*I.J. Mathematical Sciences and Computing,* **2020, 2, 18-60**
Published Online April 2020 in MECS (http://www.mecs-press.net)
DOI: 10.5815/ijmsc.2020.02.02

***Available online at http://www.mecs-press.net/ijmsc***

# Optimal Control Dynamics: Multi-therapies with Dual Immune Response for Treatment of Dual Delayed HIV-HBV Infections

Bassey, B. Echeng*

* *Department of Mathematics, Cross River University of Technology, 540252, Calabar, Nigeria*

*Received: 15 August 2019; Accepted: 15 October 2019; Published: 08 April 2020*

**Abstract**

It has been of concern for the most appropriate control mechanism associated with the growing complexity of dual HIV-HBV infectivity. Moreso, the scientific ineptitude towards an articulated mathematical model for co-infection dynamics and accompanying methodological application of desired chemotherapies inform this present investigation. Therefore, the uniqueness of this present study is not only ascribed by the quantitative maximization of susceptible state components but opined to an insight into the epidemiological identifiability of dual HIV-HBV infection transmission routes and the methodological application of triple-dual control functions. Using ODEs, the model was formulated as a penultimate 7-Dimensional mathematical dynamic HIV-HBV model, which was then transformed to an optimal control problem, following the introduction of multi-therapies in the presence of dual adaptive immune system and time delay lags. Applying classical Pontryagin's maximum principle, the system was analyzed, leading to the derivation of the model optimality system and uniqueness of the system. Specifically, following the dual role of the adaptive immune system, which culminated into triple-dual application of multi-therapies, the investigation was characterized by dual delayed HIV-HBV virions decays from infected double-lymphocytes in a biphasic manner, accompanied by more complex decay profiles of infectious dual HIV-HBV virions. The result further led to significant triphasic maximization of susceptible double-lymphocytes and dual adaptive immune system (cytotoxic T-lymphocytes and humeral immune response) achieved under minimal systemic cost. Therefore, the model is comparatively a monumental and intellectual accomplishment, worthy of emulation for related and future dual infectivity.

**Index Terms:** HIV-HBV-infectivity, time-delay-lag, triple-dual-control-functions, double-lymphocyte, systemic-cost, monolytic-infection, lentivirus, triphasic-maximization



* Corresponding author.
E-mail address:

**NOTATIONS**

**HIV** – human immunodeficiency virus
**HBV** – hepatitis B virus
**CTL** – cytotoxic T-lymphocytes
**HIR** – humoral immune response
**HAART** – highly active antiretroviral therapy
**cccDNA** – covalently closed circular DNA
**HBeAg** – hepatitis B encore antigens
**HBsAg** – hepatitis B surface antigens
**Anti-HBeAg** – anti hepatitis B e antigens
**RTI** – reverse transcriptase inhibitors
**PIs** – protease inhibitors
**IFN-$\alpha$** - alpha-interferon
**NAs** – nucleoside analogues
**L*max*** – maximum saturated double lymphocytes
**DNA** – deoxyribonucleic acid
**ALT** – alanine aminotransferase

## 1. Introduction

Globally, the nomenclature HIV-1 and/or HIV/AIDS have been asserted as an integral component of human immune system with CD4+ T lymphocytes as route victim. This assertion emanated from the fact that no outright medical cure established for this deadly disease [1]. Moreso, HIV infection has concurrently been aggravated by the multiplicity of its allied infections, which includes coinfections and/or dual infections of the types: HIV-hepatitis B virus, HIV-tuberculosis, HIV-hepatitis C virus, HIV-influenza virus, HIV-pathogeneses, HIV-Ebola virus, HIV-listeriosis, HIV-zika virus, etc, [1- 5].

Following the similarities in infection dynamics, this present study consider the menacing effects of dual delayed HIV-HBV infections. The co-infections of human immunodeficiency virus (HIV) and hepatitis B virus (HBV) present significant challenges to the health care providers world-wide with persistent co-infections leading to deadly acquire immunodeficiency syndrome (AIDS), unprecedented rapid cirrhosis, hepatocellular carcinoma, increase in morbidity and mortality rate beyond those caused by monolytic HIV or HBV infection [2, 6-10]. As a monolytic infection, HIV is a lentivirus with death as its lethal consequence if proper and timely medical suppressive and treatment measures are not offered. On the other hand, hepatitis B is a liver infection caused by hepatitis B virus (HBV), which if allowed under off-treatment, leads to chronic liver cirrhosis, liver cancer and hepatocellular carcinoma or even death [1, 10, 11]. Of note, HBV as a prototype member of the Hepadnaviridae family (hepatotropic DNA virus) is one of the hepadnaviruses with string infection affinity to the liver cells and traceable to the pancreas, kidney and mononuclear cells [9, 12].

Furthermore, due to the biological similarities of dual HIV-HBV infectivity, it has been adduced that all HIV-1 infected patients should be screen for HBV infection and vice-versa. Moreso, infection with HBV had become more violent in patients co-infected with human immunodeficiency syndrome. This is obvious as HIV infected individuals are prong to HBV infection, the reverse may be rare [9]. Therefore, HIV/HBV dual infected individuals are at risk of chronic hepatitis, cirrhosis and hepatocellular carcinoma with often resistance and the experience of HAART toxicity. The high death toll caused by dual HIV-HBV infectivity accounted for over 36.7 million people living with HIV as at end of 2016 and a death toll of 1 million in 2016, declared by the World Health Organization (WHO), [13]. On the other hand, 2-billion world-wide are infected with HBV, accounting for approximately 350 million chronic cases and estimated 600,000 death consequence to chronic hepatitis B virus infection [9, 14]. Complicatedly, the ubiquitous and asymptomatic nature of HIV at onset of infection couple with initial response of anti-HIV immune system often make the incubation period predominantly unascertained [1, 15, 16]. This is to say that the incubation period of HBV, which is $30-180$ days is also not fully understood, since majority of infection cases are clinically known after acute stage of infection [2. 17].

The co-transmission mode of these co-virions ranges from percutaneous exposures i.e. direct contact with blood, semen to body fluid from an infected person. Other mode include: sharing of contaminated and unsafe therapeutic drug injection needles, perinatal and sexual exposures with an infected person, nosocomial transmission; vertical transmission and sharing of personal effects i.e. toothbrush, razor, tattooing and acupuncture, barbing equipment, non-compliance with aseptic techniques, non-availability of testing equipment,

reuse of disposable injecting devices, multiple dose of medication vials, ritual scarification (in parts of Africa) and occult infection transmission [9, 18-24]. Therefore, it can be said that dual HIV-HBV similarities lies in its transmission vessel known to be the reverse transcriptase enzyme in replication; the tendency to develop chronic infection, which are difficult to treat and their immune capacity of genomic mutation resulting to rapid mutant strains [9]. Of note, the dichotic characteristic of HIV and HBV is the never recover from infection by viral load, even when on cohesive medical care. However, monolytic HBV infected patients who recover from infection never get infected by the virus, since system is permanently immune [20]. Moreso, the viral genomes, which can integrate within the host genome is obligatory for HIV lifecycle but is not the case for HBV.

Like HIV, the risk factors associated with chronic HBV infection are the possible development of liver fibrosis, cirrhosis and hepatocellular carcinoma causing an estimated 650,000 deaths per year [12, 25]. Categorically, the risk factors of chronic HBV include its progression to HBsAg, anti-HB e Ag, and HBV DNA; and the problem of experiencing HAART toxicity. Peculiar to co-infected HIV/HBV patient, is the high liver related mortality rate when compared to either monolytic infection [56]. The model [69] established the fact that for co-infected individuals, the virological persistency of chronic HBV in HIV infected population is routed to the intracellular HBV replication intermediate, called covalently closed circular DNA (*ccc*DNA). The model had suggested elimination of the *ccc*DNA as the only possible cure of chronic HBV. Thus, the consequential effect of co-infectivity of HIV-HBV in addition to rapid progression of liver cirrhosis due to low $CD4^+$ T cell counts are decrease rate of HBeAg clearance, rapid replication of HBV and decrease inflammatory response to chronic hepatitis B.

The treatment of co-infection HIV/HBV concurrently can be effectively managed if a coherent diagnosis and complete monitoring of this co-infection along with understanding the mechanisms of possible drugs resistance are adequately given the needed commitment. This is obvious following drugs variability and risk of complications, which assumed great limitations in liver biopsy [26]. Moreso, coming from the view point of monolytic virology (HIV or HBV), suppression of viral replication is the main aim of therapy. For HIV infection, the varying chemotherapies have been categorized into transcriptase inhibitors (RTI) and protease inhibitors (PIs). Related models with the application of RTI and PIs on mono-HIV infection dynamics can be found in [1, 27-29]. From related literature, among possible known chemotherapies for monolytic HBV infection is the interferon in the form of standard or pegylated, which is often recommended for chronic HBV infection. The IFN-$\alpha$ is known for the elimination of infected cells by reducing the *ccc*DNA. Complementing the clinical function of IFN-$\alpha$ is the nucleos(t)ide analogues (NAs). It is the clinical attributes of the aforementioned chemotherapies that envisage it choice for this present investigation. The respective role of these chemotherapies will be outline in section 2.

Non-the-less, in spite of the significant role of these chemotherapies at monolytic infection levels, a systematic combination of these drugs for dual infectivity often result to not only altering the drugs history for HBV but notably, interferon is limited to patients with high alanine aminotransferase (ALT) levels, low HBV DNA levels and those with positive HB e Ag status [30, 31]. Therefore, for co-infectivity of HIV/HBV, the choice of chemotherapies must be a major concern to avoid the overlapping influence of a particular drug on the other. It can then be insinuated that following the complexity associated with co-infectivity, the seeming measurable approach to understanding infections dynamics, choice of chemotherapies and methodological applications as well as associated resistivity had been through mathematical modeling and classical numerical methods.

In collaboration with this present study, mathematical models formulated to account for the monolytic HIV, HBV infections include [32-40]. The inclusion of the vital role of adaptive immune system and delay intracellular as defense mechanism were studied by [1, 2, 6, 15, 20, 27, 41-48]. Other monolytic models, which had focused on the methodological application of treatment strategies and optimal maximization of healthy population, can be found in [1, 2, 16, 28, 29, 49-60]. Remarkably, taking precedence from existing literatures, classical mathematical models for co-infections of HIV-HBV have been a rare event. From available literatures on co-infections of HIV-HBV, only natural history, challenges and on drugs resistivity have been discussed. For instance, the study [9] conducted a review on HIV/HBV con-infections: epidemiology, natural history and

treatment. The study [10] highlighted the global challenges associated with HIV-HBV co-infections. The characteristic of drug resistant HBV in an international collaborative study of HIV-HBV infected individuals on extended lamivudine therapy was conducted by [61], while dually active HIV/HBV antiretroviral as protection against incident hepatitis B infections: potential for prophylaxis was studied by [62]. Moreso, the results from a multicenter studied in Italy accounted for the correlation of HIV, HBV and HBC infections in a prison inmate population [63].

Therefore, to the best knowledge of this present investigation, these previous studies have been devoid of an articulated mathematical model for co-infection dynamics and accompanying methodological application of desired chemotherapies. This singular yet enormous scientific ineptitude forms the motivating integral factor for this present investigation. Theoretically, the unique characteristics of this present study is anticipated to integrate the biological components in the nature of adaptive immune system as both state component and as treatment measurable functions as well as the exponential time delay lags. Of note, the motivating questions that fronted this investigation are thus: since the study envisage dual HIV-HBV infections under dual pair control functions in addition to the control measures of dual immune system, will the specify treatment functions of HIV have adverse effect on intended positive control functions of HBV and vice versa? Secondly, admitting the dual role of dual adaptive immune system on HIV-HBV is it acceptable to assume that if the end result of investigation proves against the mutual expectations of optimal maximization of healthy $CD3^+$ T lymphocytes and $CD4^+$ T-lymphocytes (double lymphocytes), then control function must have been counterproductive? Otherwise, our investigation is anticipated to lead to either eradication or sufficient maximization of double lymphocytes.

Thus, using ODEs, the present model is formulated as penultimate 7-Dimensional mathematical dual HIV-HBV dynamic augmented model arising from the inductive understanding of models [1, 2]. The model seek as its objective, to account for the methodological application of choice multi-therapies in the presence of dual adaptive immune system and intracellular delay function following the interplay of dual HIV-HBV with double lymphocyte cells. More objectively, the novelty of the present study lies in the proposed methodological application of triple-dual control functions with the incorporation of growth logistic term and exponential time delay lags for a dual HIV-HBV infections. Furthermore, the study concurrently aims at advancing via optimal control theory, a functional scientific control and/or eradication of these deadly dual infections, which is presumably the first in the annals of co-infectivity studies. However, it is pertinent to note that due to anticipated complexity associated with dual infections, the present model intentionally do not consider infections latent cells and non-cytotoxic carrying processes, which are often established at acute stages [49].

Ipsofacto, the organization of this present paper is an embodiment of seven sections with section 1 devoted to the introductory aspect. Constituting the material and methods of section 2, are the problem statement and mathematical equations; and the analysis of model basic properties, which include system invariant and boundedness of solutions as well as system equilibria are explicitly discussed. Section 3 focuses on the optimal control problem formulation, characterization of optimal control and the existence of an optimal control dual-pair. The optimality system and uniqueness form the fulcrum of section 4. We introduced a number of illustrative examples to validate the model ingenuity in section 5. The resultant outcome of experimental simulations are discussed and presented in section 6. Finally, on the basis of the findings, section 7 is devoted to an incisive and succinct conclusion and remarks with embedment of obtained results as appendices. The entire study is anticipated to be a monumental and equivocal representation of intellectual advancement towards the eradication of the seeming insurmountable deadly dual HIV-HBV infections.

## 2. Material and Methods

Constituting the material and methods of this section, are the model problem statement and mathematical equations for an untreated dual delayed HIV-HBV infections with natural adaptive immune response as both state components and as defense mechanism. Here, the study also investigates the basic properties of the model (without chemotherapies), which include system positivity invariant and boundedness of solutions. The last

part of this section is devoted to the system stability analysis for an untreated dual delayed HIV-HBV model.

*2.1 Problem Statement and Mathematical Equations*

In bracketing the innovative ideas of the current study, we bring to bear three closely compactible models [1, 2, 50], among those highlighted in section 1. First, we consider mathematical model for a dual delayed HIV-pathogen infections under immune effectors response and multiple chemotherapies as presented by model [50]. The dynamics of that model was governed by

$$\begin{aligned}
\frac{dU_T}{dt} &= \frac{b}{1+V+P} + gU_T\left(1-\frac{U_T+I_T}{U_{\max}}\right) - \alpha_1 U_T - (1-r_1(t))[h_1V+h_2P]U_T \\
\frac{dI_T}{dt} &= (1-r_1(t))\,\mathrm{e}^{-\alpha_2\tau}\mathrm{U}_T(\mathrm{t}-\tau)[h_1V(t-\tau)-h_2P(t-\tau)] - \left(z_v+z_p\right)\alpha_2 I_T - qI_TM \\
\frac{dV}{dt} &= (1-r_2(t))z_v\alpha_2 I_T - \alpha_3 V \\
\frac{dP}{dt} &= (1-r_2(t))z_p\alpha_2 I_T - \alpha_4 P \\
\frac{dM}{dt} &= cI_TM - dM
\end{aligned} \tag{1}$$

where $U_T(t), I_T(t), V(t), P(t), M(t),$ denoted the concentration of uninfected cells, infected cells, free viral load, free infectious pathogens and immune effectors response respectively. Details of this model could be found as cited.

With the introduction of intrinsic virulence as state variables and specification of infected cytotoxic T-lymphocyte cells into viral load infected cells and pathogen infected cells as well as subdivision of immune effectors response into effectors of CTLs and precursors of CTLs, the model [1], considered optimal dynamics of dual pair treatment functions of dual delayed HIV-pathogen infections. The epidemiological governing equations were derived as:

$$\begin{aligned}
\dot{T}_u &= b_p + \sigma V + \lambda P - \alpha_1 T_u - (\beta V + \delta P)RT_u \\
\dot{I}_v &= \beta e^{-\alpha_2\omega} VRT_u - (\alpha_2 + k)I_v - q_1 I_v Z \\
\dot{I}_p &= \delta e^{-\alpha_3\omega} PRT_u - (\alpha_3 + d)I_p - q_2 I_p Z \\
\dot{V} &= kI_v - (\alpha_4 + \sigma)V \\
\dot{P} &= dI_p - (\alpha_5 + \lambda)P \\
\dot{W} &= cI_v I_p T_u W - \rho I_v I_p W - \alpha_6 W \\
\dot{Z} &= \rho I_v I_p W - \alpha_7 Z \\
\dot{R} &= R_0 - R
\end{aligned} \tag{2}$$

where $T_u(t), I_v(t), I_p(t), V(t), P(t), W(t), Z(t)$ and $R(t)$ defined the system state variables with more parameter definitions as contained in model [1].

Like viral load, hepatitis B virus, which possesses significant similar characteristics of HI-virus, was investigated under the caption “mathematical modeling of the adaptive immune responses in the early stage of

the hepatitis B virus infection, [2]. The study established the dynamics of the early stage of HBV under off treatment scenario as:

$$\begin{aligned}
\frac{dx}{dt} &= rx(t)\left(1-\frac{T(t)}{T_{\max}}\right)-\beta\frac{v(t)x(t)}{T(t)}\\
\frac{dy}{dt} &= \beta e^{-k\tau}\frac{v(t-\tau)x(t-\tau)}{T(t-\tau)}-ay(t)-py(t)z(t)\\
\frac{dv}{dt} &= aNy(t)-\delta v(t)-qv(t)w(t)\\
\frac{dw}{dt} &= gv(t)w(t)-hw(t)\\
\frac{dz}{dt} &= cy(t)z(t)-bz(t)
\end{aligned} \tag{3}$$

where $T(t)=x(t)+y(t)$ and $x(t), y(t), v(t), w(t), z(t)$ denoted the concentrations of uninfected cells, infected cells, viruses, antibodies and cytotoxic T-lymphocytes (CTLs). Here, we also refer readers to cited model for further details. Thus, from the intuitive point of reviews of models [1, 2, 50], it is noted that model (1) focuses on HIV and general pathogeneses studied under multiple treatments and cytotoxic T-lymphocytes in the presence of time delay lag. Model (2) represented an expanded idea of model (1) with the incorporation of two state variables leaping from the class of infected cells and the virus ingress as state variables. Now, following the fact that HBV possesses quite large characteristic properties and functioned under similar conditions, the transformative ideas of HIV dynamics was conveniently implemented on HBV infection as depicted by model (3). Notably, natural source and decay rates of uninfected cells as well as replication rate of infected cells were not identified.

Thus, in this present paper endowed by the innovative ideas of the aforementioned models and motivated by their scientific lapses, we articulate and formulate an intriguing 7-Dimensional dual delayed HIV-HBV dynamic infections model. Here, the study seek as a penultimate model to account for the most probable clinical methodological optimal application of triple-dual control functions for the treatment and possible eradication of intricating dual delayed HIV-HBV infection on susceptible double lymphocyte cells. Moreso, the interplay of these dual virions with multi-therapies is anticipated in the presence of time delay lag; and dual function of cellular immune response (CTLs) and humoral immune response (antibodies). Therefore, if the population subgroups are representative of the system state variables measured in units' volume of $cells/mm^3$, such that $T_u$ define the uninfected double lymphocyte cells, $T_i$ - the viral load infected lymphocyte cells and $T_b$ - the B-virus infected hepatocytes , then the free infectious viral load and infectious hepatitis B virus are denoted by $V_i$ and $V_b$. Other subpopulation are the cellular immune response and the humeral immune response capped as $Q$ and $Z$. Thus, the derived simplified epidemiological non-linear 7-Dimensional differential system is governed by the following equations:

$$
\begin{aligned}
\frac{dT_u}{dt} &= b_p + s\left(1-\frac{L(t)}{L_{\max}}\right)T_u(t) - \left[\frac{\beta_1(1-u_1)V_i(t)+\beta_2(1-r_1)V_b(t)}{L(t)}\right]T_u(t) - \mu_T T_u(t)\\
\frac{dT_i}{dt} &= \beta_1 e^{-\mu_i\omega_1}(1-u_1)\left[\frac{V_i(t-\omega_1)T_u(t-\omega_1)}{L(t-\omega_1)}\right] - (q_1+\alpha_1)T_i(t) - g_1T_i(t)Q(t)\\
\frac{dT_b}{dt} &= \beta_2 e^{-\mu_b\omega_2}(1-r_1)\left[\frac{V_b(t-\omega_2)T_u(t-\omega_2)}{L(t-\omega_2)}\right] - (q_2+\alpha_2)T_b(t) - g_2T_b(t)Q(t)\\
\frac{dV_i}{dt} &= (1-u_2)q_1p_1T_i(t) - \alpha_3V_i(t) - \tau_1V_i(t)Z(t) \qquad , \qquad (4)\\
\frac{dV_b}{dt} &= (1-r_2)q_2p_2T_b(t) - \alpha_4V_b(t) - \tau_2V_b(t)Z(t)\\
\frac{dQ}{dt} &= d_1(T_i(t)+T_b(t))Q(t) - \alpha_5Q(t)\\
\frac{dZ}{dt} &= d_2(V_i(t)+V_b(t))\,Z(t) - \alpha_6Z(t)
\end{aligned}
$$

with

$$L(t) = T_u(t) + T_i(t) + T_b(t) \qquad (5)$$

and having initial conditions: $T_u(0)=T_{(u)0}, T_i(0)=T_{(i)0}, T_b(0)=T_{(b)0}, V_i(0)=V_{(i)0}, V_b(0)=V_{(b)0}, Q(0)=Q_0$ and $Z(0)=Z_0$ for all $t=t_0$. Hence, model (4) is the mathematical representation of the system basic equations and schematically depicted by fig. 1, below: Of note, the liver, which is the main victim of hepatitis B virus is a member of the immunological organ known as the $CD3^+$ lymphocytes or hepatic lymphocyte repertoire or better called liver lymphocytes. Biologically, the site for viral load infection is the $CD4^+$ T lymphocyte. Therefore, through this text, we shall refer as ***double-lymphocytes*** to define the site for the system HIV-HBV dual infections.

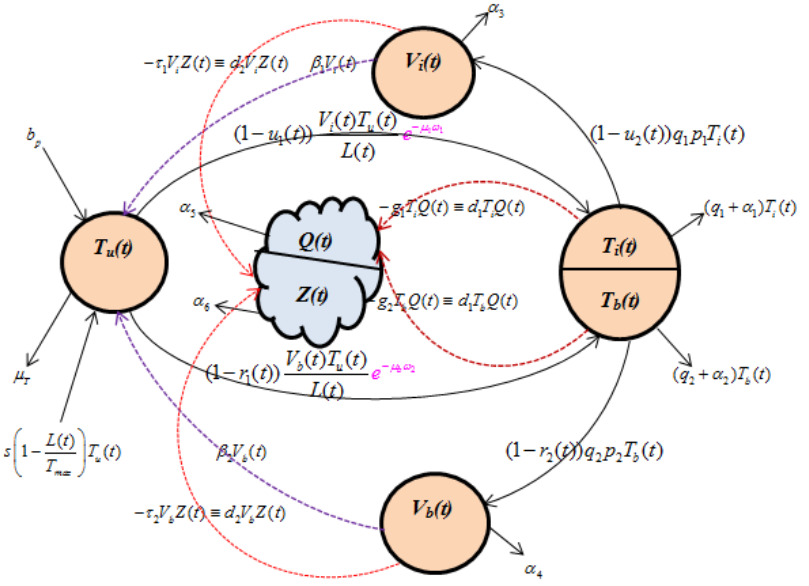



Fig.1. Schematic representation of dual HIV-HBV infection and multiple treatment dynamics

The verification of model ingenuity is conducted using the biological state variables and parameter values as inscribed in tables (1 & 2) below.

Table 1 Description of state variables with values for model (4)

| Variables | Dependent variables<br>Description | Initial values | Units |
|---|---|---|---|
| $T_u(t)$ | Uninfected double lymphocyte cells population | 0.5 | $cell/mm^3$ |
| $T_i(t)$ | Viral load infected T-lymphocyte cells population | 0.02 | $cell/mm^3$ |
| $T_b(t)$ | B-virus infected hepatocyte cells population | 0.02 | $cell/mm^3$ |
| $V_i(t)$ | Infectious free HI-virus population | 0.08 | $copiesml^{-1}$ |
| $V_b(t)$ | Infectious free HB-virus population | 0.07 | $copiesml^{-1}$ |
| $Q(t)$ | Cytotoxic T-Lymphocytes (immune effector response) - CTLs | 0.04 | $cell/mm^3$ |
| $Z(t)$ | Antibodies (humoral immune response) - HIR | 0.02 | $cell/mm^3$ |
| $L_{\max}(t)$ | Maximum saturated double lymphocyte cells | $\in[0,1]$ | |

***Note**: Table 1, is a reflection of models [1, 2, 42, 50], modified to accommodate the present investigation.*

Intuitively, from fig. 1, the biological descriptions of the terms associated with equations of model (4) can be deduced as follows: in the first equation, the first and second terms - $b_p, s\left(1-T(t)/L_{\max}\right)$ denotes the source rate of uninfected double lymphocyte cells with maximum per-capita proliferation rate $s$, and having logistic term $\left(1-T(t)/L_{\max}\right)$ that depends on the double lymphocytes size, $L_{\max}$. The healthy double lymphocytes becomes infected by the dual virions at the rate $-\left((\beta_1 V_i)+(\beta_2 V_b)/L\right)$, as depicted by the third term, where $\beta_1, \beta_2$ are constants of infection rates. The last term $\mu_T$, represent rate of natural decay of uninfected double lymphocytes. This last term is among the differentiating attribute of this present model when compared to model [2]. From the second and third equations, the respective first terms $\beta_1 e^{-\mu_i \omega_1} V_i(t-\omega_1)/L(t-\omega_1)$ and $\beta_2 e^{-\mu_b \omega_2} V_b(t-\omega_2)/L(t-\omega_2)$, describes the rate of inflow of infected double lymphocytes arising from infectious viral load and B-virus and having exponential rate of infections $e^{-\mu_i \omega_1}$ and $e^{-\mu_b \omega_2}$, which reflects death rate of new non-virions producing infections. The $\omega_1, \omega_2$, denotes infection time lag. This time lag defines the period the newly infected cells becomes actively infectious. The second terms $(q_1+\alpha_1)T_i$ and $(q_2+\alpha_2)T_b$ describe the rate of replications of infected double lymphocyte cells and death rates due to infections. The last terms $g_1 T_i Q$ and $g_2 T_b Q$ denotes clearance rates of infected double lymphocyte cells by cellular immune response (CTLs).

The fourth and fifth equations depicted the dual virions infectious dynamics. Precisely, dual virions particles are produced at the rates $q_1 p_1$ for $T_i$ and $q_2 p_2$ for $T_b$ with $p_{i=1,2}$ as the numbers of free virions growth rates from infected double lymphocytes lifespan. Infectious virions decay at the rates $\alpha_3 V_i$ and $\alpha_4 V_b$, while decay due to antibodies defense mechanism are denoted by $\tau_1 V_i Z$ and $\tau_2 V_b Z$ respectively. From the sixth and seventh equations, the first terms define the generation constants $d_1, d_2$ of cellular immune response and humoral immune response, which are directly proportional to the production rates of infected and infectious hepatocyte cells $(T_i, T_b)$. Lastly, both adaptive immune response decay at the rates $\alpha_5$ and $\alpha_6$ respectively. Of

note, the parameters $d_1, d_2$ is known for its contributive role as the strength of lytic components denoted by $d_1(T_i + T_b)Q$ and $d_2(V_i + V_b)Z$ .

Table 2 Summary of constants and parameter values for model (4)

| Parameter symbols | Parameters and constants<br>Description | Initial values | Units |
|---|---|---|---|
| $b_p$ | Inflow source of uninfected double lymphocyte cells | 0.5 | $mm^3 d^{-1}$ |
| $s$ | Per-capita proliferation rate of double lymphocyte cells | 0.5 | $day^{-1}$ |
| $\beta_{i=1,2}$ | Rate of virions infections on susceptible hepatocyte cells | $1.8\times10^{-3}; 3.6\times10^{-5}$ | $cells\ virions^{-1} d^{-1}$ |
| $\mu_T$ | Natural decay rate of uninfected double lymphocytes | 0.2 | $d^{-1}$ |
| $\mu_i$ | Death rate of infected HIV non-virus producing cells | $1.1\times10^{-2}$ | $d^{-1}$ |
| $\mu_b$ | Death rate of infected HBV non-virus producing cells | $3.9\times10^{-3}$ | $d^{-1}$ |
| $\omega_{i=1,2}$ | Time delay lags for infectious double lymphocyte (intracellular delays) | 0.5; 0.1 | $day$ |
| $q_{i=1,2}$ | Replication rates of HIV and HBV by infected double lymphocyte | 0.48; 0.46 | - |
| $g_{i=1,2}$ | Clearance rate of infected hepatocytes( $T_i$ , $T_b$ ) by CTLs | 0.5; 0.1 | $mm^3 cells^{-1} d^{-1}$ |
| $p_{i=1,2}$ | Production rates of virions infectious HIV and HBV | 50; 480 | - |
| $\tau_{i=1,2}$ | Clearance rates of infectious virions by antibodies (HIR) | $0.05; 10^{-12}$ | $mm^3 d^{-1}$ |
| $d_{i=1,2}$ | Activation rates of effectors (CTLs) and antibodies (HIR) | 0.005; 0.013 | $mm^3 cells^{-1} d^{-1}$ |
| $\alpha_1$ | Death rate of viral load infected T-lymphocyte cells | 0.02 | $d^{-1}$ |
| $\alpha_2$ | Death rate of HB-virus infected hepatocyte cells | 0.053 | $d^{-1}$ |
| $\alpha_3$ | Infectious viral load death rate | 0.4 | $mm^3 d^{-1}$ |
| $\alpha_4$ | Infectious B-virus death rate | 0.67 | $mm^3 d^{-1}$ |
| $\alpha_5$ | Decay rate of CTLs | 0.1 | $d^{-1}$ |
| $\alpha_6$ | Decay rate of HIR | 0.1 | $d^{-1}$ |
| $u_{i=1,2}$ | Treatment control functions for $T_u, T_i, V_i$ | $u_i \in [0,1)$ | |
| $r_{i=1,2}$ | Treatment control functions for $T_u, T_b, V_b$ | $r_i \in [0,1)$ | |
| $A_1, B_1$ | Optimal weight ratio on $u_1, r_1$ | 25000 | |
| $A_2, B_2$ | Optimal weight ratio on $u_2, r_2$ | 250 | |

***Note**: Table 2, is a reflection of models [1, 2, 42, 50], modified to accommodate the present investigation.*

Thus, from the system basic model, we observe that in addition to assumptions of monolytic HIV and HBV infections of models [1, 2], the model is guided by following assumptions:

**Assumption 1**

i. Susceptible double lymphocyte population is assumed to be free of any other infections except dual HIV-HBV infections.
ii. Double lymphocytes and virions are uniformly distributed.
iii. The process of replication of dual adaptive immune system is ignored.
iv. Infection latent cells and non-cytotoxic carrying processes are ignored.
v. Exponential time delay lags, $\omega_{i=1,2} > 0$.
vi. Only population with dual HIV-HBV is considered.

Next, since model (4) completely represent a set of living organisms, then it becomes worthwhile to investigate the model properties in terms of analysis of basic properties of system model.

*2.2 Analysis of Basic Properties of Model*

In this sub-section, we investigate the model basic properties, which include the system state variables invariant and boundedness of solutions as well as the stability analysis of disease-free equilibrium state for an untreated dual delayed HIV-HBV infected model.

*2.2.1 System invariant and boundedness of solutions*

For an untreated dual delay HIV-HBV model, where $u_{i=1,2} = 0$ and $r_{i=1,2} = 0$ for all $t = 0$, our basic model (4) is simplified to a linear system of the form:

$$\begin{aligned}
\frac{dT_u}{dt} &= b_p + s\left(1-\frac{L(t)}{L_{\max}}\right)T_u(t) - \left[\frac{\beta_1 V_i(t) + \beta_2 V_b(t)}{L(t)}\right]T_u(t) - \mu_T T_u(t)\\
\frac{dT_i}{dt} &= \beta_1 e^{-\mu_i \omega_1}\left[\frac{V_i(t-\omega_1)T_u(t-\omega_1)}{L(t-\omega_1)}\right] - (q_1+\alpha_1)T_i(t) - g_1 T_i(t)Q(t)\\
\frac{dT_b}{dt} &= \beta_2 e^{-\mu_b \omega_2}\left[\frac{V_b(t-\omega_2)T_u(t-\omega_2)}{L(t-\omega_2)}\right] - (q_2+\alpha_2)T_b(t) - g_2 T_b(t)Q(t)\\
\frac{dV_i}{dt} &= q_1 p_1 T_i(t) - \alpha_3 V_i(t) - \tau_1 V_i(t)Z(t)\\
\frac{dV_b}{dt} &= q_2 p_2 T_b(t) - \alpha_4 V_b(t) - \tau_2 V_b(t)Z(t)\\
\frac{dQ}{dt} &= d_1(T_i(t)+T_b(t))Q(t) - \alpha_5 Q(t)\\
\frac{dZ}{dt} &= d_2(V_i(t)+V_b(t))\,\mathrm{Z}(t) - \alpha_6 Z(t)
\end{aligned} \quad . \qquad (6)$$

So, we see that model (6) represents a system of 7-Dimensional delayed differential equations for which we are required to define the system initial functions and the functional framework. In this case, suppose $N = C\left([-\omega_i, 0]_{i=1,2}; \Re^7\right)$ is the Banach space of continuous mapping from $[-\omega_i, 0]_{i=1,2}$ to $\Re^7$ equip with the sup-norm $\|\xi\| = \sup_{-\omega_i \le t \le 0} \xi(t)$, then the initial functions of the system verify the following:

$$\left(T_u(\theta), T_i(\theta), T_b(\theta), V_i(\theta), V_b(\theta), Q(\theta), Z(\theta)\right) \in N . \qquad (7)$$

Moreso, from biological point of view, these initial functions $T_u(\theta), T_i(\theta), T_b(\theta), V_i(\theta), V_b(\theta), Q(\theta)$ and

$Z(\theta)$ assume non-negative values i.e.

$$T_u(\theta) \geq 0, T_i(\theta) \geq 0, T_b(\theta) \geq 0, V_i(\theta) \geq 0, V_b(\theta) \geq 0, Q(\theta) \geq 0, Z(\theta) \geq 0\ , \forall t \in [-\omega_{i=1,2}, 0]\,. \tag{8}$$

Equation (8) is inert if

$$L_{\max} \geq L(t) = T_u(t) + T_i(t) + T_b(t) > 0\ , \forall t \in [-\omega_{i=1,2}, 0]\,. \tag{9}$$

Therefore, the resulting solutions of model (6) about the invariant and boundedness of solutions is satisfied by the following theorem.

**Theorem 1** For any given initial functions satisfying conditions (7) and (8), the system (6) has a unique solution and in addition, this solution is invariant and bounded for all $t \geq 0$.

**Proof.** From classical theory of functional differential equations [2, 50], it is noticed that system (6) is locally Lipschitzian at $t = 0$, where $t_m$ is the maximal existence time for the solution of system (6). Observe that if $T_u(0) = 0$, then $T_u(t) \equiv 0\ \forall t > 0$. Hence, it can be assumed that $\dot{T}_u(t) > 0$. Observe also that $T_i(0) = 0$, then from equation (8), we have $\dot{T}_i(0) = \beta_1\left((V_i(-\omega_1)T_u(-\omega_1))/L(-\omega_1)\right) \geq (0,t)$, which implies that for $t > 0$, we have $\dot{T}_i(t) > 0$. Similarly, if $T_b(0) = 0$ then $\dot{T}_b(0) = \beta_2\left((V_b(-\omega_2)T_u(-\omega_2))/L(-\omega_2)\right) \geq (0,t)$, which imply that for $t > 0$, we have $\dot{T}_b(t) > 0$. Moreso, if $V_i(0) = 0$ then $\dot{V}_i(0) = q_1 p_1 T_i(0) > 0$, which imply that for $t > 0$, we have $\dot{V}_i(t) > 0$. This is to say that if $V_b(0) = 0$ then $\dot{V}_b(0) = q_2 p_2 T_b(0) > 0$, which imply that for $t > 0$, we have $\dot{V}_b(t) > 0$. Furthermore, if $Q(0) = 0, Z(0) = 0$, then $Q(t) \equiv 0, Z(t) \equiv 0\ \forall t > 0$. Thus, it can be assumed that $Q(0) > 0, Z(0) > 0$.

Now, we then first assume that there is $t_m > t_1 > 0$ such that $T_u(t_1) = 0$ and $T_u(t) > 0$, $T_i(t) > 0$, $T_b(t) > 0$, $V_i(t) > 0$ $V_b(t) > 0$ for $t \in [0, t_1]$. Observe that

$$\frac{dT_u}{dt} = b_p + s\left(1 - \frac{L(t)}{L_{\max}}\right)T_u(t) - \left[\frac{\beta_1 V_i(t) + \beta_2 V_b(t)}{L(t)}\right]T_u(t) - \mu_T T_u(t)\,. \tag{10}$$

Then, it is easy to show that $0 < L(t) < L_{\max}$ for $t \in [0, t_1]$. We then see that

$$\frac{dT_u}{dt} \geq -\left[\frac{\beta_1 V_i(t) + \beta_2 V_b(t)}{L(t)}\right]T_u(t)\,,$$

which clearly implies that $T_i(t), T_b(t) < L(t)$, for $t \in [0, t_1]$. These observations implies that for $t \in [0, t_1]$, we have

$$\frac{dT_u}{dt} \geq -\left[\frac{\beta_1 V_i(t) + \beta_2 V_b(t)}{T_i(t) + T_b(t)}\right]T_u(t)\,.$$

Hence,

$$T_u(t_1) \geq T_u(0)e^{-\int_0^{t_1}\left(\frac{\beta_1 V_i(s) + \beta_2 V_b(s)}{T_i(s) + T_b(s)}\right)ds} > 0\,, \tag{11}$$

which contradicts initial assumption. Thus, following similar approach, we can prove that all the state variables of system (6) are invariant, which proves the positivity of solutions in $t \in [0, t_m)$.

Next, we prove for the boundedness of solutions of the system (6) by considering the following functions. Let

$$M(t) = \left((p_1 + p_2)d_1 d_2\right)e^{-(\mu_i\omega_1 + \mu_b\omega_2)}T_u(t) + \left((p_1 + p_2)d_1 d_2\right)T_i(t + \omega_1) + \left((p_1 + p_2)d_1 d_2\right)T_b(t + \omega_2)$$

$$+\frac{d_1d_2}{2}V_i(t+\omega_1)+\frac{d_1d_2}{2}V_b(t+\omega_2)+\frac{d_1d_2}{2}Q(t+\omega_1)+(p_1+p_2)d_1(q_1+q_2)Z(t+\omega_2)\,. \tag{12}$$

From equation (6), substituting the state variables, we have

$$\begin{aligned}\frac{M(t)}{dt}&=\left((p_1+p_2)d_1d_2\right)e^{-(\mu_i\omega_1+\mu_b\omega_2)}\left[b_p+s\left(1-\frac{L(t)}{L_{\max}}\right)T_u(t)-\left[\frac{\beta_1V_i(t)+\beta_2V_b(t)}{L(t)}\right]T_u(t)-\mu_TT_u(t)\right]\\&+\left((p_1+p_2)d_1d_2\right)\left[\beta_1e^{-\mu_i\omega_1}\frac{V_i(t)T_u(t)}{L(t)}-(q_1+\alpha_1)T_i(t+\omega_1)-g_1T_i(t+\omega_1)Q(t+\omega_1)\right]\\&+\left((p_1+p_2)d_1d_2\right)\left[\beta_2e^{-\mu_b\omega_2}\frac{V_b(t)T_u(t)}{L(t)}-(q_2+\alpha_2)T_b(t+\omega_2)-g_2T_b(t+\omega_2)Q(t+\omega_2)\right]\\&+\frac{d_1d_2}{2}\left[q_1p_1T_i(t)-\alpha_3V_i(t+\omega_1)-\tau_1V_i(t+\omega_1)Z(t+\omega_1)\right]\\&+\frac{d_1d_2}{2}\left[q_2p_2T_b(t+\omega_2)-\alpha_4V_b(t+\omega_2)-\tau_2V_b(t+\omega_2)Z(t+\omega_2)\right]\\&+\frac{d_1d_2}{2}\left[d_1(T_i(t+\omega_1)+T_b(t+\omega_2))Q(t+\omega_1)-\alpha_5Q(t+\omega_1)\right]\\&+\left((p_1+p_2)d_1(q_1+q_2)\right)\left[d_2(V_i(t+\omega_1)+V_b(t+\omega_2))Z(t+\omega_2)-\alpha_6Z(t+\omega_2)\right]\end{aligned}\,. \tag{13}$$

Since $0<L(t)<L_{\max}$, $T_u(t)<L_{\max}$, $-T_u(t)L(t)<-T_u(t)$ for $t>0$, it follows that

$$\begin{aligned}\frac{dM(t)}{dt}&\le\left((p_1+p_2)d_1d_2\right)e^{-(\mu_i\omega_1+\mu_b\omega_2)}\left[b_p+s\left(1-\frac{L(t)}{L_{\max}}\right)T_u(t)\right]\\&-\frac{\left((q_1+q_2)(p_1+p_2)d_1d_2\right)}{2}\left[T_i(t+\omega_1)+T_b(t+\omega_1)\right]\\&-\frac{(\alpha_3+\alpha_4)d_1d_2}{2}\left[V_i(t+\omega_1)+V_b(t+\omega_1)\right]\\&-\frac{\alpha_5d_2(\tau_1+\tau_2)}{2}Q(t+\omega_1)-(p_1+p_2)d_1(g_1+g_2)\alpha_6Z(t+\omega_2)\,.\end{aligned} \tag{14}$$

Suppose, we set $\eta=\min\left(s/L_{\max},(q_1+q_2)/2,(\alpha_3+\alpha_4)/2,\alpha_5,\alpha_6\right)$, then we obtain

$$\frac{dM(t)}{dt}\le\left((p_1+p_2)d_1d_2\right)e^{-(\mu_i\omega_1+\mu_b\omega_2)}-\eta M(t)\,. \tag{15}$$

Using Gronwall's Lemma, we see that $M(t)$ is bounded and so are the functions $T_u(t),T_i(t),T_b(t),V_i(t),V_b(t),Q(t)$ and $Z(t)$, which ensure that the solutions exist globally. Therefore, the results obtain shows that the components of the solution of system (6) are invariant for all $t\in[0,t_m)$. Hence, the boundedness of $T_u(t),T_i(t),T_b(t),V_i(t),V_b(t),Q(t)$ and $Z(t)$ on $t\in[0,t_m)$ implies that $t_m=\infty$. This completes the proof. □

*2.2.2 Equili*bria and stability analys*is*

For a system of linear model (6), which represents an untreated dual delayed HIV-HBV infection dynamics, it is obvious that the model is associated with complexity in-terms of state variables and accompanying parameters. This implies that the system equilibria and stability analysis are bound to be somewhat complex. Not-with-standing, we show the ability of the model to exhibit multiple locally asymptomatically steady states,

which defines all possible equilibrium points. First, model (6) has disease-free equilibrium $E_0 = (b_p/\mu_T, 0, 0, 0, 0, 0, 0)$. This corresponds to the maximal level of healthy double lymphocyte cells with biological meaning, provided the system reproduction number $R_0$ is

$$R_0 = \frac{L_{\max}(\beta_1+\beta_2) + b_p(q_1+q_2)e^{-(\mu_i\omega_1+\mu_b\omega_2)}}{(\alpha_1+\alpha_2)(\alpha_3+\alpha_4)} < 1. \tag{16}$$

Then, it can be deduced from the DFE and equation (16) that viral load infected cells, B-virus infected cells, free viral load, infectious B-virus, cellular immune response and humeral immune response are all zero. This can also be said of the second equilibrium $E_1 = (T_{(u)1}, T_{(i)1}, T_{(b)1}, V_{(i)1}, V_{(b)1}, 0, 0)$, which represents the no immune response equilibrium with

$$\begin{cases} T_{(u)1} = \dfrac{L_{\max}(\beta_1+\beta_2)(q_1+q_2)(p_1+p_2)}{R_0(\alpha_3+\alpha_4)s}(R_0-1) \\ T_{(i)1} = \dfrac{L_{\max}\beta_1 q_1 p_1}{(\alpha_3+\alpha_4)s}(R_0-1) \\ T_{(b)1} = \dfrac{L_{\max}\beta_2 q_2 p_2}{(\alpha_3+\alpha_4)s}(R_0-1) \\ V_{(i)1} = \dfrac{L_{\max}\beta_1 (q_1 p_1)^2}{(\alpha_3+\alpha_4)^2 R_0 s}(R_0-1) \\ V_{(b)1} = \dfrac{L_{\max}\beta_2 (q_2 p_2)^2}{(\alpha_3+\alpha_4)^2 R_0 s}(R_0-1) \end{cases}. \tag{17}$$

This equilibrium exists provided $R_0 > 1$ in addition to several other biological meanings.

More analytically, from model (6), let $\delta = (T_u, T_i, T_b, V_i, V_b, Q, Z)$, represent the vectorial capacity of model (6), then in vector form, we have

$$\frac{d\delta}{dt} = f(t, \delta; x), \tag{18}$$

where $f(t, \delta; x)$ denotes the RHS of the ODEs and $x$, the system vector parameter as in table (2). Therefore, solving equation (18), we deployed a readily compatible Runge-Kutter of order 4 to obtain the equilibria $\overline{x}_k$, i.e. $f(t, \delta; x) = 0$. The Jacobian matrix is then computed from the partial derivative

$$\frac{\partial f(t, \delta; x)}{\partial \delta} = \left[\frac{\partial f_i(t, \delta; x)}{\partial \delta_i}\right]. \tag{19}$$

For an off-treatment scenario of model (6), the Jacobian with $\Omega_i, \forall i = 1, 2, ...., 13$

$$\Omega_1 = s\left(1 - \frac{2T_u + T_i + T_b}{L_{\max}}\right) - \frac{(\beta_1 V_i T_b + \beta_2 V_b T_i)}{(T_u + T_i + T_b)^2} - \mu_T, \quad \Omega_2 = -\beta_1 e^{-\mu_i\omega_1}\frac{V_i T_u}{(T_u+V_i)^2} - (q_1+\alpha_1) - g_1 Q,$$

$$\Omega_3 = -\beta_2 e^{-\mu_b\omega_2}\frac{V_b T_u}{(T_u+V_b)^2} - (q_2+\alpha_2) - g_2 Q, \ \Omega_4 = -\alpha_3 - \tau_1 Z, \ \Omega_5 = -\alpha_4 - \tau_2 Z,$$

$$\Omega_6 = d_1(T_i + T_b) - \alpha_5,\ \Omega_7 = d_2(V_i + V_b) - \alpha_6,\ \Omega_8 = -\frac{sT_u}{L_{\max}} + \frac{(\beta_1 V_i + \beta_2 V_b)T_u}{(T_u + T_b)^2},$$

$$\Omega_9 = -\frac{sT_u}{L_{\max}} + \frac{(\beta_1 V_i + \beta_2 V_b)T_u}{(T_u + T_i)^2},\ \Omega_{10} = \beta_1 e^{-\mu_i \omega_1} \frac{T_u}{(T_u + T_i + T_b)},$$

$$\Omega_{11} = \beta_2 e^{-\mu_b \omega_2} \frac{T_u}{(T_u + T_i + T_b)},\ \Omega_{12} = -\frac{\beta_1 T_u}{(T_u + T_i + T_b)} \text{ and } \Omega_{13} = -\frac{\beta_2 T_u}{(T_u + T_i + T_b)}$$

is obtained as:

$$J = \begin{pmatrix} \Omega_1 & \Omega_8 & \Omega_9 & \Omega_{12} & \Omega_{13} & 0 & 0 \\ \beta_1 e^{-\mu_i \omega_1} \frac{V_i T_i}{(T_u + T_b)^2} & \Omega_2 & -\beta_1 e^{-\mu_i \omega_1} \frac{V_i T_u}{(T_u + V_b)^2} & \Omega_{10} & 0 & -g_1 T_i & 0 \\ \beta_2 e^{-\mu_b \omega_2} \frac{V_b T_b}{(T_u + T_b)^2} & -\beta_2 e^{-\mu_b \omega_2} \frac{V_b T_u}{(T_u + V_b)^2} & \Omega_3 & 0 & \Omega_{11} & -g_1 T_b & 0 \\ 0 & q_1 p_1 & 0 & \Omega_4 & 0 & 0 & -\tau_1 V_i \\ 0 & 0 & q_2 p_2 & 0 & \Omega_5 & 0 & -\tau_2 V_b \\ 0 & d_1 Q & d_1 Q & 0 & 0 & \Omega_6 & 0 \\ 0 & 0 & 0 & d_2 Z & d_2 Z & 0 & \Omega_7 \end{pmatrix} \quad .(20)$$

Thus, from equation (20), the dynamic ODE that is linearized about the equilibria $\overline{x}_k$, is obtained by substituting computed $\overline{x}_k$ for $x$ in equation (20). The basis of linearization is to ensure that for eigenvalues with negative real part, the equilibria $\overline{x}_k$ are locally asymptotically stable. This affirms the fact that in addition to system equilibria $E_0$ and $E_1$, there are several other physical steady states and non-physical steady state, which could be derived from those of [1, 2, 15, 16, 42].

Now, using the above basic properties as background, we can then address the main goal of our investigation, which amount to the maximization of the system performance index measured in terms of the concentration of susceptible double lymphocyte cells and dual adaptive immune system induced by minimal chemotherapy cost. This utmost task is achieved following an acceptable methodological application of desired chemotherapies within a finite time interval.

## 3. Optimal Control Problem and Mathematical Analysis

With the introduction of multi-therapies and following the biological behavior of dual adaptive immune system as also treatment outfit, we will devote this section to the optimal control formulation investigation of its invariant and boundedness of solutions. Also discussed in this section is the mathematical analysis for the derived model. This involves the system optimal characterization and existence of optimal dual-pair control.

### *3.1 Optimal Control Problem for HIV-HBV Model*

By definition, optimal control is concerned with the maximization of uninfected target population and the affected immune system, while suppressing affected disease(s) under anticipated minimized systemic cost, following the methodological application of desired control functions [50]. Therefore, in this section, we seek an optimal control of dual delayed HIV-HBV multi-therapies, which allow the maximization of healthy double

lymphocytes concentration as well as maximal cellular immune response and humeral immune response. We also, concern the study with the maximal suppression of both viral load and B-virus inclusive of infected double lymphocyte cells under presumed systemic cost.

In this investigation, we consider our dual-pair control functions in the form: reverse transcriptase inhibitors – RTI and protease inhibitors – PIs for HIV; standard interferon-$\alpha$ (sINF-$\alpha$) and nucleoside analogues - NAs in addition to the dual role of adaptive immune system (cellular immune response – CTLs and humeral immune response – HIR). Hence, the control initial, triple-dual control functions, otherwise known as tri-linear control functions.

Mathematically, in stating the optimization control problem, we first assume that both viral control function denoted by $u_1$ , $u_2$ ;and that of B-virus by $r_1$ , $r_2$ all varies with time and has antiviral effect on virions production. Clinically, the control functions $u_1$ , $r_1$ exhibits similar function as is the case for $r_2$ , $u_2$ in their respective T-lymphocytes. The roles of these control functions are defined as follows:

**Definition 1**

i. Reverse transcriptase inhibitor denoted by $u_1$, represent drug efficacy in blocking new vital load infection.
ii. Standard interferon-$\alpha$ denoted by $r_1$ is responsible for the elimination of infected cells and reduction of *ccc*DNA and blocking of new B-virus infections in the liver cells.
iii. Protease inhibitors denoted by $u_2$ is the efficacy of chemotherapy in inhibiting viral load replication.
iv. Nucleoside analogues (i.e. lamivudine) denoted by $r_2$ represents efficacy of drug in elongation of DNA and inhibition of HBV replication.

**Definition 2**

i. Cellular immune response mediated by cytotoxic T-lymphocytes (CTLs) is a body defense mechanism, which is initiated at the onset of HIV-HBV infection and is responsible for the killing of infected liver cells.
ii. Humoral immune response initiated by the antibodies is protein-like B-cells responsible for the neutralization and inhibition of virus proliferation.

In line with definitions 1& 2, we consider the control version of model (6), which is time inclusive of model (4), as:

$$
\begin{aligned}
\frac{dT_u(t)}{dt} &= b_p + s\left(1-\frac{L(t)}{L_{\max}}\right)T_u(t) - \left[\frac{\beta_1(1-u_1(t))V_i(t)+\beta_2(1-r_1(t))V_b(t)}{L(t)}\right]T_u(t) - \mu_T T_u(t)\\
\frac{dT_i(t)}{dt} &= \beta_1 e^{-\mu_i\omega_1}(1-u_1(t))\left[\frac{V_i(t-\omega_1)T_u(t-\omega_1)}{L(t-\omega_1)}\right] - (q_1+\alpha_1)T_i(t) - g_1T_i(t)Q(t)\\
\frac{dT_b(t)}{dt} &= \beta_2 e^{-\mu_b\omega_2}(1-r_1(t))\left[\frac{V_b(t-\omega_2)T_u(t-\omega_2)}{L(t-\omega_2)}\right] - (q_2+\alpha_2)T_b(t) - g_2T_b(t)Q(t)\\
\frac{dV_i(t)}{dt} &= (1-u_2(t))q_1p_1T_i(t) - \alpha_3V_i(t) - \tau_1V_i(t)Z(t)\\
\frac{dV_b(t)}{dt} &= (1-r_2(t))q_2p_2T_b(t) - \alpha_4V_b(t) - \tau_2V_b(t)Z(t)\\
\frac{dQ(t)}{dt} &= d_1(T_i(t)+T_b(t))Q(t) - \alpha_5Q(t)\\
\frac{dZ(t)}{dt} &= d_2(V_i(t)+V_b(t))\,\mathrm{Z}(t) - \alpha_6Z(t)
\end{aligned}
\quad , \qquad (21)
$$

with conditions and parameters descriptions as earlier mentioned in model (4). For this optimal problem (21), the properties of boundedness and positivity of solutions is defined by the following theorem.

**Theorem 2** For any initial conditions $T_u(\theta), T_i(\theta), T_b(\theta), V_i(\theta), V_b(\theta), Q(\theta)$ and $Z(\theta)$, satisfying equations (7) and (8), the system (21) has a unique solution; Moreso, this solution is non-negative and bounded for all $t \geq 0$.

**Proof.** The proof for this theorem is omitted since it is similar to those of theorem 1 and ([42], Thm. 2, pg. 5-7).

Now, from the Jacobian (20), the control functions $u_{i=1,2}(t)$ and $r_{i=1,2}(t)$ are bounded and Lebesgue integrable function. Moreso, by definition 1, virions production under chemotherapies are $(1-u_1(t))q_1 p_1$ for HIV and $(1-r_1(t))q_2 p_2$ for HBV. Clinically, if $(u_2, r_2) = 1$, then inhibition of infections are 100% efficacious, otherwise, no inhibition if $(u_2, r_2) = 0$. On a similar note, if the control functions $(u_1, r_1)$ represents efficacy of chemotherapies in blocking new dual HIV-HBV infections, then the infection rates in the presence of multi-therapies are $(1-u_1(t))\beta_1$ and $(1-r_1(t))\beta_2$. Therefore, the optimization problem that maximizes the goal of study is defined by the following objective functional

$$H(u_i, r_i)_{i=1,2} = \int_{t_0}^{t_f} \left\{ T_u(t) + Q(t) + Z(t) - \left[ \frac{(A_1 + B_1)}{2}(u_1 + r_1)^2 + \frac{(A_2 + B_2)}{2}(u_2 + r_2)^2 \right] \right\} dt, \tag{22}$$

subject to equation (21) as constraint and having $t_f$ as treatment time limit.

We see from equation (22) that four positive constants $A_{i=1,2} \geq 0$ and $B_{i=1,2} \geq 0$ are introduced. These parameters denote treatment optimal weight factors, which define benefit-cost on chemotherapies $u_{i=1,2}, r_{i=1,2}$ respectively. Thus, since our goal is that of maximization of the objective functional, which then translate to the minimization of viral load and B-virus, while maximizing uninfected double lymphocyte cells and increase in the levels of affected adaptive immune response, then we seek an optimal control dual-pair $(u^*_{i=1,2}, r^*_{i=1,2})$ such that

$$H(u^*_{i=1,2}, r^*_{i=1,2}) = \max_{0 \leq u_i, r_i \leq 1} \{ H(u_i, r_i) : (u_i, r_i) \in J \}$$

where $J := \{(u_i, r_i) \setminus u_i, r_i$ is Lebesgue-measurable with $a_i \leq u_i \leq b_i$, $m_i \leq r_i \leq n_i$, $t \in [t_0, t_f], \forall i = 1,2\}$ a control set.

**Remark 1** The introduction of linearization control functions $A_{i=1,2} \geq 0$ and $B_{i=1,2} \geq 0$ is of essence, since it serves as simple nonlinear controls. Moreso, benefits on cost are nonlinear and cases of drugs side-effect are adequately considered, [1, 64].

**Proposition 1** The inequalities of the control set $\{a_i \leq u_i \leq b_i < 1, m_i \leq r_i \leq n_i < 1, t \in [t_0, t_f], \forall i = 1,2\}$ on chemotherapies holds against any hazardous drugs side-effect and justifies the optimal weights $A_{i=1,2} \geq 0$ and $B_{i=1,2} \geq 0$.

### *3.2 Mathematical Analysis of an Optimal Control Dual-pair*

In this subsection, we consider the theoretical analysis of the system optimal control characterization and existence of an optimal control dual-pair.

#### *3.2.1 System optimal control characterization*

To be able to establish the existence of an optimal control dual-pair, we are required to identify the optimal control characteristics, which define the penalty terms on constraints. This is visible using classical Pontryagin's maximum principle, which involves convert solving of our optimization problem into maximizing the Hamiltonian argument defined by the Lagrangian [64]:

$$\begin{aligned} G &\equiv G\left(t, T_u, T_i, T_b, V_i, V_b, Q, Z, u_1, r_1, u_2, r_2, \lambda_i\right) \\ &= T_u(t) + Q(t) + Z(t) - \left[\frac{(A_1 + B_1)}{2}(u_1 + r_1)^2 + \frac{(A_2 + B_2)}{2}(u_2 + r_2)^2\right] \\ &\quad + \sum_{i-1}^{7} \lambda_i f_i + w_{11}(t)(b_1 - u_1) + w_{12}(t)(u_1 - a_1) + w_{21}(t)(b_2 - u_2) \\ &\quad + w_{22}(t)(u_2 - a_2) + x_{11}(t)(m_1 - r_1) + x_{12}(t)(r_1 - m_1) \\ &\quad + x_{21}(t)(n_2 - r_2) + x_{22}(t)(r_2 - m_2) \end{aligned} \quad , \tag{23}$$

where $w_{12}(t), \ldots\ldots\ldots, x_{22}(t) \geq 0$ are penalty multipliers satisfying

$$w_{11}(t)(b_1 - u_1) = 0, w_{12}(t)(u_1 - a_1) = 0 \qquad \text{at optimal } u_1^*$$

$$w_{21}(t)(b_2 - u_2) = 0, w_{22}(t)(u_2 - a_2) = 0 \qquad \text{at optimal } u_2^*$$

$$x_{11}(t)(m_1 - r_1) = 0, x_{12}(t)(r_1 - m_1) = 0 \qquad \text{at optimal } r_1^*$$

$$x_{21}(t)(n_2 - r_2) = 0, x_{22}(t)(r_2 - m_2) = 0 \qquad \text{at optimal } r_2^*,$$

and which ensures that $u_i^* \in [0,1]$ and $r_i^* \in [0,1]$, for all $i = 1,2$. From equation (23), the functions $\lambda_i(t), \mathrm{i}-1, \ldots., 7$ are the model adjoint variables, which determine the adjoint system and the function $f_i$ for $i = 1, \ldots., 7$ is the system dynamics defined by

$$\begin{aligned} f_1 &= b_p + s\left(1 - \frac{L(t)}{L_{\max}}\right)T_u(t) - \left[\frac{\beta_1(1-u_1(t))V_i(t) + \beta_2(1-r_1(t))V_b(t)}{L(t)}\right]T_u(t) - \mu_T T_u(t) \\ f_2 &= \beta_1 e^{-\mu_i \omega_1}(1-u_1(t))\left[\frac{V_i(t-\omega_1)T_u(t-\omega_1)}{L(t-\omega_1)}\right] - (q_1 + \alpha_1)T_i(t) - g_1 T_i(t)Q(t) \\ f_3 &= \beta_2 e^{-\mu_b \omega_2}(1-r_1(t))\left[\frac{V_b(t-\omega_2)T_u(t-\omega_2)}{L(t-\omega_2)}\right] - (q_2 + \alpha_2)T_b(t) - g_2 T_b(t)Q(t) \\ f_4 &= (1-u_2(t))q_1 p_1 T_i(t) - \alpha_3 V_i(t) - \tau_1 V_i(t)Z(t) \\ f_5 &= (1-r_2(t))q_2 p_2 T_b(t) - \alpha_4 V_b(t) - \tau_2 V_b(t)Z(t) \\ f_6 &= d_1(T_i(t) + T_b(t))Q(t) - \alpha_5 Q(t) \\ f_7 &= d_2(V_i(t) + V_b(t))\,\mathrm{Z}(t) - \alpha_6 Z(t) \end{aligned} \quad . \tag{24}$$

From here, we then examine all the possible controls for $u_i^*$ and $r_i^*$ including those of boundary conditions $0 \le u_i^*, r_i^* \le 1$ for all $i = 1,2$.

i. The case of the set $\{t \setminus 0 < u_i^*(t), r_i^*(t) < 1\} : (w_{ij}, x_{ij}) = 0$ for all $i, j = 1,2$. The unconstrained optimality conditions $u_i^* \in [0,1]$ and $r_i^* \in [0,1]$ for $i, j = 1,2$ can be solve using the Pontryagin's maximum principle, which state that

$$\frac{\partial G}{u_1^*} = 0, \frac{\partial G}{r_1^*} = 0, \frac{\partial G}{u_2^*} = 0 \text{ and } \frac{\partial G}{r_2^*} = 0.$$

Then, we find $\frac{\partial G}{u_i^*} = 0, \frac{\partial G}{r_i^*} = 0$ for $i = 1,2$ and solve for $u_1^*, r_1^*, u_2^*$ and $r_2^*$ by setting the partial derivative of $G$ equal to zero i.e.

$$\frac{\partial G}{u_1^*} = -(A_1 + B_1)u_1^*(t) + \lambda_1(t)\left(\frac{\beta_1 V_i(t) T_u(t)}{(T_u + T_i + T_b)^2}\right) - \lambda_2(t)\left(\beta_1 e^{-\mu_i \omega_1} \frac{V_i(t-\omega_1) T_u(t-\omega_1)}{(T_u + T_i)^2}\right) - w_{11} + w_{12} = 0 \quad \text{at } u_1^*$$

$$\frac{\partial G}{r_1^*} = -(A_1 + B_1)r_1^*(t) + \lambda_1(t)\left(\frac{\beta_2 V_b(t) T_u(t)}{(T_u + T_i + T_b)^2}\right) - \lambda_3(t)\left(\beta_2 e^{-\mu_b \omega_2} \frac{V_b(t-\omega_2) T_u(t-\omega_2)}{(T_u + T_b)^2}\right) - x_{11} + x_{12} = 0 \quad \text{at } r_1^*$$

$$\frac{\partial G}{u_2^*} = -(A_2 + B_2)u_2^*(t) - \lambda_4(t) q_1 p_1 T_i(t) - w_{21} + w_{22} = 0 \quad \text{at } u_2^*$$

and

$$\frac{\partial G}{r_2^*} = -(A_2 + B_2)u_2^*(t) - \lambda_5(t) q_2 p_2 T_b(t) - x_{21} + x_{22} = 0 \quad \text{at } r_2^*.$$

Solving for the optimal controls $u_i^*$ and $r_i^*$ for $w_{ij} = 0$ and $x_{ij} = 0$, we have

$$u_1^*(t) = \frac{1}{(A_1 + B_1)}\left[\lambda_1(t)\left(\frac{\beta_1 V_i(t) T_u(t)}{(T_u + T_i + T_b)^2}\right) - \lambda_2(t)\left(\beta_1 e^{-\mu_i \omega_1} \frac{V_i(t-\omega_1) T_u(t-\omega_1)}{(T_u + T_i)^2}\right)\right], \tag{25}$$

$$r_1^*(t) = \frac{1}{(A_1 + B_1)}\left[\lambda_1(t)\left(\frac{\beta_2 V_b(t) T_u(t)}{(T_u + T_i + T_b)^2}\right) - \lambda_3(t)\left(\beta_2 e^{-\mu_b \omega_2} \frac{V_b(t-\omega_2) T_u(t-\omega_2)}{(T_u + T_b)^2}\right)\right], \tag{26}$$

$$u_2^*(t) = -\frac{1}{(A_2 + B_2)}\left[\lambda_4(t) q_1 p_1 T_i(t)\right] \tag{27}$$

and

$$r_2^*(t) = -\frac{1}{(A_2 + B_2)}\left[\lambda_5(t) q_2 p_2 T_b(t)\right]. \tag{28}$$

Furthermore, we consider the characterization at the boundaries for $u_i^* = 0, r_i^* = 0, u_i^* = 1$ and $r_i^* = 1$ as well as non-boundary cases.

ii. The set $\{t \setminus u_i^*(t), r_i^*(t) = 0, i = 1,2\} : w_{1j} \ge 0, x_{1j} \ge 0, w_{i2} = 0, x_{i2} = 0$ for all $i, j = 1$.

The optimal controls are given by

$$0 = \frac{\lambda_1(t)\left(\frac{\beta_1 V_i(t)T_u(t)}{(T_u+T_i+T_b)^2}\right) - \lambda_2(t)\left(\beta_1 e^{-\mu_i\omega_1}\frac{V_i(t-\omega_1)T_u(t-\omega_1)}{(T_u+T_i)^2}\right) - w_{1j}}{(A_1+B_1)}.$$

Since $w_{1j} \geq 0$, we have

$$\frac{\lambda_1(t)\left(\frac{\beta_1 V_i(t)T_u(t)}{(T_u+T_i+T_b)^2}\right) - \lambda_2(t)\left(\beta_1 e^{-\mu_i\omega_1}\frac{V_i(t-\omega_1)T_u(t-\omega_1)}{(T_u+T_i)^2}\right)}{(A_1+B_1)} \leq 0.$$

Ensuring that $u_1^*$ is non-negative, we apply the notation

$$u_1^*(t) = \left(\frac{\lambda_1(t)\left(\frac{\beta_1 V_i(t)T_u(t)}{(T_u+T_i+T_b)^2}\right) - \lambda_2(t)\left(\beta_1 e^{-\mu_i\omega_1}\frac{V_i(t-\omega_1)T_u(t-\omega_1)}{(T_u+T_i)^2}\right)}{(A_1+B_1)}\right)^+.$$

Similarly,

$$r_1^*(t) = \left(\frac{\lambda_1(t)\left(\frac{\beta_2 V_b(t)T_u(t)}{(T_u+T_i+T_b)^2}\right) - \lambda_3(t)\left(\beta_2 e^{-\mu_b\omega_2}\frac{V_b(t-\omega_2)T_u(t-\omega_2)}{(T_u+T_b)^2}\right)}{(A_1+B_1)}\right)^+,$$

$$u_2^*(t) = \left(-\frac{1}{(A_2+B_2)}\left[\lambda_4(t)q_1 p_1 T_i(t)\right]\right)^+$$

and

$$r_2^*(t) = \left(-\frac{1}{(A_2+B_2)}\left[\lambda_5(t)q_2 p_2 T_b(t)\right]\right)^+.$$

iii. The case for the set $\{t \setminus u_i^*(t), r_i^*(t) = 1, i = 1,2\} : w_{i1} = 0, x_{2j} = 0, w_{2j} \geq 0, x_{2j} \geq 0$ for all $i, j = 2$.

The optimal controls are obtained as:

$$1 = \frac{\lambda_1(t)\left(\frac{\beta_1 V_i(t)T_u(t)}{(T_u+T_i+T_b)^2}\right) - \lambda_2(t)\left(\beta_1 e^{-\mu_i\omega_1}\frac{V_i(t-\omega_1)T_u(t-\omega_1)}{(T_u+T_i)^2}\right) + w_{2j}}{(A_1+B_1)},$$

which implies that

$$0 \leq w_{2j} = \lambda_1(t)\left(\frac{\beta_1 V_i(t)T_u(t)}{(T_u+T_i+T_b)^2}\right) - \lambda_2(t)\left(\beta_1 e^{-\mu_i\omega_1}\frac{V_i(t-\omega_1)T_u(t-\omega_1)}{(T_u+T_i)^2}\right) - (A_1+B_1).$$

Therefore,

$$u_1^*(t)=\left(\frac{\lambda_1(t)\left(\frac{\beta_1 V_i(t)T_u(t)}{(T_u+T_i+T_b)^2}\right)-\lambda_2(t)\left(\beta_1 e^{-\mu_i\omega_1}\frac{V_i(t-\omega_1)T_u(t-\omega_1)}{(T_u+T_i)^2}\right)}{(A_1+B_1)}\right)\geq 1.$$

Also,

$$r_1^*(t)=\left(\frac{\lambda_1(t)\left(\frac{\beta_2 V_b(t)T_u(t)}{(T_u+T_i+T_b)^2}\right)-\lambda_3(t)\left(\beta_2 e^{-\mu_b\omega_2}\frac{V_b(t-\omega_2)T_u(t-\omega_2)}{(T_u+T_b)^2}\right)}{(A_1+B_1)}\right)\geq 1,$$

$$u_2^*(t)=\left(-\frac{1}{(A_2+B_2)}\left[\lambda_4(t)q_1p_1T_i(t)\right]\right)\geq 1$$

and

$$r_2^*(t)=\left(-\frac{1}{(A_2+B_2)}\left[\lambda_5(t)q_2p_2T_b(t)\right]\right)\geq 1.$$

Therefore, on this set, we must choose

$$u_1^*(t)=\min\left\{\left(\frac{\lambda_1(t)\left(\frac{\beta_1 V_i(t)T_u(t)}{(T_u+T_i+T_b)^2}\right)-\lambda_2(t)\left(\beta_1 e^{-\mu_i\omega_1}\frac{V_i(t-\omega_1)T_u(t-\omega_1)}{(T_u+T_i)^2}\right)}{(A_1+B_1)}\right),1\right\},$$

Also,

$$r_1^*(t)=\min\left\{\left(\frac{\lambda_1(t)\left(\frac{\beta_2 V_b(t)T_u(t)}{(T_u+T_i+T_b)^2}\right)-\lambda_3(t)\left(\beta_2 e^{-\mu_b\omega_2}\frac{V_b(t-\omega_2)T_u(t-\omega_2)}{(T_u+T_b)^2}\right)}{(A_1+B_1)}\right),1\right\},$$

$$u_2^*(t)=\min\left\{\left(-\frac{1}{(A_2+B_2)}\left[\lambda_4(t)q_1p_1T_i(t)\right]\right),1\right\}$$

and

$$r_2^*(t)=\min\left\{\left(-\frac{1}{(A_2+B_2)}\left[\lambda_5(t)q_2p_2T_b(t)\right]\right),1\right\}.$$

Thus, the characterization of the optimal controls is complete by compatibly combining the three cases for $u_1^*, r_1^*, u_2^*$ and $r_2^*$ defined by the following proposition.

**Proposition 2** The optimal controls for the optimality problem of equation (21) with limits $0\leq a_i\leq u_i^*\leq b_i<1$ and $0\leq m_i\leq r_i^*\leq n_i<1$ is completely characterized by

$$u_1^*(t)=\min\left\{\max\left\{a_1,\left\{\frac{\lambda_1(t)\left(\frac{\beta_1 V_i(t)T_u(t)}{(T_u+T_i+T_b)^2}\right)-\lambda_2(t)\left(\beta_1 e^{-\mu_i\omega_1}\frac{V_i(t-\omega_1)T_u(t-\omega_1)}{(T_u+T_i)^2}\right)}{(A_1+B_1)}\right\}^+,b_1\right\}\right\}, \tag{29}$$

$$r_1^*(t)=\min\left\{\max\left\{m_1,\left\{\frac{\lambda_1(t)\left(\frac{\beta_2 V_b(t)T_u(t)}{(T_u+T_i+T_b)^2}\right)-\lambda_3(t)\left(\beta_2 e^{-\mu_b\omega_2}\frac{V_b(t-\omega_2)T_u(t-\omega_2)}{(T_u+T_b)^2}\right)}{(A_1+B_1)}\right\}^+,n_1\right\}\right\}, \tag{30}$$

$$u_2^*(t)=\min\left\{\max\left\{a_2,-\frac{1}{(A_2+B_2)}\left[\lambda_4(t)q_1p_1T_i(t)\right]\right\}^+,b_2\right\} \tag{31}$$

and

$$r_2^*(t)=\min\left\{\max\left\{m_2,-\frac{1}{(A_2+B_2)}\left[\lambda_5(t)q_2p_2T_b(t)\right]\right\}^+,n_2\right\}. \tag{32}$$

**Remark 2** Intuitively, the optimal controls as inscribed by proposition 2, are concurrently a representation of system circulating terms i.e. healthy and infected double lymphocyte cells, the dual virions and their adjoint variables.

### *3.2.2 Existence of an optimal dual-pair control*

In deriving the system optimal problem as depicted by equations (21) and (22), certain parameter restrictions were imposed. Take for instance, the term $L_{\max}$, which denotes the maximum limit of healthy double lymphocytes. If the death rate at $L_{\max}$ is to be greater than the source supply rate, then the inequality

$$\mu_T L_{\max} > b_p \tag{33}$$

holds. Otherwise, population size must always be lower than $L_{\max}$ such that endemic tendency due to infectious virions are constantly accommodated. Moreso, if population ever gets near $L_{\max}$, then population growth will slow-down, [1, 65]. Of note, proves for existence and uniqueness of an optimal control requires system upperbounds. Therefore, if $T_u(t) < L_{\max}$, then the upperbounds on the solutions of active infectious state variables are derived as:

$$\frac{d\hat{T}_i}{dt}=\beta_1 e^{-\mu_i\omega_1}V_i T_{(u)\max} \qquad \hat{T}_i(t_0)=T_{(i)0}$$

$$\frac{d\hat{T}_b}{dt}=\beta_2 e^{-\mu_b\omega_2}V_b T_{(u)\max} \qquad \hat{T}_b(t_0)=T_{(b)0}$$

$$\frac{d\hat{V}_i}{dt}=q_1p_1\hat{T}_i \qquad \hat{V}_i(t_0)=V_{(i)0}$$

$$\frac{d\hat{V}_b}{dt} = q_2 p_2 \hat{T}_b \qquad \hat{V}_b(t_0) = V_{(b)0}$$

Or

$$\begin{pmatrix} \dot{T}_i \\ \dot{T}_b \\ \dot{V}_i \\ \dot{V}_b \end{pmatrix} = \begin{pmatrix} 0 & 0 & \beta_1 e^{-\mu_i \omega_1} V_i T_{(u)\max} & 0 \\ 0 & 0 & 0 & \beta_2 e^{-\mu_b \omega_2} V_b T_{(u)\max} \\ q_1 p_1 & 0 & 0 & 0 \\ 0 & q_1 p_1 & 0 & 0 \end{pmatrix} \begin{pmatrix} T_i \\ T_b \\ V_i \\ V_b \end{pmatrix} \tag{34}$$

where $(\beta_1, \beta_2) > 0, \mu_i > 0, \mu_b > 0$ and $\omega_{i=1,2} \geq 0$.

From equation (34), it becomes obvious that the system is linearly bounded with supersolutions $\dot{T}_i, T_b, \dot{V}_i, V_b$ uniformly bounded as well. Thus, the existence result follows from the theorem hereof.

**Theorem 3** Given proposition 1 and the inequality (33), there exist optimal dual-pair controls $(u_i^*, r_i^*)_{i=1,2} \in J$ that maximizes the objective functional

$$\max_{(u_i, r_i) \in J} H(u_i, r_i) = H(u_i^*, r_i^*), \forall i = 1, 2.$$

**Proof** Invoking existence results from ([50], Thm. 2, pg. 26-27, [66], Thm. 4.1, pg. 68-69, [67]), we first check for the following properties:

($C_1$) The class of all control sets $u_i(t), r_i(t), i = 1, 2$ are Lebesgue-integrable functions on $[t_0, t_f]$ with value in the admissible control sets and such that the corresponding state variables are satisfied and are non-empty.

($C_2$) The admissible control set $J$, is convex and closed.

($C_3$) The RHS of the state system is continuous and bounded by linear functions of $u_i(t)$ and $r_i(t), i = 1, 2$ with coefficients that depends on proposition 1 and on the control variables.

($C_4$) The integrand of the object functional is concave on $J$.

($C_5$) There exist constants $c_1, c_2 > 0$ and $\alpha > 1$ such that the integrand

$$H(T_u, Q, Z, u_i, r_i) \leq c_2 - c_1 \left( |u_1 + r_1|^2 + |u_2 + r_2|^2 \right)^{\alpha/2}, i = 1, 2 \tag{35}$$

where

$$H(T_u, Q, Z, u_i, r_i) = T_u(t) + Q(t) + Z(t) - \left[ \frac{(A_1 + B_1)}{2} (u_1(t) + r_1(t))^2 + \frac{(A_2 + B_2)}{2} (u_2(t) + r_2(t))^2 \right]. \tag{36}$$

The boundedness of the state system equations with dual-pair controls (21) ensures the existence of a solution. Therefore, we can deduce that the set of controls and the corresponding state variables are non-empty and thus satisfy condition ($C_1$). By definition, the control set is convex and closed, which ensures condition ($C_2$). Furthermore, since the system exhibits dual bi-linear in $u_i(t), r_i(t), i = 1, 2$, the right hand-side of (21) verifies condition ($C_3$) for a simple fact that solutions are bounded. On condition ($C_4$), we apply the Hessian matrix for $H$ as follows:

$$\Upsilon_H = \begin{pmatrix} -(A_1 + B_1) & 0 \\ 0 & -(A_2 + B_2) \end{pmatrix}$$

with determinant

$$\det(\Upsilon_H) = (A_1 + B_1)(A_2 + B_2) \geq 0, \forall (u_i, r_i)_{i=1,2} \in J .$$

Then, $H$ is concave on $J$. Moreso, for condition ($C_5$), we have

$$H(T_u, Q, Z, u_i, r_i) \leq c_2 - c_1 \left( | A_1 + B_1 |^2 + | A_2 + B_2 |^2 \right),$$

with $c_2$ depending on the upper bound on $T_u, Q, Z$ and $c_1 = \min\left( \frac{A_1 + B_1}{2} + \frac{A_2 + B_2}{2} \right) > 0$. We deduce that there exists an optimal control dual-pair $(u_i, r_i)_{i=1,2} \in J$ such that

$$\max_{(u_i, r_i) \in J} H(u_i, r_i) = H(u_i^*, r_i^*), \forall i = 1, 2 .$$

Hence, we complete the proof. □

## 4. Optimality System and Uniqueness

Following the fact that we are pre-occupied by a tri-linear maximization endorsed by the existence prove of an optimal control dual-pair, this section is devoted to the derivation of the model optimality system and the uniqueness verification.

### *4.1 Optimality System for a Dual HIV-HBV Control Dual-pair*

Extending classical principle of Pontryagin's approach as noted by [1], optimality system which defines the biological behavior of system state variables is a vital component of an optimal control problem, following the application of desired chemotherapy. The approach is also use for determining the growth or clearance rate of the state variables.

**Definition 3** We define an optimality system as an embodiment of the state system couple with the adjoint system with initial conditions and transversality conditions together with derived optimal control pair.

Now, from the stand point of definition 3, it is obvious that we already obtain the system model with stated initial conditions as well as the optimal control dual-pair. Therefore, to complete the derivation of the model optimality system, a well-posed adjoint system and transversality conditions is necessary. By definition, the model adjoint system is given by

$$\frac{d\lambda_i}{dt} = -\frac{\partial G}{\partial \phi_i}$$

where $\phi_i, i = 1, ..., 7$ are the state variables. Moreso, for a maximization problem of the type:

$$\max_{(u_i, r_i) \in J} H(u_i, r_i) = F(T_u(t) + \int_{t_0}^{t_f} f_0(T_u, u_i, r_i)) dv , , i = 1, 2$$

which is subject to the system $\frac{dT_u}{dt} = f(t, T_u, u_i, r_i)$ and such that $T_u(t)$ belong to some set $k(T_u(t))$, we derive the following transversality conditions on the adjoint variable as

$$\lambda_i(t) = \bar{\upsilon} F(T_u(t)) + \sum_{i=1}^{m} c_i k_i(T(t)) , \tag{37}$$

with $F$ denoting terminal cost. But our control problem has no terminal cost. Then $F(T(t)) = 0$. Also, the

problem is without any resulting set. Rather, we have desired end result emanating from free-state variables. Again, the implication is that the summation term is zero. Therefore, the transversality conditions on adjoint variable is

$$\lambda_i(t) = 0\ ,\ i = 1,....,7\ . \tag{38}$$

Furthermore, in line with definition 2, we differentiate equation (23) to obtain the adjoint system as stated by the following theorem:

**Theorem 4** For any optimal control dual-pair $(u_i^*, r_i^*)_{i=1,2}$ and any solutions $(T_u^*, T_i^*, T_b^*, V_i^* V_b^* Q^*, Z^*)$ of the corresponding state system (21), there exist adjoint variables $\lambda_1, \lambda_2, \lambda_3, \lambda_4, \lambda_5, \lambda_6$ and $\lambda_7$ satisfying the equations

$$\begin{aligned}
\lambda_1'(t) &= 1 - \lambda_1(t)\left[ s(1 - \frac{L^*(t)}{L_{\max}}) - \frac{sT_u^*(t)}{L_{\max}} - \left( \frac{\beta_1(1-u_1^*(t))V_i^*(t) + \beta_2(1-r_1^*(t))V_b^*(t)}{L^*(t)} \right) - \mu_T \right] \\
&\quad -\lambda_2(t+\omega_1)(u_1^*(t+\omega_1 - 1)\beta_1 e^{-\mu_i \omega_1}\left( \frac{V_i^*(t)T_i^*(t)}{L^{*2}(t)} \right) - (q_1 + \alpha_1) \\
&\quad -\lambda_3(t+\omega_2)(r_1^*(t+\omega_2 - 1)\beta_2 e^{-\mu_b \omega_2}\left( \frac{V_b^*(t)T_b^*(t)}{L^{*2}(t)} \right) - (q_2 + \alpha_2) \\
\lambda_2'(t) &= \lambda_1(t)\left[ \frac{sT_u^*(t)}{L_{\max}} - \left( \frac{\beta_1(1-u_1^*(t))V_i^*(t)T_u^*(t) + \beta_2(1-r_1^*(t))V_b^*(t)T_u^*(t)}{L^{*2}(t)} \right) \right] + \lambda_2(t)\left[ (1-u_1^*(t))\beta_1 \frac{V_i^*(t)T_i^*(t)}{L^{*2}(t)} - g_1 Q^*(t) \right] \\
&\quad +\lambda_3(t)(1-r_1^*(t))\beta_2\left( \frac{V_b^*(t)T_u^*(t)}{L^{*2}(t)} \right) + \lambda_4(t)\left( (1-u_2^*(t)) \right) q_1 p_1 + \lambda_6(t) d_1 Q^*(t) \\
\lambda_3'(t) &= \lambda_1(t)\left[ \frac{sT_u^*(t)}{L_{\max}} - \left( \frac{\beta_1(1-u_1^*(t))V_i^*(t)T_u^*(t) + \beta_2(1-r_1^*(t))V_b^*(t)T_u^*(t)}{L^{*2}(t)} \right) \right] \\
&\quad +\lambda_2(t)\left[ (1-u_1^*(t))\beta_1 \frac{V_i^*(t)T_i^*(t)}{L^{*2}(t)} \right] + \lambda_3(t)\left[ (1-r_1^*(t))\beta_2\left( \frac{V_b^*(t)T_u^*(t)}{L^{*2}(t)} \right) - g_2 Q^*(t) \right] \\
&\quad +\lambda_5(t)\left( (1-r_2^*(t)) \right) q_2 p_2 + \lambda_6(t) d_1 Q^*(t) \\
\lambda_4'(t) &= -\lambda_1(t)\left( \frac{\beta_1(1-u_1^*(t))V_i^*(t)T_u^*(t)}{L^*(t)} \right) + \lambda_2(t)\left( \frac{\beta_1(1-u_1^*(t))V_i^*(t)T_u^*(t)}{L^*(t)} \right) - \lambda_4(t)\left( \alpha_3 + \tau_1 Z^*(t) \right) + \lambda_7(t) d_1 Z^*(t) \\
\lambda_5'(t) &= -\lambda_1(t)\left( \frac{\beta_2(1-r_1^*(t))V_b^*(t)T_u^*(t)}{L^*(t)} \right) + \lambda_3(t)\left( \frac{\beta_2(1-r_1^*(t))V_b^*(t)T_u^*(t)}{L^*(t)} \right) - \lambda_5(t)\left( \alpha_4 + \tau_2 Z^*(t) \right) + \lambda_7(t) d_2 Z^*(t) \\
\lambda_6'(t) &= -\lambda_2(t) g_1 T_i^*(t) - \lambda_3(t) g_2 T_b^*(t) + \lambda_6(t)\left( d_1(T_i^*(t) + T_b^*(t)) - \alpha_5 \right) \\
\lambda_7'(t) &= -\lambda_4(t)\tau_1 V_i^*(t) - \lambda_6(t)\tau_2 V_b^*(t) + \lambda_7(t)\left( d_2(V_i^*(t) + V_b^*(t)) - \alpha_6 \right),
\end{aligned}$$

with $L^*(t) = T_u^*(t) + T_i^*(t) + T_b^*(t)$ and $\lambda_i(t) = 0, i = 1,....,7$ as the transversality conditions. Moreso, the dual-pair controls are given by proposition 2.

**Proof** Invoking optimality system results of [1, 42], we see that the transversality conditions and adjoint equations are as follows:

$$\frac{d\lambda_i(t)}{dt} = -\frac{\partial G}{\partial \phi_i},\ i = 1,....,7,$$

where $\frac{\partial G}{\partial \phi_i}$ is depicted by equation (39). Then,

$$\begin{cases} \lambda_1'(t) = -\frac{\partial G}{\partial T_u}(t) & \lambda_1(t_f) = 0 \\ \lambda_2'(t) = -\frac{\partial G}{\partial T_i}(t) & \lambda_2(t_f) = 0 \\ \lambda_3'(t) = -\frac{\partial G}{\partial T_b}(t) & \lambda_3(t_f) = 0 \\ \lambda_4'(t) = -\frac{\partial G}{\partial V_i}(t) & \lambda_4(t_f) = 0. \\ \lambda_5'(t) = -\frac{\partial G}{\partial V_B}(t) & \lambda_5(t_f) = 0 \\ \lambda_6'(t) = -\frac{\partial G}{\partial Q}(t) & \lambda_6(t_f) = 0 \\ \lambda_7'(t) = -\frac{\partial G}{\partial Z}(t) & \lambda_7(t_f) = 0 \end{cases} \quad (40)$$

Next, we recall the derive dual-pair optimal controls $u_1^*, r_1^*, u_2^*$ and $r_2^*$ from proposition 2. Therefore, the target optimality system is obtain by compatibly combining equations (21) and (40) upon substituting equations (29)-(32) into equations (21) and equation (39) into equation (40). That is, the optimality system is derived as:

$$\frac{dT_u^*}{dt} = b_p + s\left(1 - \frac{L^*(t)}{L_{\max}}\right)T_u^*(t) - \left[\frac{\beta_1(1-u_1^*(t))V_i^*(t) + \beta_2(1-r_1^*(t))V_b^*(t)}{L^*(t)}\right]T_u^*(t) - \mu_T T_u^*(t)$$

$$\frac{dT_i^*}{dt} = \beta_1 e^{-\mu_i \omega_1}(1-u_1^*(t))\left[\frac{V_i^*(t-\omega_1)T_u^*(t-\omega_1)}{L^*(t-\omega_1)}\right] - (q_1+\alpha_1)T_i^*(t) - g_1 T_i^*(t)Q^*(t)$$

$$\frac{dT_b^*}{dt} = \beta_2 e^{-\mu_b \omega_2}(1-r_1^*(t))\left[\frac{V_b^*(t-\omega_2)T_u^*(t-\omega_2)}{L^*(t-\omega_2)}\right] - (q_2+\alpha_2)T_b^*(t) - g_2 T_b^*(t)Q^*(t)$$

$$\frac{dV_i^*}{dt} = (1-u_2^*(t))q_1 p_1 T_i^*(t) - \alpha_3 V_i^*(t) - \tau_1 V_i^*(t)Z^*(t)$$

$$\frac{dV_b^*}{dt} = (1-r_2^*(t))q_2 p_2 T_b^*(t) - \alpha_4 V_b^*(t) - \tau_2 V_b^*(t)Z^*(t)$$

$$\frac{dQ^*}{dt} = d_1(T_i^*(t) + T_b^*(t))Q^*(t) - \alpha_5 Q^*(t)$$

$$\frac{dZ^*}{dt} = d_2(V_i^*(t) + V_b^*(t))Z^*(t) - \alpha_6 Z^*(t)$$

$$\lambda_1'(t) = -1\left\{1 - \lambda_1(t)\left[s(1 - \frac{L^*(t)}{L_{\max}}) - \frac{sT_u^*(t)}{L_{\max}} - \left(\frac{\beta_1(1-u_1^*(t))V_i^*(t) + \beta_2(1-r_1^*(t))V_b^*(t)}{L^*(t)}\right) - \mu_T\right]\right.$$

$$-\lambda_2(t+\omega_1)(u_1^*(t+\omega_1-1)\beta_1 e^{-\mu_i\omega_1}\left(\frac{V_i^*(t)T_i^*(t)}{L^{*2}(t)}\right)-(q_1+\alpha_1)$$

$$-\lambda_3(t+\omega_2)(r_1^*(t+\omega_2-1)\beta_2 e^{-\mu_b\omega_2}\left(\frac{V_b^*(t)T_b^*(t)}{L^{*2}(t)}\right)-(q_2+\alpha_2)\Bigg\}$$

$$\lambda_2'(t)=-1\Bigg\{\lambda_1(t)\left[\frac{sT_u^*(t)}{L_{\max}}-\left(\frac{\beta_1(1-u_1^*(t))V_i^*(t)T_u^*(t)+\beta_2(1-r_1^*(t))V_b^*(t)T_u^*(t)}{L^{*2}(t)}\right)\right]$$

$$+\lambda_2(t)\left[(1-u_1^*(t))\beta_1\frac{V_i^*(t)T_i^*(t)}{L^{*2}(t)}-g_1Q^*(t)\right]+\lambda_3(t)(1-r_1^*(t))\beta_2\left(\frac{V_b^*(t)T_u^*(t)}{L^{*2}(t)}\right)$$

$$+\lambda_4(t)\left((1-u_2^*(t)\right)q_1p_1+\lambda_6(t)d_1Q^*(t)\Bigg\}$$

$$\lambda_3'(t)=-1\Bigg\{\lambda_1(t)\left[\frac{sT_u^*(t)}{L_{\max}}-\left(\frac{\beta_1(1-u_1^*(t))V_i^*(t)T_u^*(t)+\beta_2(1-r_1^*(t))V_b^*(t)T_u^*(t)}{L^{*2}(t)}\right)\right]+\lambda_2(t)\left[(1-u_1^*(t))\beta_1\frac{V_i^*(t)T_i^*(t)}{L^{*2}(t)}\right]$$

$$+\lambda_3(t)\left[(1-r_1^*(t))\beta_2\left(\frac{V_b^*(t)T_u^*(t)}{L^{*2}(t)}\right)-g_2Q^*(t)\right]+\lambda_5(t)\left((1-r_2^*(t)\right)q_2p_2+\lambda_6(t)d_1Q^*(t)\Bigg\} \tag{41}$$

$$\lambda_4'(t)=-1\Bigg\{-\lambda_1(t)\left(\frac{\beta_1(1-u_1^*(t))V_i^*(t)T_u^*(t)}{L^*(t)}\right)+\lambda_2(t)\left(\frac{\beta_1(1-u_1^*(t))V_i^*(t)T_u^*(t)}{L^*(t)}\right)$$

$$-\lambda_4(t)\left(\alpha_3+\tau_1Z^*(t)\right)+\lambda_7(t)d_1Z^*(t)\Bigg\}$$

$$\lambda_5'(t)=-1\Bigg\{-\lambda_1(t)\left(\frac{\beta_2(1-r_1^*(t))V_b^*(t)T_u^*(t)}{L^*(t)}\right)+\lambda_3(t)\left(\frac{\beta_2(1-r_1^*(t))V_b^*(t)T_u^*(t)}{L^*(t)}\right)$$

$$-\lambda_5(t)\left(\alpha_4+\tau_2Z^*(t)\right)+\lambda_7(t)d_2Z^*(t)\Bigg\}$$

$$\lambda_6'(t)=-1\Big\{-\lambda_2(t)g_1T_i^*(t)-\lambda_3(t)g_2T_b^*(t)+\lambda_6(t)\left(d_1(T_i^*(t)+T_b^*(t))-\alpha_5\right)\Big\}$$

$$\lambda_7'(t)=-1\Big\{-\lambda_4(t)\tau_1V_i^*(t)-\lambda_6(t)\tau_2V_b^*(t)+\lambda_7(t)\left(d_2(V_i^*(t)+V_b^*(t))-\alpha_6\right)\Big\},$$

with $L^*(t)=T_u^*(t)+T_i^*(t)+T_b^*(t)$, $\lambda_i(t)=0, i=1,....,7$ and where

$$u_1^*(t)=\min\left\{\max\left\{a_1,\left(\frac{\lambda_1(t)\left(\frac{\beta_1V_i(t)T_u(t)}{(T_u+T_i+T_b)^2}\right)-\lambda_2(t)\left(\beta_1e^{-\mu_i\omega_1}\frac{V_i(t-\omega_1)T_u(t-\omega_1)}{(T_u+T_i)^2}\right)}{(A_1+B_1)}\right)\right\}^+,b_1\right\},$$

$$r_1^*(t)=\min\left\{\max\left\{m_1,\left(\frac{\lambda_1(t)\left(\frac{\beta_2 V_b(t)T_u(t)}{(T_u+T_i+T_b)^2}\right)-\lambda_3(t)\left(\beta_2 e^{-\mu_b\omega_2}\frac{V_b(t-\omega_2)T_u(t-\omega_2)}{(T_u+T_b)^2}\right)}{(A_1+B_1)}\right)\right\}^+,n_1\right\},$$

$$u_2^*(t)=\min\left\{\max\left\{a_2,-\frac{1}{(A_2+B_2)}\left[\lambda_4(t)q_1p_1T_i(t)\right]\right\}^+,b_2\right\}$$

and

$$r_2^*(t)=\min\left\{\max\left\{m_2,-\frac{1}{(A_2+B_2)}\left[\lambda_5(t)q_2p_2T_b(t)\right]\right\}^+,n_2\right\}.$$

*4.2 Uniq*ueness of Opti*mality System*

In affirmation of our derived optimality system, we establish the system uniqueness for possibly a small time interval. Aligning with existence of optimal control dual-pair, we have that

$$T_u<T_{(u)\max},$$

which implies that the system have a finite upperbounds; a necessary condition for the proof of uniqueness of optimality system. Thus, the system uniqueness is completely defined by the following theorem with proof guided by the lemma hereof.

**Lemma 1** The control dual-pair functions $(u_i^*,r_i^*)(z)=(\min(z,a_i,b_i))),\forall i-1,2$ is Lipschitz continuous in $z$, where $a_i<b_i$ are fixed constants.

**Theorem 5** Let the time interval $t_f$ be as small as possible, then the bounded solutions of the optimality system are unique.

**Proof** The proof is invoked from the uniqueness of optimality results of [1, 3, 55]. Now, suppose $(T_u,T_i,T_b,V_i,V_b,Q,Z,\lambda_1,\lambda_2,\lambda_3,\lambda_4,\lambda_5,\lambda_6,\lambda_7)$ and $(\overline{T}_u,\overline{T}_i,\overline{T}_b,\overline{V}_i,\overline{V}_b,\overline{Q},\overline{Z},\overline{\lambda}_1,\overline{\lambda}_2,\overline{\lambda}_3,\overline{\lambda}_4,\overline{\lambda}_5,\overline{\lambda}_6,\overline{\lambda}_7)$ are two solutions of the model optimality system (41). Then we choose $\lambda>0$ such that the values of the solutions are obtained by setting

$$\begin{cases}T_u=g^{\delta t}e,T_i=g^{\delta t}f,T_b=g^{\delta t}h,V_i=g^{\delta t}l,V_b=g^{\delta t}j,Q=g^{\delta t}k,Z=g^{\delta t}m,\\ \lambda_1=g^{\delta t}p,\lambda_2=g^{\delta t}q,\lambda_3=g^{\delta t}s,\lambda_4=g^{\delta t}t,\lambda_5=g^{\delta t}u,\lambda_6=g^{\delta t}w,\lambda_7=g^{\delta t}x\\ \overline{T}_u=g^{\delta t}\overline{e},\overline{T}_i=g^{\delta t}\overline{f},\overline{T}_b=g^{\delta t}\overline{h},\overline{V}_i=g^{\delta t}\overline{l},\overline{V}_b=g^{\delta t}\overline{j},\overline{Q}=g^{\delta t}\overline{k},\overline{Z}=g^{\delta t}\overline{m},\\ \overline{\lambda}_1=g^{\delta t}\overline{p},\overline{\lambda}_2=g^{\delta t}\overline{q},\overline{\lambda}_3=g^{\delta t}\overline{s},\overline{\lambda}_4=g^{\delta t}\overline{t},\overline{\lambda}_5=g^{\delta t}\overline{u},\overline{\lambda}_6=g^{\delta t}\overline{w},\overline{\lambda}_7=g^{\delta t}\overline{x}.\end{cases}\tag{42}$$

Now, substituting equation (42) into optimal control dual-pair of equations (29)-(32), the derive solutions becomes:

$$u_1^*(t) = \min\left\{\max\left\{a_1, \left(\frac{\left(\frac{\beta_1 ple}{(e+f+h)^2}\right) - \left(\beta_1 q e^{-\mu_i \omega_1} \frac{l(t-\omega_1)e(t-\omega_1)}{(e+f)^2}\right)}{(A_1+B_1)}\right)\right\}, b_1\right\}$$

$$r_1^*(t) = \min\left\{\max\left\{m_1, \left(\frac{\left(\frac{\beta_2 pje)}{(e+f+h)^2}\right) - \left(\beta_2 s e^{-\mu_b \omega_2} \frac{j(t-\omega_2)e(t-\omega_2)}{(e+h)^2}\right)}{(A_1+B_1)}\right)\right\}, n_1\right\}$$

$$u_2^*(t) = \min\left\{\max\left\{a_2, -\frac{1}{(A_2+B_2)}\left[tfq_1 p_1\right]\right\}, b_2\right\}$$

$$r_2^*(t) = \min\left\{\max\left\{m_2, -\frac{1}{(A_2+B_2)}\left[uhq_2 p_2\right]\right\}, n_2\right\}$$

and

$$\overline{u}_1^*(t) = \min\left\{\max\left\{a_1, \left(\frac{\left(\frac{\beta_1 \overline{p}\,\overline{l}\overline{e}}{(\overline{e}+\overline{f}+\overline{h})^2}\right) - \left(\beta_1 \overline{q} e^{-\mu_i \omega_1} \frac{\overline{l}(t-\omega_1)\overline{e}(t-\omega_1)}{(\overline{e}+\overline{f})^2}\right)}{(A_1+B_1)}\right)\right\}, b_1\right\}$$

$$\overline{r}_1^*(t) = \min\left\{\max\left\{m_1, \left(\frac{\left(\frac{\beta_2 \overline{p}\overline{j}\overline{e})}{(\overline{e}+\overline{f}+\overline{h})^2}\right) - \left(\beta_2 \overline{s} e^{-\mu_b \omega_2} \frac{\overline{j}(t-\omega_2)\overline{e}(t-\omega_2)}{(\overline{e}+\overline{h})^2}\right)}{(A_1+B_1)}\right)\right\}, n_1\right\}$$

$$\overline{u}_2^*(t) = \min\left\{\max\left\{a_2, -\frac{1}{(A_2+B_2)}\left[\overline{t}\overline{f}q_1 p_1\right]\right\}, b_2\right\}$$

$$\overline{r}_2^*(t) = \min\left\{\max\left\{m_2, -\frac{1}{(A_2+B_2)}\left[\overline{u}\overline{h}q_2 p_2\right]\right\}, n_2\right\}.$$

Next, we substitute $T_u = g^{\delta t} e$ and all corresponding terms into the ODE of equation (41) and then differentiate to obtain

$$e'+\lambda e = b_p + s\left(1-\frac{L^*(t)}{L_{\max}}\right)g^{\delta t}e - \left[\frac{\beta_1(1-u_1^*(t))g^{\delta t}l+\beta_2(1-r_1^*(t))g^{\delta t}j}{L^*(t)}\right]g^{\delta t}e-\mu_T g^{\delta t}e$$

$$f'+\lambda f = \beta_1 e^{-\mu_i\omega_1}(1-u_1^*(t))\left[\frac{g^{\delta t}l(t-\omega_1)g^{\delta t}e(t-\omega_1)}{L^*(t-\omega_1)}\right]-(q_1+\alpha_1)g^{\delta t}f-g^{\delta t}(ek)g_1$$

$$h'+\lambda h = \beta_2 e^{-\mu_b\omega_2}(1-r_1^*(t))\left[\frac{g^{\delta t}j(t-\omega_2)g^{\delta t}e(t-\omega_2)}{L^*(t-\omega_2)}\right]-(q_2+\alpha_2)g^{\delta t}h-g^{\delta t}(hk)g_2$$

$$l'+\lambda l = (1-u_2^*(t))q_1p_1g^{\delta t}f-\alpha_3 g^{\delta t}l-\tau_1 g^{\delta t}(lm)$$

$$j'+\lambda j = (1-r_2^*(t))q_2p_2g^{\delta t}h-\alpha_4 g^{\delta t}j-\tau_2 g^{\delta t}(jm)$$

$$k'+\lambda k = d_1 g^{\delta t}(f+h)g^{\delta t}k-\alpha_5 g^{\delta t}k$$

$$m'+\lambda m = d_2 g^{\delta t}(l+j)g^{\delta t}m-\alpha_6 g^{\delta t}m$$

$$\lambda'+\lambda p = -1\Bigg\{1-g^{\delta t}p\left[s(1-\frac{L^*(t)}{L_{\max}})-\frac{sg^{\delta t}e}{L_{\max}}-\left(\frac{\beta_1(1-u_1^*(t))g^{\delta t}(lf)+\beta_2(1-r_1^*(t))g^{\delta t}(jh)}{L^*(t)}\right)-\mu_T\right]$$

$$-g^{\delta t}q(t+\omega_1)[u_1^*(t+\omega_1-1)]\beta_1 e^{-\mu_i\omega_1}\left(\frac{g^{\delta t}(lf)}{L^{*2}(t)}\right)-(q_1+\alpha_1)$$

$$-g^{\delta t}s(t+\omega_2)[r_1^*(t+\omega_2-1)]\beta_2 e^{-\mu_b\omega_2}\left(\frac{g^{\delta t}(jh)}{L^{*2}(t)}\right)-(q_2+\alpha_2)\Bigg\}$$

.
.
. (43)
.

$$x'+\lambda x = -1\Big\{-g^{\delta t}x\tau_1 g^{\delta t}l-g^{\delta t}u\tau_2 g^{\delta t}j+g^{\delta t}x\left(d_2 g^{\delta t}(l+j)-\alpha_6\right)\Big\}.$$

The process is then followed by performing the subtraction of state solutions $\overline{T}_u$ from $T_u$, $\overline{T}_i$ from $T_i$, . . . . . , $\overline{\lambda}_1$ from $\lambda_1$, ……., $\overline{\lambda}_7$ from $\lambda_7$ and then multiply the obtained result by appropriate difference of functions and integrate from $t_0$ to $t_f$. The final resulting fourteen integral equations are summed and uniqueness of the system solution derived by using estimation approach. That is, invoking lemma 1, the first result is derived as:

$$\left|u_1^*-\overline{u}_1^*(t)\right| \le \frac{1}{(A_1+B_1)}\left|\begin{array}{l}\left(\dfrac{\beta_1 ple}{g^{\delta t}(e+f+h)^2}-g^{\delta t}\dfrac{\beta_1\overline{p}\,\overline{l}\overline{e}}{(\overline{e}+\overline{f}+\overline{h})^2}\right)- \\ \left(\dfrac{\beta_1 qe^{-\mu_i\omega_1}(le)(t-\omega_1)}{g^{\delta t}(e+f)^2}+\dfrac{\beta_1\overline{q}e^{-\mu_i\omega_1}(\overline{l}\overline{e})(t+\omega_1)}{g^{\delta t}(\overline{e}+\overline{f})^2}\right)\end{array}\right|,$$

$$\left|r_1^*-\overline{r}_1^*(t)\right| \le \frac{1}{(A_1+B_1)}\left|\begin{array}{l}\left(\dfrac{\beta_2 pje}{g^{\delta t}(e+f+h)^2}-\dfrac{\beta_2\overline{p}\,\overline{j}\overline{e}}{g^{\delta t}(\overline{e}+\overline{f}+\overline{h})^2}\right)- \\ \left(\dfrac{\beta_2 se^{-\mu_b\omega_2}(je)(t-\omega_2)}{g^{\delta t}(e+f)^2}+\dfrac{\beta_2\overline{s}e^{-\mu_b\omega_2}(\overline{j}\overline{e})(t+\omega_2)}{g^{\delta t}(\overline{e}+\overline{f})^2}\right)\end{array}\right|,$$

$$\left|u_2^*(t)-\overline{u}_2^*(t)\right| \le \frac{1}{(A_2+B_2)}\left|q_1 p_1(tf)-q_1 p_1(\overline{tf})\right|$$

and

$$\left|r_2^*(t)-\overline{r}_2^*(t)\right| \le \frac{1}{(A_2+B_2)}\left|q_2 p_2(uh)-q_2 p_2(\overline{uh})\right|.$$

Illustrating explicitly the use of estimate on $\left|u_1^*-\overline{u}_1^*(t)\right|$ for the first variable $T_u(t)$, we have

$$\begin{aligned}
&\frac{1}{2}\left(e-\overline{e}\right)^2(t_f)+\lambda_1\int_{t_0}^{t_f}\left(e-\overline{e}\right)^2 dt \\
&\quad\le \int_{t_0}^{t_f}\mu_T\left|e-\overline{e}\right|dt+\left[\int_{t_0}^{t_f}\left|u_1^* e-\overline{u}_1^*\overline{e}\right|\left|e-\overline{e}\right|dt\right]+g^{\delta t}k\int_{t_0}^{t_f}\left|f-\overline{f}\right|\left|e-\overline{e}\right|dt+\int_{t_0}^{t_f}\left|u_1^* e-\overline{u}_1^*\overline{e}\right|\left|e-\overline{e}\right|dt \\
&\quad\le \phi_1\int_{t_0}^{t_f}\left|e-\overline{e}\right|^2+\left|l-\overline{l}\right|^2+\left|j-\overline{j}\right|^2+\left|p-\overline{p}\right|^2]dt+\phi_2 g^{\delta t_f}\int_{t_0}^{t_f}\left[\left|e-\overline{e}\right|^2+\left|l-\overline{l}\right|^2+\left|j-\overline{j}\right|^2\right]dt
\end{aligned}$$

where, the constants $\phi_1$ and $\phi_2$ depends on the coefficients and on bounds of the state and adjoints. Combining the fourteen estimates, we see that the following inequality holds:

$$\begin{aligned}
&\frac{1}{2}(t_f)\left[(e-\overline{e})^2+(f-\overline{f})^2+.....+(m-\overline{m})^2\right]+\frac{1}{2}(t_0)\left[(p-\overline{p})^2+.....+(m-\overline{m})^2\right] \\
&\quad+\lambda\int_{t_0}^{t_f}\left[(e-\overline{e})^2+(f-\overline{f})^2+.....+(m-\overline{m})^2+(p-\overline{p})^2+.....+(m-\overline{m})^2\right]dt \\
&\quad\le\left(\phi_1+\phi_2 e^{3\lambda t_f}\right)\int_{t_0}^{t_f}\left[(e-\overline{e})^2+(f-\overline{f})^2+.....+(p-\overline{p})^2+.....+(m-\overline{m})^2\right]dt
\end{aligned}$$

for all $t_0=0$. Thus, we conclude from the above that

$$\left(\lambda-\tilde{\phi}_1+\tilde{\phi}_2 e^{3\lambda t_f}\right)\int_{t_0}^{t_f}\left[(e-\overline{e})^2+(f-\overline{f})^2+.....+(p-\overline{p})^2+.....+(m-\overline{m})^2\right]dt\le 0,$$

where $\tilde{\phi}_1,\tilde{\phi}_2$ depends on the coefficients and bounds on $e, f, ....., m$. If we choose $\lambda$ such that $\lambda>\tilde{\phi}_1+\tilde{\phi}_2$ and $t_f<\frac{1}{3\lambda}\ln\left(\frac{\lambda-\tilde{\phi}_1}{\tilde{\phi}_2}\right)$, then $e=\overline{e}, f=\overline{f}, h=\overline{h}, ....., m=\overline{m}, ....., x=\overline{x}$. Hence, the solution is unique for sufficiently small time $t$. □

Optimally, the uniqueness of optimality system for a small time interval is a two point boundary problem consequence to opposite time orientation and the state equations defined by initial and final time conditions. Moreso, the dual-pair optimal controls $[u_i, r_i]_{i=1,2}$ are characterized by the unique solution of optimality system. Therefore, from epidemiological view point, we deduce from Thm, 5, that if $\lambda>\left((A_1+B_1)+(A_2+B_2)\right)$ and $t_f<\frac{1}{3\lambda}\ln\left(\frac{\lambda-(\tilde{A}_1+\tilde{B}_1)}{(\tilde{A}_2+\tilde{B}_2)}\right)$ such that $\lambda>(A_2+B_2)\lhd 0$, then infection is said to be asymptotically stable.

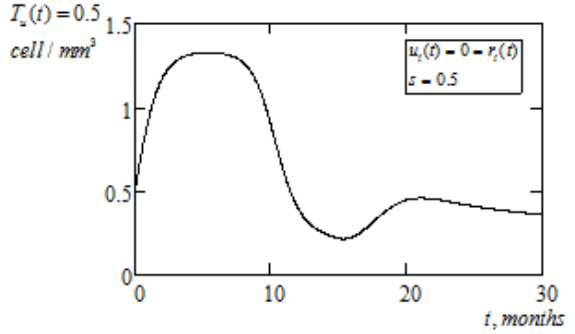
Adversely if $t_f > \frac{1}{3\lambda}\ln\left(\frac{\lambda-(\tilde{A}_1+\tilde{B}_1)}{(\tilde{A}_2+\tilde{B}_2)}\right)$, such that $\lambda > \left((A_1+B_1)+(A_2+B_2)\right)$, then global endemicity is bound to occur.

## 5. Numerical Simulations

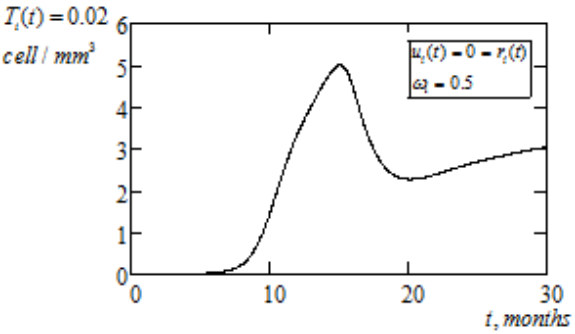
Here, noting that this study initial data are certified clinical data modified in tune with the present model (see notes on tables (1 & 2), we verify in accordance with the objective of this study, the e ingenuity of our derived system model. For simplicity, model simulations will be considered in the sequence of derivations. This includes the simulation of the system basic model (6) for the case of untreated dual delayed HIV-HBV infections, followed by the derived optimality system, the optimal dual-pair control functions and the objective functional of the system. Of note, the entire simulations are conducted via in-built Runge-Kutter of order precision 4 in a Mathcad surface. Importantly, the mathematical outcomes of our simulations are carefully presented in the appendices for the purpose of simplification.

### *5.1 Simulation of Basic Model (without control functions)*

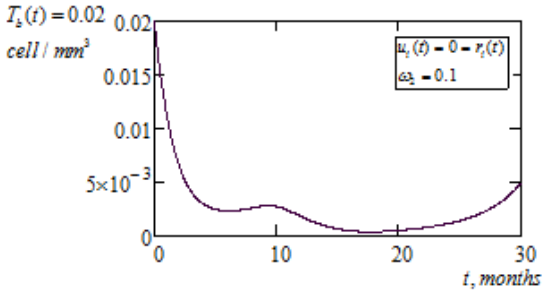
Fundamentally, it is worth initiating the computational aspect of the system basic model equation (6). This is obvious as it is leverage to our derived optimality system. Commendably, the epidemiological status of dual delayed HIV-HBV infections dynamics under off-treatment scenario is adequately represented by the following simulations. This is to say that invoking model (6) with $u_{i=1,2} = 0$ and $r_{i=1,2} = 0$, the following fig. 2(a-g) is obtained:



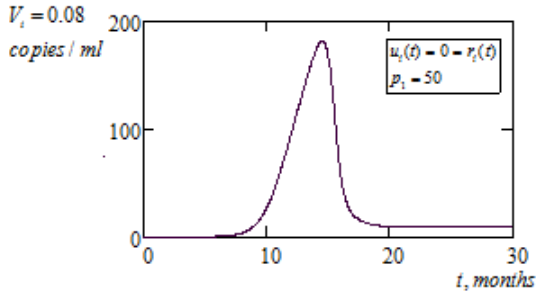

a) Uninfected double lymphocyte cells
Under off-treatment, $b_u = 0.5 mm^2 d^{-1}$



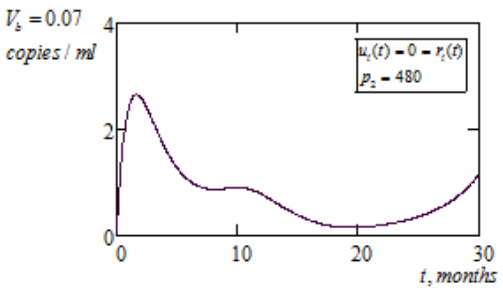

b) Viral load infected T-lymphocyte cells
Under off-treatment, $q_1 = 0.48$



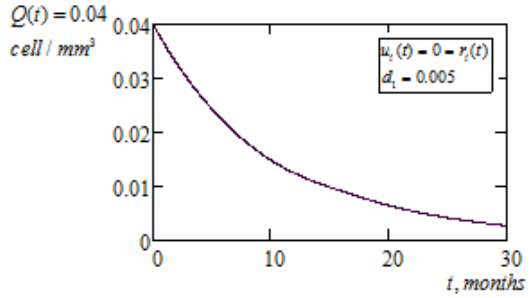

c) B-virus infected hepatocyte cells under Off-treatment $q_2 = 0.46$



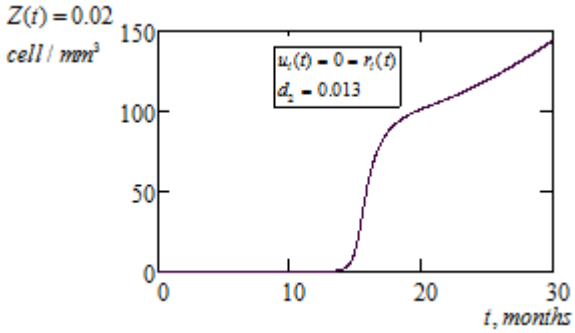

d) Infectious viral load under off-treatment, $q_1 = 0.48$




e) Infectious B-virus under off-treatment, $q_2 = 0.46$




f) Cytotoxic T-lymphocytes response to HIV-HBV infection under off-treatment




g) Antibodies response to HIV-HBV infection under off-treatment

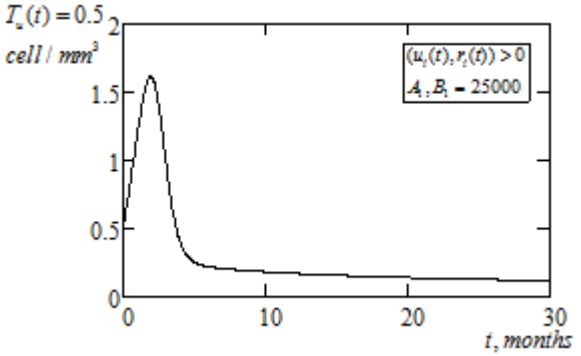
Fig. 2(a-g). Epidemiological representations of untreated dual delayed HIV-HBV infection dynamics

Fig. 2(a-g) represents the dynamical flow of dual delayed HIV-HBV infections under off-treatment setting. Typically, figure 2(a) clearly shows the early asymptomatic stage infection where the infection is yet to opening manifest within the first 10 months. This can be attributed to the initial response from dual adaptive immune system. We also observed depletion of susceptible double lymphocyte cells under an unchecked dual HIV-HBV infection scenario after $t_f \geq 10$ months to a value $T_u(t) \leq 0.215 cell/mm^3$. This is evident by the increasing rate of infected sub-population of HIV and HBV infected double lymphocyte cells as depicted by fig. 2(b & c). The depletion of infected HBV cells is due to the fact that the physiological manifestation of HBV infection takes much longer period, thus undulating pictorial structure. Also, it is observed that replication of virions (infectious HIV and HBV) occurred due to the off-treatment situation – fig. 2(d & e). Furthermore, the initial active defensive response from cellular immune response (CTLs) and humoral immune response (antibodies) is seen to succumb to the severe forces of untreated dual HIV-HBV virions – fig. 2(f & g). In particular, the rising nature of the antibodies explains the fact that the amount of infectious HBV determines the replication of antibodies with value $Z(t) \leq 144.302 cell/mm^3$. Mathematically, we present the summary of the resulting variations of the dynamical flow of healthy population, HIV-HBV coinfcted double lymphocyte cells, infectious dual virions and those of dual adaptive immune system in **appendix A**.

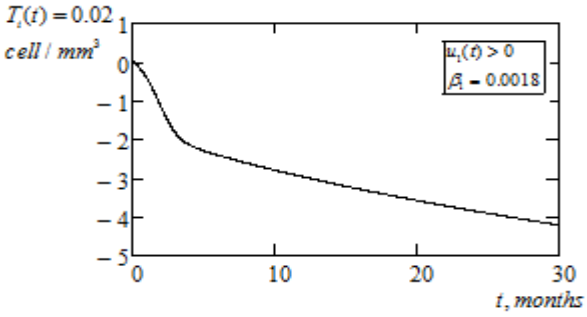
### *5.2 Simulation Model for the Optimality System (with dual tri-linear control functions)*

Notably, when the human system is exposed to systematic infections, which affect the immune system, the affected system are bound to collapse if timely intervention is not in place. However, the introduction of competent chemotherapy could result to the enhancement of the immune efficiency. Therefore, the introduction of peculiar multi-therapies by this investigation is aim at not only de-phasing the progress of infections but to also activate the efficiency of affected immune system. Thus, the introduction of $u_{i=1,2} > 0$ and $r_{i=1,2} > 0$, representing reverse transcriptase inhibitors and protease inhibitors; standard interferon-$\alpha$ and nucleoside analogues activates the dual immune response. Hence, the initial - dual tri-linear treatment functions.

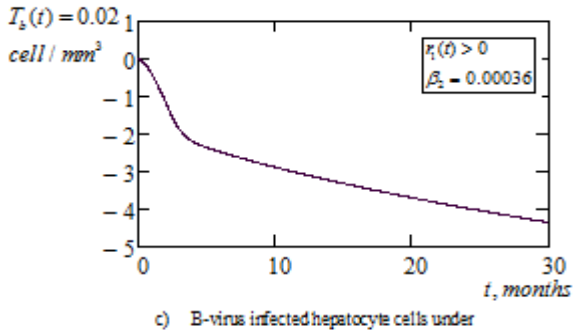
Guided by propositions 1 & 2, toxicity of chosen chemotherapies are clinically observed under optimal weight factors: $A_1 = 25000, A_2 = 250, B_1 = 25000, B_2 = 250$ and having limit bounds of $a_1 = 0, a_2 = 0.2, b_1 = 0.4, b_2 = 0.9;\ m_1 = 0.1, m_2 = 0.4, n_1 = 0.4, n_2 = 0.7$. Then, fig. 3(a-g) depicts the optimality system with well-posed optimal control functions.



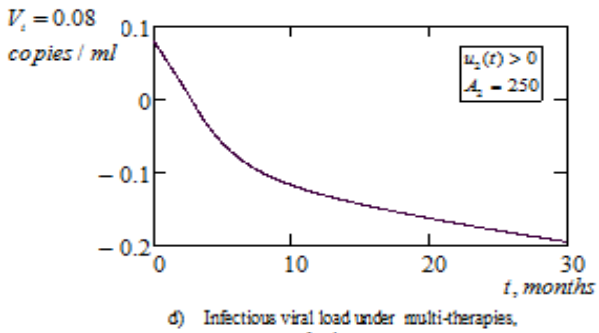

a) Uninfected double lymphocyte cells under multi-therapies, $b_2 = 0.5 mm^2 d^{-1}$



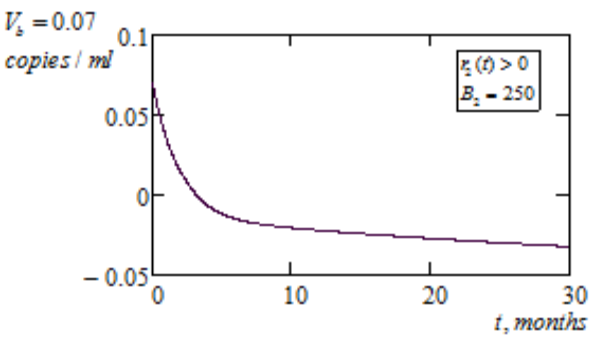

b) Viral load infected T-lymphocyte cells under off-treatment, $g_1 = 0.5 mm^3 cell^{-1} d^{-1}$



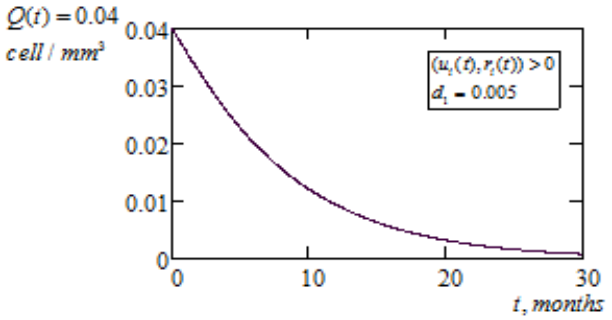

c) B-virus infected hepatocyte cells under multi-therapies, , $g_2 = 0.1 mm^3 cell^{-1} d^{-1}$



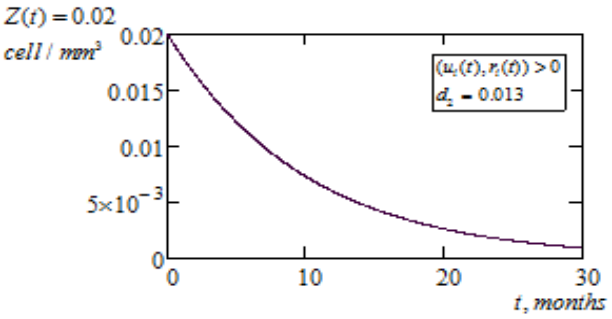

d) Infectious viral load under multi-therapies, $\tau_1 = 0.05 mm^3 d^{-1}$




e) Infectious B-virus under multi-therapies, $\tau_2 = 10^{-2} mm^3 d^{-1}$




f) Cytotoxic T-lymphocytes response to HIV-HBV infection under multi-therapies




g) Antibodies response to HIV-HBV infection under multi-therapies

Fig. 3(a-g). Epidemiological dynamics of dual delayed HIV-HBV infections under multi-therapies and activated dual adaptive immune response

From fig. 3(a), we observed that following systematic application of choice chemotherapies, susceptible double lymphocyte cells exhibit tremendous increase with stability after $t_f \geq 10$ months, which indicates acceptability of choice drugs. Moreso, the decline in both HIV infected cells and HBV infected cells as depicted by fig. 3(b & c) vindicates the outcome of fig. 3(a). It is also observed from fig. 3(d & e), the depletion of both HIV and HBV virions following the administration of structured chemotherapies within study validity period. Furthermore, the dynamic response of dual immune system, which is determined by the rate of infection growth and enhanced by induced chemotherapies are clearly seen in the gradual decline and stability of both CTLs and antibodies as in fig. 3(f & g) respectively. Thus, the quantitative expression of fig. 3(a-g) is given in **appendix B**.

*5.3 Simulation of Optimal Control Functions and Objective Functional*

Furthermore, we simulate the system control functions (29)-(32) as an outlet to the quantitative description of drugs toxicity and the amount of drugs required. Fig. 4(a-d) depicts the various quantities and the commercial values of chemotherapies required to keep under control, the deadly dual-delayed HIV-HBV infections.

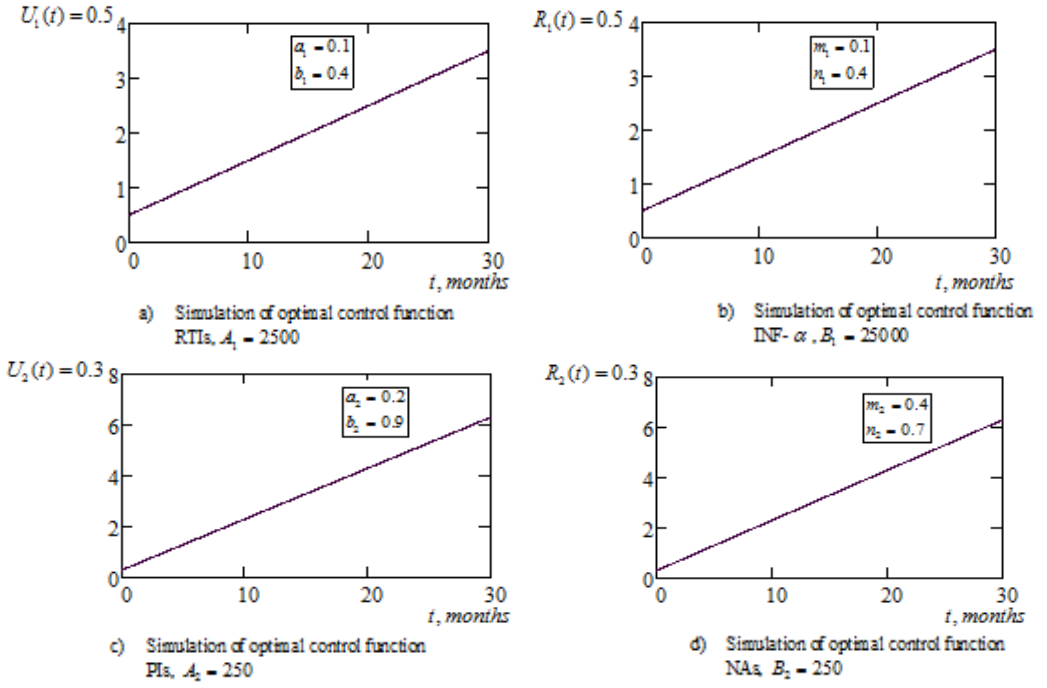



Fig. 4 (a-d) Graphical representations of optimal control functions for dual delayed HIV-HBV infections

Fig. 4(a & b) construed some smooth linear functions, which are typical of optimal dynamics. Clearly, the amount of RTI required is seen to be in the range $0.5 \le u_1^*(t) \le 3.5$ for all $t_f \le 30$ months, which is significantly small amount of RTI. Standard interferon-$\alpha$ exhibit similar tendency with that of RTI, which value in the range of $0.5 \le r_1^*(t) \le 3.5$ for all $t_f \le 30$ months. On the other hand, fig. 4(c & d) portrait the respective amount of PIs and NAs required in the range of $0.3 \le u_i(t), r_i(t) \le 6.3$ combating free infectious dual HIV-HBV infectivity for all $_f \le 30$ months.

Finally, we simulate system (22), which defines the objective functional to be maximized. This step depicts the optimal control pairs in relation to maximized double lymphocyte healthy population and the restoration of active immune system. Fig. 5 represent maximized $T_u(t), Q(t)$ and $Z(t)$ :

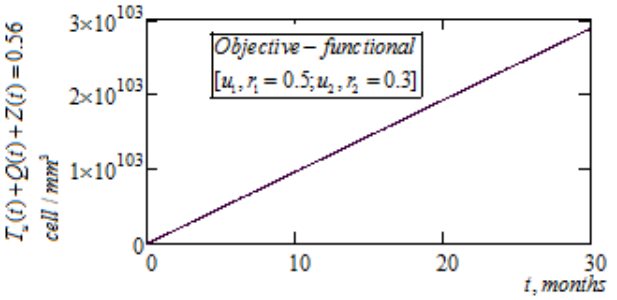



Fig. 5. Simulation of objective functional for pair-dual treatment with $A_1, B_1 = 25000; A_2, B_2 = 250$

From fig. 5, we have a linear inclination indicating the overall commercial value of triple dual control functions, which clinically combat the influx of dual HIV-HBV infections. Notably, for treatment duration of $t_f \leq 30$ months, chemotherapies value is in the range of $0.16 \leq (u_i, r_i) \leq 2.879 \times 10^{103}, \forall i - 1, 2$, which are 56% of double lymphocyte cells and normalized dual adaptive immune system restored.

## 6. Discussion

In this study, a number of closely related models were carefully highlighted, which gave the motivational focus of investigation. A presumably the first model, the study formulated an articulated 7-Dimensional dynamic dual HIV-HBV co-infectivity. The study is characterized by the epidemiological identifiability of dual infection transmission routes and the methodological application of triple-dual control functions following the dual role of adaptive immune system. The model was frame under the interplay of dual vector components (HIV and HBV) on the host victims – double lymphocyte cells ($CD4^+$ T-lymphocyte cells and $CD3^+$ T-lymphocyte cells) in the presence of immunity time delay lags. The model positivity and boundedness of solutions was investigated to justify the state variables as representation of set of living organisms. Achieving the maximization goal of the study, the system derived model was transformed to an optimal control problem. An approach that allowed the application of classical optimal control theory – the Pontryagin's maximum principle.

The analysis led to the establishment of the existence of optimal control dual-pair and the optimality system as well as the uniqueness of the system. Starting with the off-treatment scenario, the system basic model (6) was first simulated to investigate the dual infection transmission dynamics. Fig. 2(a-g) clearly demonstrated the infection properties ranging from the gradual undulating decline of the susceptible double lymphocyte cells – fig. 2(a). This is vindicated by the similar magnitude of undulating inclination of infected double lymphocytes and infectious HIV and HBV virions – fig. 2(b-e). The antibodies appeared to be more responsive capered to the intensity of the cytotoxic T-lymphocytes – fig. 2(f & g).

Furthermore, following the introduction of choice multi-therapies $(u_i, r_i) > 0, i - 1, 2$ under regulated optimal weight factors and limit bounds, we observed initial increase in the amount of susceptible double lymphocytes, which attained stability after 10 months of cogent structured multi-therapies – fig. 3(a). Of note, tremendous biphasic decays of both infected double lymphocyte cells and dual virions were established as in fig. 3 (b-e). These significant declines by infected victims and the vectors are further explained by the gradual decline of both adaptive immune systems – fig. 3(f & g). This attained result was an improvement when compared to those of models [1, 2]. Precisely, both infected double lymphocytes and dual infectious virions were eliminated in the interval $t_f \leq 10$ months. The model analysis was further expanded by the verification of the amount of chemotherapies required for the duration of experimental period – fig. 4(a-d). This explained the optimal maximization of treatment cost with PRI and INF-$\alpha$ more on demand. The overall commercial implications of chemotherapies needed for the triphasic maximization of double lymphocyte cells and dual adaptive immune system were explicitly demonstrated by fig. 5. The entire experiment conducted via in-built Runge-Kutter of order precision 4 in a Mathcad surface.

## 7. Conclusion

A presumed first articulated mathematical model for the optimal dynamics of dual delayed HIV-HBV infections had been formulated and studied by this present paper. The model entails a penultimate 7-Dimensional mathematical equations, which accounted for the identifiability of dual delayed HIV-HBV infection transmission routes and the methodological application of triple-dual treatment control functions. Moreso, the study presented an articulated mathematical model for co-infection dynamics and accompanying methodological application of desired chemotherapies with the incorporation of dual adaptive immune response in the presence of time delayed lag. The study upon transformation of the model to an optimal control problem

was mathematically analyzed using classical Pontryagin's maximum principle. From a set of four numerical examples simulated, results showed that under off-treatment scenario, susceptible double lymphocyte cells population decays was eminent and characterized by biphasic endemic infection atmosphere. Furthermore, elimination of both infected double lymphocyte cells and dual HIV-HBV virions was accompanied by more complex decay profiles of infectious dual HIV-HBV virions, achieved at the earliest time interval of $3 \leq t_f \leq 10$ months. This had been vindicated by the tri-phasic maximization of susceptible double lymphocytes and dual adaptive immune system, which further justified the investigation. The study is therefore not only recommended for further enhanced articulated model but served as a monumental scientific intelligent that can be convincingly adopted to investigate the insight into multi-infection dynamics and prevention methods.

## References


[1] Bassey E. B. (2018) Dynamic optimal control model for dual-pair treatment functions of dual delayed HIV-pathogen infections. Journal of Mathematical Sciences: Advances and Applications, 51(1): 1-50.

[2] Allali K., Meskaf A. and Tridane A. (2018) Mathematical modeling of the adaptive immune responses in the early stage of the HBV infection. International Journal of Differential Equations, 2018(1): 1-13.

[3] Hattaf K. and Yousfi N. (2018) Modeling the adaptive immunity and both modes of transmission in HIV infection. Computation, 6(37): 1-18.

[4] Kirschner, D. (1999) Dynamics of Co-infection with M. Tuberculosis and HIV-1. Theoretical Population Biology, 55, 94-109.

[5] Bassey, B. E. and Lebedev, K. A. (2015) On Mathematical Modeling of the Effect of Bi-Therapeutical Treatment of Tuberculosis Epidemic. Journal of Mathematics and Statistics, 9(1-4), 1-7.

[6] Ferrari C. (2015) HBV and the immune response. Liver International, 35(1): 121–128.

[7] Rehermann B. and Nascimbeni M. (2005) Immunology of hepatitis B virus and hepatitis C virus infection. Nature Reviews Immunology, 5(3): 215–229.

[8] Waters J., Pignatelli M., Galpin S., Ishihara K., and Thomas H. C. (1986) Virus-neutralizing antibodies to hepatitis B virus: The nature of an immunogenic epitope on the S gene peptide. Journal of General Virology, 67(11): 2467–2473.

[9] Hagiwara S., Nishida N., and Kudo M. (2015) Antiviral therapy for chronic hepatitis B: Combination of nucleoside analogs and interferon. World Journal of Hepatolog y, 7(23): 2427–2431.

[10] Atteena P. K. Bultery M., Hu D. J. nad Jamieson D. J. (2012) HIV-HBV co-infection – A global challenge. N. Engl J. Med., 366(19): 1749-1752.

[11] Hoffman C. J. and Thio C. L. (2007) Clinical implications of HIV and Hepatitis B co-infection in Asia and Africa. Lancet Infect Dis., 7, 402-409. [PubMed:17521593]

[12] Nasal M. (2015) HBV cccDNA: Viral persistence reservoir and key obstacle for a cure of chronic hepatitis B. Gut, 64, 1972-1984.

[13] WHO (2017) HIV/AIDS, Facts sheet, July, 2017. Retrieved date: [26, November, 2018], online available at http://www.who.int/mediacentre/factsheets/fs360/en/

[14] Alavian S. M. (2010) Hepatitis B virus infection in Iran: Changing the epidemiology. Iran J clin infect Dis., 5, 51-61.

[15] Zhu H. and Zou X. (2009) Dynamics of a HIV-1 infection model with cell-mediated immune response and intracellular delay. Discrete and continuous dynamical systems, series B, 12(2): 511–524.

[16] Culshaw, R., Ruan, S. and Spiteri, R. J. (2004) Optimal HIV Treatment by Maximizing Immune Response. Journal of Mathematical Biology, 48, 5, 545-562.

[17] Webster G. J. M., Reignat S., Miani M. K., etal. (2000) Incubation phase of acute hepatitis B in man: Dynamics of cellular immune mechanisms. Hepatology, 32(5): 1117-1124.

[18] World Health Organization (2018) Progress towards access to hepatitis B treatment worldwide. WHO Website. Retrieved date: [27, November, 2018], online available at http://www.who.int/hepatitis/news-events/cdc-hepatitis-b-article/en/

[19] Lavanchy D. (2004) Hepatitis B virus epidemiology, disease burden, treatment and current emerging prevention and control measures. J. Viral Hepat., 11, 97-107. [CrossRef][PubMed]

[20] Dontwi I. K., Frempong N. K. nad Wiah E. N. (2010) Using mathematical model to depict the immune respovse to Hepatitis B virus infection. American Journal of Sc. & Ind. Res., 1(3): 516-528.

[21] Van Steenbergen J. E., Niesters H.G., Op de Coul E.L., Van Doornum G. J., Osterhaus A. D., Leentvaar-Kuijpers A., Coutinho R. A., Van den Hoek J. A.(2002) Molecular epidemiology of hepatitis B virus in Amsterdam 1992-1997. J Med Virol., 66, 159-65.

[22] Fisker N., Pedersen C., Lange M., Nguyen N.T., Nguyen K.T., Georgsen J.and Christensen P. B. (2004) Molecular epidemiology of hepatitis B virus infections in Denmark. J Clin Virol., 31, 46-52.

[23] Hauri A.M., Armstrong G. L, Hutin Y.J. (2004) The global burden of disease attributable to contaminated injections given in health care settings. Int J STD AIDS, 15, 7-16.

[24] Ataei B., Tayeri K., Kassaeian N., Farajzadegan Z., Babak A. (2010) Hepatitis B and C among Patients Infected with Human Immunodeficiency Virus in Isfahan, Iran: Sero-prevalence and Associated Factors. Hepat Mon, 10, 188-92.

[25] WHO. (2015) Hepatitis B. Fact sheet no. 204, Updated March, 2015. Retrieved date: [26, November, 2018], online available at https://www.who.int/news-room/fact-sheets/detail/hepatitis-b

[26] Tsui J. I., French A. L., etal. (2007) Prevalence and long-trem effects of occult hepatitis B virus infection in HIV-infected women. Clin Infect Dis, 45, 736-40.

[27] Yousfi N., Hattaf K. and Tridane, A. (2011) Modeling the adaptive immune response in HBV infection. J. Math. Biol., 63, 933–957. [CrossRef] [PubMed]

[28] Manna K. and Chakrabarty S. P. (2018) Combination therapy of pegylated interferon and lamivudine and optimal controls for chronic hepatitis B infection. Int. J. Dynam. Control, 354-368. [CrossRef]

[29] Bassey E. (2017) On Optimal Control Pair Treatment: Clinical Management of Viremia Levels In Pathogenic-Induced HIV-1 Infections. Biomed J Sci & Tech Res., 1(2) BJSTR. MS.ID.000204, 1-9. http://biomedres.us/pdfs/BJSTR.MS.ID.000204.pdf

[30] Sherman M. (2009) Strategies for managing co-infection with hepatitis B virus and HIV. Cleve Clin J Med, 76, S30-3. [19465707] [http://dx.doi.org/10.3949/ccjm.76.s3.07]

[31] Iser D. M., Sasadeusz J. J. (2008) Current treatment of HIV/hepatitis B virus co-infection. J Gastroenterol Hepatol, 23:699-706. [18410604] [http://dx.doi.org/10.1111/j.1440-1746.2008.05382.x]

[32] Nowak M. A., Bonhoeffer S., Hill A. M., Boehme R., Thomas H. C. and Mcdade H. (1996) Viral dynamics in hepatitis B virus infection," Proceedings of the National Acadamy of Sciences of the United States of America, 93(9): 4398–4402.

[33] Wang, K. and Wang, W. (2007) Propagation of HBV with spatial dependence. Math. Biosci. 210, 78–95. [CrossRef] [PubMed]

[34] Zheng Y., Min L., Ji Y., Su Y., Kuang Y. (2010) Global stability of endemic equilibrium point of basic virus infection model with application to HBV infection. J. Syst. Sci. Complex, 23, 1221–1230. [CrossRef]

[35] Li J., Wang K. and Yang Y. (2011) Dynamical behaviors of an HBV infection model with logistic hepatocyte growth. Math. Comput. Model, 54, 704–711. [CrossRef]

[36] Bassey B. E. and Lebedev K. A.(2015) On mathematical model of the impact of verimia levels and condom use: preventive measures for the spread of HIV/AIDS// Materials of the XVIII-th International scientific-practical conference "modern science: Actual problems and ways of their solution" (Russian Federation, Lipetsk, July 20, 2015). – Ed. M. J. Levin. – Lipetsk: "maximum information technology", 2015. – 160c. /47-56 стр. http://elibrary.ru/author_items.asp?authorid=801157

[37] Ouattara D. A. (2005) Mathematical Analysis of the HIV-1 Infection: Parameter Estimation, Therapies Effectiveness and Therapeutical Failures. Proceedings of the 2005 IEEE, Engineering in Medicine and Biology 27th Annual Conference, Shanghai, 1-4 September 2005, 821-824.

[38] Gumel A. B., Zhang X., Shirakumar P. N., Garba M. L. nad Sahai B. M. (2002) A new mathematical model for accessing therapeutic strategies for HIV infection. Journal of Theoretical Medicine, 4(20: 147-155.

[39] Bassey B. E. and Lebedev K. A. (2015) On mathematical modeling of the impact of numerical stability of the treatment of vertical transmitted HIV/AIDS infections//Proceedings of the XVI-th international scientific conference "scientific potential with time-Russia (Russian Federation, Lipetsk, August 10, 2015.)/ Ed. by M. J. Levin. – Lipetsk: "maximum information technology", №5(13): 7-19.
http://elibrary.ru/author_items.asp?authorid=801157

[40] Srivastava V. K., Awasthi M. K. and Kumar S. (2004) Numerical approximation for HIV infection of CD4+ T cells mathematical model. Ain Shams Engineering Journal, 5, 625-629.

[41] Hattaf K., Tridane A. and Yousfi N. (2017) A review of mathematical modeling of Hepatitis B and immune response. 9th Pan African Congress of Mathematicians 2017: Symposium, PACOM2017, 1-1.

[42] Danane J. and Allali K. (2018) Mathematical Analysis and Treatment for a Delayed Hepatitis B Viral Infection Model with the Adaptive Immune Response and DNA-Containing Capsids. High-Throughput, 7(35): 1-16.

[43] Jiang C. and Wang W. (2014) Complete classification of global dynamics of a virus model with immune responses. Discret. Contin. Dyn. Syst., Ser. B 2014, 19, 1087–1103.

[44] Meskaf A. Allali K. and Tabit, Y. (2017) Optimal control of a delayed hepatitis B viral infection model with cytotoxic T-lymphocyte and antibody responses. Int. J. Dyn. Control, 5, 893–902. [CrossRef]

[45] Manna K. and Chakrabarty S. P. (2015) Chronic hepatitis B infection and HBV DNA-containing capsids: Modeling and analysis. Commun. Nonlinear Sci. Numer. Simul., 22, 383–395. [CrossRef]

[46] Hattaf K. and Yousfi, N. (2012) Optimal control of a delayed HIV infection model with immune response using an efficient numerical method. Biomathematics, 2012, 1-7. [CrossRef]

[47] Nowak M. A. and Bangham C. R. (1996) Population dynamics of immune response to persistent viruses. Science, 272, 74-79.

[48] Rosenberg E. S., Altfeld M., Poon S. H., Phillips M. N., Wilkes B.M., Eldridge R. L., Robbins G. K., D'Aquila R. T., Goulder P. J. and Walker B. D. (2000) Immune Control of HIV-1 after Early Treatment of Acute Infection. Nature, 407:523–526.

[49] Eikenberry S., Hews S., Nagy J. D. and Kuang Y. (2009) The dynamics of a delay model of hepatitis B virus infection with logistic hepatocyte growth. Mathematical Biosciences and Engineering, 6(2): 283–299.

[50] Bassey E. B. (2017) Optimal control model for immune effectors response and multiple chemotherapy treatment (MCT) of dual delayed HIV - pathogen infections. SDRP Journal of Infectious Diseases Treatment & Therapy, 1(1) 1-18.

[51] Meskaf A., Allali K. Tabit and Y. (2017) Optimal control of a delayed hepatitis B viral infection model with cytotoxic T-lymphocyte and antibody responses. International Journal of Dynamics and Control, 5(3): 893–902.

[52] Forde J. E., Ciupe S. M., Cintron-Arias A. and Lenhart S. (2016) Optimal control of drug therapy in a hepatitis B model. Applied Sciences, 6(8): articleno, 219, Switzerland.

[53] Mouofo P. T., Tewa J. J., Mewoli B. and Bowong S. (2013) Optimal control of a delayed system subject to mixed control state constraints with application to a within-host model of hepatitis virus B. Annual Reviews in Control, 37(2): 246–259.

[54] Schmitz J. E, et al. (1999) Control of Viremia in Simian Immunodeficiency Virus Infection by CD8 (þ) Lymphocytes. Science, 283, 857–860.

[55] Fister K. R., Lenhart, S. and McNally, J. S. (1998) Optimizing chemotherapy in an HIV Model. Electr. J. Diff. Eq., 32, 1-12.

[56] Velichenko V.V. and Pritykin D. A. (2006) Numerical Methods of Optimal Control of the HIV-Infection Dynamics. Journal of Computer and Systems Sciences International, 45(6): 894–905.

[57] Adams B. M., Banks H. T., Hee-Dae K. and Tran H. T. (2004) Dynamic Multidrug Therapies for HIV: Optimal and STI Control Approaches. Retrieved date: [24, January, 2019], online available at http://citeseerx.ist.psu.edu/viewdoc/summary?doi=10.1.1.400.9056

[58] Adams B. M., Banks H. T., Davidian M., Kwon Hee-Dae, Tran H. T., Wynne S. N. and Rosenberg E.S. (2005) HIV Dynamics: Modeling, Data Analysis, and Optimal Treatment Protocols. J. Comp. Appl. Math., 184, 10-49. Retrieved date: [24, January, 2019], online available at
http://citeseer.ist.psu.edu/viewdoc/summary?doi=10.1.1.115.8107

[59] Bassey B. E. (2017) Dynamic optimal control model for period multiple chemotherapy (PMC) treatment of dual HIV-pathogen infections. J Anal Pharm Res., 6(3): 00176, 1-22. DOI: 10.15406/japlr.2017.06.00176

[60] Thomsen A. R, Nansen A., Christensen J. P., Andreasen S. O. and Marker O. (1998) CD40 Ligand is Pivotal to Efficient Control of Virus Replication in Mice Infected with Lymphocytic Choriomeningitis Virus. J Immunol, 161, 4583–4590.

[61] Mathew G. V., Bartholomeusz A., Locarnini S., etal. (2006) Characteristics of drug resistant HBV in an international collaborative study of HIV-HBV infected individuals on extended lamivudine therapy. AIDS2006, 20, 863–870.

[62] Shilaih M., Marzel A., Scherrer U. A.,etal. (2016) Dually Active HIV/HBV Antiretroviral as Protection against incident Hepatitis B infections: Potential for Prophylaxis. Journal of Infectious Diseases, 214, 599-606.

[63] Babudieri S., Longo B., Sarmati L, etal. (2005) Correlates of HIV, HBV, and HCV infections in a Prison inmate population: Results from a multicentre study in Italy. Journal of Medical Virology, 76, 311–317.

[64] Fleming W. and Rishel R. (1975) Deterministic and Stochastic Optimal Control. Springer Verlag, New York

[65] Lukes D. L. (1982) Differential Equations: Classical to Controlled, vol. 162 of Mathematics in Science and Engineering, Academic Press, New York, NY, USA.

[66] Perelson S. A., Kirschner E. D. and De Boer R. (1993) Dynamics of HIV-infection of CD4+ T cells. Mathematical Biosciences, 114, 81-125.

[67] Tridane A., Hattaf K., Yafia R., and Rihan F. A. (2016) Mathematical modeling of HBV with the antiviral therapy for the immunocompromised patients. Communications in Mathematical Biology and Neuroscience, 2016, 1-31.

**Authors' Profiles**

**Bassey Echeng B.**, a philosopher of Computational Mathematics and Informatics, M.Sc. in Industrial Mathematics, and B. Sc. in Mathematic/Statistics. He is a lecturer, a member of the laboratory and mathematical association and presently the Co-coordinator and Head of General mathematics, Cross River University of Technology, Calabar, Nigeria. He is a publisher and author of well over **30 papers** in reputable journals including monographs' and textbooks with citation over **328 times with 10 h-index**. **Research interests:** include but not limited to mathematical modeling, numerical methods; simulation analysis, mathematical methods, computer technology and complexes of programms.

**How to cite this paper:** Bassey, B. Echeng, " Optimal Control Dynamics: Multi-therapies with Dual Immune Response for Treatment of Dual Delayed HIV-HBV Infections", International Journal of Mathematical Sciences and Computing(IJMSC), Vol.6, No.2, pp.18-60, 2020. DOI: 10.5815/ijmsc.2020.02.02

## APPENDICES

## Appendix A:

Table 3 Off-treatment of dual HIV-HBV scenario

| Numerical summary | | |
|---|---|---|
| **Fig. 2** | **Population dynamics** | **Evaluation (in months)** |
| a. $T_u(t)$ | - Initial increase of susceptible double lymphocyte cells due to adaptive immune defense.<br>- Declined thereafter due to incessant invasion by dual virions. | $0.5 \le T_u(t) \le 1.327$ for all $3 \le t_f \le 10$.<br>$1.327 \ge T_u(t) \ge 0.215$ for all $10 \le t_f \le 30$. |
| b. $T_i(t)$ | - Rapid viral load infected cells increases.<br>- Slight decrease due to response from adaptive immune response. | $0.996\times10^{-3} \le T_i(t) \le 5.005$ for all $3 \le t_f \le 14$.<br>$5.005 \ge T_i(t) \ge 3.00$ for all $14 \le t_f \le 30$. |
| c. $T_b(t)$ | - Sharp decrease due to excessive present of virions.<br>- Gradual increase due to response from adaptive immune system. | $0.02 \ge T_b(t) \ge 3.884\times10^{-4}$ for all $3 \le t_f \le 20$.<br>$3.884\times10^{-4} \le T_b(t) \le 5\times10^{-3}$ for all $20 \le t_f \le 30$. |
| d. $V_i(t)$ | - Rapid viral load increase in the present of off-treatment.<br>- Decrease but attain endemic stability. | $0.08 \le V_i(t) \le 181.828$ for all $3 \le t_f \le 14$.<br>$181.828 \ge V_i(t) \ge 10.00$ for all $14 \le t_f \le 30$. |
| e. $V_b(t)$ | - Undulated viral load increases.<br>- Declined slightly and then increases. | $0.07 \le V_b(t) \le 2.653$ for all $3 \le t_f \le 20$.<br>$2.563 \ge V_b(t) \ge 1.2$ for all $20 \le t_f \le 30$. |
| f. $Q(t)$ | - Gradual decline due to consistent proliferation of untreated virions. | $0.04 \le Q(t) \le 2.725\times10^{-3}$ for all $3 \le t_f \le 30$. |
| g. $Z(t)$ | - Initial low stability at $3 \le t_f \le 14$ and then attain undulating increase. | $0.011 \le Z(t) \le 144.302$ for all $14 \le t_f \le 30$. |

## Appendix B:

Table 4 On-treatment of dual HIV-HBV scenario

| Numerical summary | | |
|---|---|---|
| **Fig. 3** | **Population dynamics** | **Evaluation (in months)** |
| a. $T_u(t)$ | - Tremendous initial increase of susceptible double lymphocyte cells.<br>- Declined to stability. | $0.5 \le T_u(t) \le 1.614$ for all $3 \le t_f \le 10$.<br>$1.614 \ge T_u(t) \ge 0.118$ for all $10 \le t_f \le 30$. |
| b. $T_i(t)$ | - Instantaneous decline, which lead to elimination of viral load infected cells. | $0.02 \le T_i(t) \le -4.212$ for all $3 \le t_f \le 30$. |
| c. $T_b(t)$ | - Instantaneous decline, which lead to elimination of B-virus infected cells. | $0.02 \ge T_b(t) \ge -4.352$ for all $3 \le t_f \le 30$. |
| d. $V_i(t)$ | - Gradual decline to zero at $t_f \le 3$ and infectious viral load eliminated thereafter. | $0.08 \le V_i(t) \le -0.195$ for all $t_f \le 30$. |
| e. $V_b(t)$ | - Gradual decline to zero at $t_f \le 3$ and infectious viral load eliminated thereafter. | $0.07 \le V_b(t) \le 0.032$ for all $t_f \le 30$. |
| f. $Q(t)$ | - Gradual decline due to restoration of susceptible population | $0.04 \le Q(t) \le 7.945 \times 10^{-4}$ for all $3 \le t_f \le 30$. |
| g. $Z(t)$ | - Gradual decline due to restoration of susceptible double lymphocyte population. | $0.02 \le Z(t) \le 9.428 \times 10^{-4}$ for all $14 \le t_f \le 30$. |