0)$ denote the disease-free equilibrium of this system. The fixed point $\bigcup_0 = (X^*, 0)$ is a globally asymptotically stable equilibrium for this system provided that $R_0 < 1$ (locally asymptotically stable) and the following two conditions satisfied:
(H1): For $\frac{dX}{dt} = F(X, 0)$, X^* is globally asymptotically stable
(H2): $G(X, Z) = MZ - \hat{G}(X, Z)$, $\hat{G}(X, Z) \geq 0$ for $(X, Z) \in \Omega$ where $M = D_Z G(X^*, 0)$ is an Metzler Matrix (the off-diagonal elements of M are nonnegative) and Ω is the region where the model makes biological meaning.