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DYNAMIC OPTIMAL CONTROL MODEL FOR DUAL-PAIR TREATMENT FUNCTIONS OF DUAL DELAYED HIV-PATHOGEN INFECTIONS

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Abstract

Affirming recent positive results for the possible eradications of dual HIV-pathogen infectivity as identified in the literature of this work, the present paper using ordinary differential equations sought and formulated an extended 8-dimensional mathematical dual delay HIV-pathogen dynamic model. The study seek and addressed the epidemiological dynamic optimal control for the application of dual-pair treatment functions following the interplay of dual delay HIV-pathogen infections with host target immune system cells. The novelty of this model is informed by the combination of dual chemotherapy and dual components of cytotoxic T-lymphocytes (CTLs) as dual-pair treatment functions in the presence of delay intracellular and intrinsic virulence index. We articulated the model as an optimal control problem and therefore, adopted classical Pontryagin's maximum principle of the optimal control theory for its analysis. System stability analysis was equally conducted and optimality system of model established. Using Runge-Kutta of order 4 in a Mathcad surface, model validity was numerically illustrated. Results emphatically

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indicated tremendous maximization of healthy $CD4^+T$ cells and maximal sustainability of precursors and effectors of CTLs. Furthermore, elimination of both virions infected T-cells and infectious virions were achieved at faster time rate under minimized systemic cost and overall commercial value on chemotherapy acquisition established. The model thus, exhibited intellectual proceeding worthy of replication on other related infectious diseases.

1. Introduction

In affirmation to the fact that the human immunodeficiency virus (HIV) and its lethal consequence – acquired immunodeficiency syndrome (AIDS) is the most dreaded disease, it has become obvious that this deadly infection is yet without any outright medical cure. Therefore, the assertion that HVI/AIDS is an integral component of the human immune system with the CD4 T lymphocytes the primary victim cannot be overemphasized. This ugly situation is said to be routed to the fact that the biological activities of this deadly disease is still not clearly known. This is due to a number of factors, which includes: the indistinguishable nature of healthy $CD4^+T$ cells from infected $CD4^+T$ cells at set point [1, 2] and the varying levels of natural anti-HIV immune response – the cytotoxic T-lymphocytes (CTLs) [3, 4].

Moreso, HIV infectivity has concurrently been aggravated by the multiplicity of its allied infections, which includes dual infections of the type: HIV-tuberculosis, HIV-hepatitis, HIV-parasitoid pathogen, etc. [5-7]. Nonetheless, since the discovery of HIV at the early 80's, understanding the infection dynamics and the methodological application of treatments, (i.e., suppressive and preventive) have been through mathematical modelling. Thus, a number of appreciable models have been formulated with the prime aim of improving the quality and prolongation of lifespan of infected patients.

Furthermore, apprehensive of the vast views and/or literatures on HIV infection preventions, we intend to conduct the present investigation based on some notable related HIV/AIDS models. For instance, a more

recent simplified yet standard model [3] had formulated using single treatment function, a 3-dimensional mathematical model that accounted for the optimal HIV treatment with complete maximization of the immune response. The governing equations of that model was given as:

$$\frac{dx}{dt} = \lambda - \delta x - \beta xy,$$

$$\frac{dy}{dt} = \beta' xy - \alpha y - \rho yz,$$

$$\frac{dz}{dt} = cxyz - hz, \tag{1}$$

where $x(t)$ and $y(t)$ are uninfected and infected $CD4^+T$ cell population at time t. Here, viral load was considered as directly proportional to source of inflow of infected cells (see [8] for details). The last state component $z(t)$ represented natural immune response population. Other variables of the equation are the parameter components with detail descriptions as contained in cited reference. The model was simulated via analytic continuation with recommendation focused on treatment interruption strategies, which allows rebuild of immune response.

As an extension of model (1), with the introduction of viral load as an entity of state component and sustaining single treatment function, the study [4] formulated 4-dimensional mathematical equations that investigated the dynamics of a HIV-1 infection model. The model incorporated cell-mediated immune response and intracellular delay. The results that follow indicated the eradication of HI-virus in the presence of significant intracellular delay, while the activities of CTLs can only help reduced the virus and thus, increase healthy $CD4^+T$ cell population.

Elevating the innovative investigation of [4], the study [9] introduced dual chemotherapy control functions, which led to the optimal control of a delayed HIV infection model with immune response using an efficient numerical method. The intent of this model was the of treatment

efficiency in inhibiting viral load population and prevention of new infections. Pontryagin's maximum principle was utilized in the system analyses and simulated using algorithm based on forward and backward difference approximation. The outcome of the investigation indicated that optimal treatment strategies actually reduced viral load and increases the concentration of uninfected $CD4^+T$ cells after five days of therapy.

Empathized by the experimental investigations of [10-19], which had focused on crucial role of cell-mediated CTLs, the study [20] gave an articulated analysis of CTLs enforced by sub-divisive account of CTLs (as precursors of CTLs denoted as CTLp and effectors of CTLs denoted as CTLe), respectively. In that study, the model incorporated CTLp and CTLe as state variables. This led to the formulation of 5-dimensional mathematical model primed with the investigation of specific regimen that could cause long-term control of HIV. The result remained quantitatively similar to those of preceding models with the assumption that high level of viral load increases the amount of immune impairment.

Of note, the seeming insurmountable nature of viral load had let to further analysis of the biological behaviour and transmission dynamics of the virus in terms of its aggressiveness. Thus, model [20] was extensively modified by model [21] with the incorporation of intrinsic virulence index denoted by $r(t)$ as a state component. This later model, using dual treatment factors, accounted for the maximization of asymptomatic stage of fast progressing HIV infected patient using embedding method. The optimal control for this model was analyzed using approximation approach of linear programing method. The results were in affirmation of the method used. Related model in this direction can be found in [22]

Recently, triggered by diverse cases of HIV complicity, dual HIV-pathogen infections was first studied by [2], where a 5-dimensional mathematical model was formulated to account for the analysis of parameter estimation of treatment of Pathogen-Induced HIV infectivity. The model using discretization method tested for the compatibility of

optimal control strategy for the estimation of model parameters. The numerical result that follows suggested the incompatibility of the technique with the model due to large error derivatives. Further dual infectivity studies can be found in [23-25].

Therefore, consumed by the aforementioned literatures, it is evidently that a number of weaknesses are identified, which includes: non-cohesive inclusion of key state components in either of the models, somewhat incoherent application of chemotherapies alongside crucial roles of immune effectors response and delay intracellular to the observatory effect of intrinsic virulence index. Precipitated by the above lapses, the present study is specifically thought to formulate a classical 8-dimensional mathematical HIV-pathogen dynamic model, which seeks to address the dynamic optimal control of dual-pair treatment functions for dual delayed HIV-pathogen infections. Furthermore, we seek to maximize the performance index, which borders around the benefits base on $CD4^+T$ cell count concentration and the positive sustainability of CTLs (= CTLp + CTLe) under targeted minimized optimal chemotherapy cost. The model involves 8-subpopulation with the incorporation of subdivided cytotoxic T-lymphocytes designated as precursors of CTLs and effectors of CTLs and intrinsic virulence index. The model is design to explore classical Pontryagin's maximum principle for the system numerical analysis.

Thoughtfully, the entire study is generated as a manuscript of seven sections with Section 1 covering the introductory aspect. In Section 2, we present the material and methods, which consist of mathematical formulation for an untreated dual HIV-pathogen infection. This is followed by a corresponding schematic representation of the model. Here, we also ascertain the state variables as representative of living organisms by verifying the positivity and boundedness of solutions for the state components. The study further investigates the stability status of the model. In Section 3, following the application of multiple chemotherapies, we transform the derived system to a classical optimal control problem; determine the optimal control characteristics and the

existence of optimal control. Section 4 is devoted to the derivation of optimality system and establishment of uniqueness of optimal control solutions using Pontryagin's maximum principle. We demonstrate the validity of our resulting optimality system numerically in Section 5. The clinical implications of achieved results are discussed in Section 6. Finally, in Section 7, we draw succinct conclusion and incisive recommendations based on findings. It is anticipated that this present study will overcome the aforementioned intellectual weaknesses of dual infections.

2. Material and Methods

The material and methods as outlined in Section 1 will be developed around the derivation of system mathematical equations for an untreated dual HIV-pathogen model, followed by a corresponding schematic representation. Also, in this section, we affirmed the non-negativity and existence of boundedness of solutions for the state variables and finally, stability analysis of the model equations.

2.1. Mathematical formulation for an untreated dual delayed HIV-pathogen model

For a smooth formulation of the present model, we desirably bring to bear, two closely related models from those highlighted in the literature [2, 21]. From [21], the governing equations were derived as:

$$\begin{aligned}
\dot{x} &= \lambda - dx - rx\nu, \\
\dot{y} &= rx\nu - \alpha y - \rho yz, \\
\dot{w} &= cxyw - qyw - bw, \\
\dot{z} &= qyw - hz, \\
\dot{\nu} &= k(1 - u_p)y - \tau\nu, \\
\dot{r} &= r_0 - u_R.
\end{aligned} \tag{2}$$

Model (2) represents the interplay of single HIV-infection on the target $CD4^+T$ cells and the articulated role of natural immune response (CTLp and CTLe) with $x(t)$, $y(t)$, $w(t)$, $z(t)$, and $r(t)$ as the state variables. The last component $r(t)$ represents an index of virus aggressiveness (intrinsic virulence). This index is assumed to increase linearly for an untreated HIV-infected patient having its growth rate constant r_0. For details of this model, we refer readers to cited reference.

For the case of dual HIV-pathogen infections, we recall the governing equations of model [2], which was derived as:

$$\begin{aligned}
\dot{T}_{(u)} &= b_{(p)} + \sigma V_{(\nu)} + \alpha P_{(p)} - \mu T_{(u)} - \beta T_{(u)} V_{(\nu)} - \delta T_{(u)} P_{(p)},\\
\dot{I}_{(\nu)} &= \beta T_{(u)} V_{(\nu)} - \tau_1 I_{(\nu)} - k I_{(\nu)},\\
\dot{I}_{(p)} &= \delta T_{(u)} P_{(p)} - \tau_2 I_{(p)} - d I_{(p)},\\
\dot{V}_{\nu} &= k I_{(\nu)} - (c + \sigma) V_{(\nu)},\\
\dot{P}_{p} &= d I_{(p)} - (e + \alpha) P_{p},
\end{aligned} \tag{3}$$

where $T_{(u)}$, $I_{(\nu)}$, $I_{(up)}$, $V_{(\nu)}$, and $P_{(p)}$ represented the model state variables. We also refer readers to cited reference for more details on model descriptions.

Therefore, leaping on the innovative ideas of models (2) and (3), we establish a clinical 8-dimensional equation that adequately represents the epidemiological and biological interplay of dual delayed HIV-pathogen infections on host target $CD4^+T$-lymphocytes studied under quadrupled treatment functions. The model equally accommodates the intracellular delay and the role of intrinsic virulence. This is to say that if the population subgroups are measured in units' volume of cell/mm^3 such that T_u-uninfected $CD4^+T$ cells, V-viral load, P-parasitoid-pathogen; then for viral load and pathogen infected $CD4^+T$

cells, we shall denote by I_ν and I_p, respectively. Other state variables includes W-precursors of cytotoxic T-lymphocytes (CTLp), Z-effectors of cytotoxic T-lymphocytes (CTLe) and virions ingress denoted by R. The resulting model equation is further guided by the following assumptions.

Assumption 1.

(i) The dynamics between virions and cytotoxic T-lymphocytes (CTLs) is dependent on host target cells and virions parameters.

(ii) Precursors of CTLs exhibit dual characteristic behaviour such as immune memory replication and effective contamination by virions.

(iii) The effective development of CTL memory by precursor of CTL depends on the efficacy and threshold of therapy administered at set point.

(iv) High re-establishment of CTL memory is dependent on early initiation of chemotherapy treatment.

Thus, the present model is governed by:

$$\begin{aligned}
\dot{T}_u &= b_p + \sigma V + \lambda P - \alpha_1 T_u - (\beta V + \delta P) R T_u, \\
\dot{I}_\nu &= \beta e^{-\alpha_2 \omega} V R T_u - (\alpha_2 + k) I_\nu - q_1 I_\nu Z, \\
\dot{I}_p &= \delta e^{-\alpha_3 \omega} P R T_u - (\alpha_3 + d) I_p - q_2 I_p Z, \\
\dot{V} &= k I_\nu - (\alpha_4 + \sigma) V, \\
\dot{P} &= d I_p - (\alpha_5 + \lambda) P, \\
\dot{W} &= c I_\nu I_p T_u W - \rho I_\nu I_p W - \alpha_6 W, \\
\dot{Z} &= \rho I_\nu I_p W - \alpha_7 Z, \\
\dot{R} &= R_0 - R,
\end{aligned} \tag{4}$$

with initial values $T_u(0) = T_{(u)0}$, $I_v(0) = I_{(v)0}$, $I_p(0) = I_{(p)0}$, $V(0) = V_0$, $P(0) = P_0$, $W(0) = W_0$, $Z(0) = Z_0$, and $R(0) = R_0$ at $t = t_0$ and satisfying the biological state variables and parameter values as describe in Tables 1 & 2. Therefore, model (4) is the standard equation that satisfies the scope of the present study with biological behaviour schematically represented as in Figure 1, below:

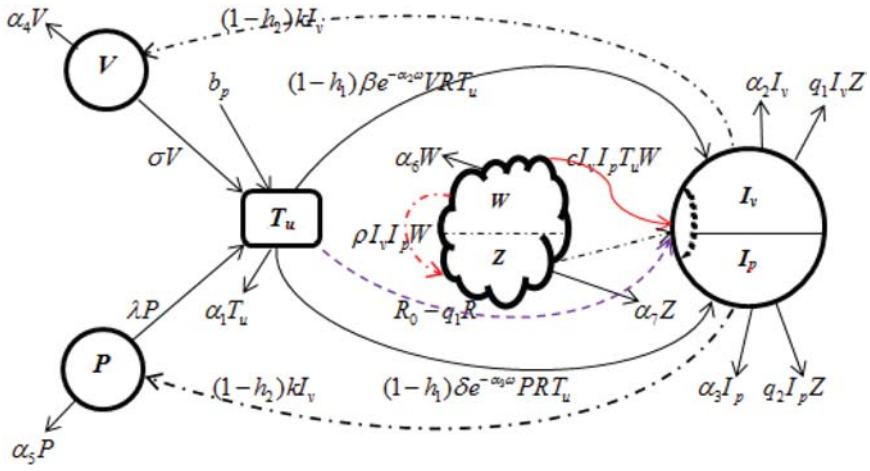


Figure 1. Schematic representation of dual delayed HIV-pathogen infections with dual-pair treatment functions (*RTI*, *PIs*, *CTLp*, *CTLe*).

The logical descriptions of epidemiological terms of model (4) are as follows: from the first equation, the first term represents the natural source rate of uninfected $CD4^+T$ cells, which is infiltrated by rates of inflow of second and third terms representing viral load and pathogen virions denoted by σV and λP, respectively. The last term $-(\beta V + \delta P)RT_u$ describe the sum differential product of uninfected $CD4^+T$ cells that becomes infected by both viral load and pathogen with R representing the aggressiveness of virions.

The second and third equations represent the biological dynamics of susceptible T-cell becoming infected following the invasion by both viral load and pathogen virions. Their respective first terms $\beta e^{-\alpha_2 \omega VRT_u}$ and $\delta e^{-\alpha_3 \omega PRT_u}$ describes the rates of inflow of infectious T-cells by both virions as product of ingress rate R and exponential rate $e^{-\alpha_i \omega}$ reflect the death rate with ω denoting the lag between the time the virions contacts target cell and the time the cell becomes actively infectious. This stage includes the progression of virions attachment and actual penetration into the cell. The second terms $(\alpha_2 + k)I_\nu$ and $(\alpha_3 + d)I_p$ presents infected T cells death rates and replications of virions by infected T cells. The last terms $q_1 I_\nu Z$ and $q_2 I_p Z$ denotes clearance rates of infected T cells by immune effectors response.

From fourth and fifth equations, we define the epidemiological interplay of both virions with its host. Their respective first terms kI_ν and dI_p describe the productive capacities of both virions by infectious T cells. The last terms $-(\alpha_4 + \sigma)V$ and $-(\alpha_5 + \lambda)P$ denotes virions death rates and rates of infections. In the sixth equation, the first term $cI_\nu I_p T_u W$ denotes the proliferation of CTLp population, which is dependent on the generation constant c and directly proportional to $I_\nu(t)$ and $I_p(t)$; healthy $CD4^+$T cells helper and the levels of CTLs. Hence, the quadruple term with CTLs acting as both target cells and treatment functions. The second term $\rho I_\nu I_p W$, which also appear as the first term of the sixth equation is the rate of differentiation of CTLp into effectors – CTLe. Both CTLp and CTLe are cleared at the rates $\alpha_6 W$ and $\alpha_7 Z$, respectively. Finally, the eighth equation defines the intrinsic virulence dynamics with index R and having linear incremental rate R_0. Of note is the linear growth of R for an untreated dual delayed HIV-pathogen infected patient. Therefore, if treatment is applied (as will be specify in Section 3), then R will experience loss rate $h_1(t)R$.

Remark 1. Precursors of CTLp are responsible for the development of immune memory, which differentiate into effectors of CTLs responsible for the active defense of foreign agents, i.e., elimination (killing) of virions.

Remark 2. The constants k, d in the second-fifth equations of model (4) are related to the coefficient β of model [26] and the state variable R in collaboration with the intrinsic virulence index $r(t)$ of models [21, 22].

Thus, following the detail description of model (4) and Remarks 1 and 2, the validity of the model becomes imperative if we can generate clinical compactible data for both state variables and parameters. Tables 1 and 2 presents the summary for the desired clinical data.

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

Variables	Dependent variables	Initial values	Units
	Description		
T_u	Uninfected T-lymph cells population	0.6	cell/mm^3
I_v	Viral load infected $CD4^+$T-lymphocytes population	0.02	cell/mm^3
I_p	Pathogen infected $CD4^+$T-lymphocytes population	0.02	cell/mm^3
V	Infectious free viral load population	0.08	copies/ml^{-1}
P	Infectious free pathogen population	0.07	copies/ml^{-1}
W	Precursors of CTLp	0.02	cell/mm^3
Z	Effectors of CTLe	0.04	cell/mm^3
R	Intrinsic virulence index	0.025	mlcopies^{-1}d^{-1}

Note: Table 1 is extracted from validated data of models [2, 21, 22].

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

Parameter symbols	Parameters and constants Description	Initial values	Units
b_p	Inflow source of uninfected $CD4^+T$ cells population	0.05	mm^3d^{-1}
α_1	Death rate of uninfected $CD4^+T$ cells	0.02	d^{-1}
α_2	Death rate of viral load infected $CD4^+T$ cells	0.02	d^{-1}
α_3	Death rate of pathogen infected $CD4^+T$ cells	0.02	mm^3d^{-1}
α_4	Death rate of viral load	0.1	mm^3d^{-1}
α_5	Death rate of pathogen	0.02	mm^3d^{-1}
α_6	Clearance rate of precursors of CTLp	0.017	d^{-1}
α_7	Clearance rate of precursors of CTLe	0.006	d^{-1}
$h_{i=1,2}$	Treatment control functions for T_u, I_ν, I_p, V, P	$h_i \in [0, 1)$	
σ	Rate viral load infection on uninfected $CD4^+T$ cells	0.2	mm^3
λ	Rate pathogen infection on uninfected $CD4^+T$ cells	0.4	mm^3
β	Replication rate of viral load	0.5	mm^3d^{-1}
δ	Replication rate of pathogen	0.5	mm^3d^{-1}
ω	Time delay lag	0.5	d^{-1}
k	Viral load replication by infected cells	5.0	mm^3d^{-1}
d	Pathogen replication by infected cells	5.0	mm^3d^{-1}
q_1	Clearance rate of I_ν by immune effectors response	0.05	mm^3d^{-1}
q_2	Clearance rate of I_p by immune effectors response	0.05	mm^3d^{-1}
c	CTLp proliferation	0.005	$mm^3cells^{-2}d^{-1}$
ρ	CTLp differentiation	0.006	$mm^3cells^{-1}d^{-1}$
R_0	Growth rate of virulence	10^{-7}	$copies^{-1}mld^{-2}$
B_1	Optimal weight ratio h_1	2000	
B_2	Optimal weight ratio h_2	25	

Note: Table 2 is a modification of data from models [2, 21, 23, 25].

Next, we verify that the key components of model (4) are all representative of living organisms by demonstrating the positivity of the state variables and boundedness of solutions.

2.2. Positivity of state variables and boundedness of solutions

From the composition of model (4), we see that the model is a set of delay differential equations and so requires specification of initial functions and their boundedness. This is to say that if $C = B([-\omega, 0], \Re^8)$ be the Banach space of continuous mapping in the interval $[-\omega, 0]$ into $\Re^8$ equipped with the sup-norm (topology of uniform convergence). Then from [4, 23, 27], we apply the fundamental theory of functional differential equations (FDEs) to show that there exists unique solutions $t_u(t)$, $i_\nu(t)$, $i_p(t)$, $\nu(t)$, $p(t)$, $w(t)$, $z(t)$, $r(t)$ to model (4) with initial values

$$(t_u(\theta), i_\nu(\theta), i_p(\theta), \nu(\theta), p(\theta), w(\theta), z(\theta), r(\theta)) \in C. \tag{5}$$

From biological point of view, these initial value functions

$t_u(\theta)$, $i_\nu(\theta)$, $i_p(\theta)$, $\nu(\theta)$, $p(\theta)$, $w(\theta)$, $z(\theta)$, $r(\theta)$ are assumed to be non-negative, i.e.,

$$\{t_u(\theta), i_\nu(\theta), i_p(\theta), \nu(\theta), p(\theta), w(\theta), z(\theta), r(\theta) \in C | C \geq 0, \text{ for } \theta \in [-\omega, 0]\}. \tag{6}$$

Therefore, the non-negative and boundedness of model (4) for which initial value functions satisfy conditions (5) and (6) is define by the following theorem.

Theorem 1. *Suppose* $t_u(t)$, $i_\nu(t)$, $i_p(t)$, $\nu(t)$, $p(t)$, $w(t)$, $z(t)$, $r(t)$ *is the solution to model* (4) *and satisfying conditions* (5) *and* (6), *then* $t_u(t)$, $i_\nu(t)$, $i_p(t)$, $\nu(t)$, $p(t)$, $w(t)$, $z(t)$, $r(t)$ *are all positive and bounded for all* $t \geq 0$ *at which the solution exists.*

Proof. Here, collaborating the result of (Theorem 1, p.7-8, [23]; Theorem 2.1, p. 514-515, [27]), we see from model (4) that

$$t_u(t) = t_u(0)e^{-\int_{t_0}^{t_f}\{\alpha_1+[\beta\nu(\xi)+\delta p(\xi)]r(\xi)\}d\xi} + \int_{t_0}^{t_f} b_p e^{-\int_{\eta}^{t_f}\{\alpha_1+[\beta\nu(\xi)+\delta p(\xi)]r(\xi)\}d\xi d\xi}\, d\eta,$$

$$i_\nu(t) = i_\nu(0)e^{-\int_{t_0}^{t_f}\{(\alpha_2+k)+q_1 z(\xi)\}d\xi}$$

$$+ \int_{t_0}^{t_f} \beta r(\eta-\omega)\nu(\eta-\tau)\nu(\eta-\omega)t_u(\eta-\omega)e^{-\alpha_2\omega}e^{-\int_{t_0}^{t_f}\{(\alpha_2+k)+q_1 z(\xi)\}d\xi}\, d\eta,$$

$$i_p(t) = i_p(0)e^{-\int_{t_0}^{t_f}\{(\alpha_3+d)+q_2 z(\xi)\}d\xi}$$

$$+ \int_{t_0}^{t_f} \delta r(\eta-\omega)\nu(\eta-\tau)\nu(\eta-\omega)t_u(\eta-\omega)e^{-\alpha_3\omega}e^{-\int_{t_0}^{t_f}\{(\alpha_3+k)+q_2 z(\xi)\}d\xi}\, d\eta,$$

$$\nu(t) = \nu(0)e^{-\int(\alpha_4+\sigma)t} + \int_{t_0}^{t_f} k i_\nu(\eta)e^{-(\alpha_4+\sigma)(t-\eta)}d\eta,$$

$$p(t) = p(0)e^{-\int(\alpha_5+\lambda)t} + \int_{t_0}^{t_f} d i_p(\eta)e^{-(\alpha_5+\lambda)(t-\eta)}d\eta,$$

$$w(t) = w(0)e^{-\alpha_6 t} + \int_{t_0}^{t_f} (c i_\nu(\xi)i_p(\xi)t_u(\xi) - \rho i_\nu(\xi)i_p(\xi) - \alpha_6)d\xi,$$

$$z(t) = z(0)e^{-\alpha_7 t} + \int_{t_0}^{t_f} (\rho i_\nu(\xi)i_p(\xi)w(\xi) - \alpha_7)d\xi,$$

and

$$r(t) = r(0)e^{-t} + \int_{t_0}^{t_f} (r_0(\xi) - 1)d\xi.$$

Positivity follows immediately from the above integral forms and conditions (5) and (6) are satisfied. Next, we verify the boundedness of solutions. We define

$$J(t) = c(k+d)e^{-(\alpha_2+\alpha_3)\omega}t_u(t) + c(k+d)[i_\nu + i_p] + \frac{c}{2}[\nu(t+\omega)p(t+\omega)] + (k+d)q_1q_2z(t+\omega),$$

and $x = \min\{\alpha_1, \alpha_2/2, \alpha_3/2, \alpha_4, \alpha_5, \alpha_6, \alpha_7\}$. By positivity of the solution, it follows that

$$\begin{aligned}
\frac{d}{dt}[J(t)] &= c(k+d)e^{-(\alpha_2+\alpha_3)\omega}[b_p + \sigma\nu(t) + \lambda p(t) - (\beta\nu(t) + \delta p(t))r(t)t_u(t)] \\
&\quad + c(k+d)\beta\delta e^{-(\alpha_2+\alpha_3)\omega}\nu(t)p(t)t_u(t) - \alpha_2 c(k+d)i_\nu(t+\omega)i_p(t+\omega) \\
&\quad - c(k+d)(q_1q_2)i_\nu(t+\omega)i_p(t+\omega)w(t+\omega) + \frac{\alpha_2 c(k+d)}{2}[(i_\nu + i_p)(t+\omega)] \\
&\quad - \frac{c(\alpha_4+\alpha_5)}{2}\nu(t+\omega)p(t+\omega) + c(k+d)(q_1q_2)[(i_\nu + i_p)(t+\omega)]z(t+\omega) \\
&\quad - (k+d)\rho(q_1q_2)(\alpha_6+\alpha_7)w(t)z(t) - (k+d)r_0(t)r(t) \\
&= c(k+d)b_p e^{-(\alpha_2+\alpha_3)\omega} - c\alpha_1(k+d)e^{-(\alpha_2+\alpha_3)\omega}t_u(t) - c\frac{(\alpha_2+\alpha_3)}{2} \\
&\quad (k+d)i_\nu(t+\omega)i_p(t+\omega) \\
&\quad - c\frac{(\alpha_4+\alpha_5)}{2}\nu(t+\omega)p(t+\omega) - (k+d)[q_1\alpha_6 + q_2\alpha_7]w(t+\omega)z(t+\omega) \\
&< c(k+d)b_p - xJ(t).
\end{aligned}$$

This implies that $J(t)$ is bounded and so are $t_u(t)$, $i_\nu(t)$, $i_p(t)$, $\nu(t)$, $p(t)$, $w(t), z(t)$, and $r(t)$. Whence, proof completed. □

Remark 3. The outcome of Theorem 1 in conjunction with conditions (5) and (6) indicates that for $i_\nu(0),\ i_p(0) > 0$ or such that $\nu(0),\ p(0)$, then $t_u(t),\ i_\nu(t),\ i_p(t),\ \nu(t),\ p(t),\ w(t),\ z(t)$, and $r(t)$ are obviously nonnegative and therefore, boundedness of solution exist for all $t \geq 0$.

2.3. Stability analysis of untreated dual delayed model

Due to the multiplicity of both state components and accompanying parameters, model (4) is a complex non-linear system and as such, we are bound to encounter somewhat level of complex stability analysis. Nonetheless, we show the ability of the model to exhibit multiple locally asymptomatically stable steady states.

Fundamentally, model (4) has an infection-free equilibrium $E_0 = (b_p/\alpha_1,\ 0,\ 0,\ 0,\ 0,\ 0,\ 0,\ 0)$ corresponding to the maximal level of healthy $CD4^+T$ cells. This meaningful biological equilibrium holds only if reproductive number

$$\Re_0 = (k + d)e^{-(\alpha_2+\alpha_3)\omega} b_p \frac{(\beta + \delta)}{\alpha_1(\alpha_4 + \alpha_5)} < 1.$$

Thus, infected cells, viral load, pathogen and immune effectors response are at zero. Of note, for a system of such with zero immune response may not be commendable for immune system surrounded by infectious virions. For $\Re > 1,$ there exist several other biological meanings. Thus, in a more specific analytical stability view of model (4), let $u = (T_u,\ I_\nu,\ I_p,\ V,\ P,\ W,\ Z,\ R)$ represent the vectorial capacity of the model, then in vector form, model (4) is written as:

$$\frac{du(t)}{dt} = f(t,\ u;\ x), \tag{7}$$

where $f(t,\ u;\ x)$ is the right side of the ODEs system and x is the vector parameters of Table 2. Therefore, for parameter values of Table 2, we compatibly explore Runge-Kutta of order 4, to conveniently solve the

equation $f(t, u; x) = 0$ for the equilibria $\bar{x}_k$. This is followed by the computation of the Jacobian matrix of system partial derivatives, i.e.,

$$\frac{\partial f(t, u; x)}{\partial u} = \left[\frac{\partial f_i(t, u; x)}{\partial u_j}\right]. \tag{8}$$

Since model (4) is that of an untreated model, then the Jacobian for an off treatment is derived as:

$$J = \begin{pmatrix} -\alpha_1 - (\beta V + \delta P) & 0 & 0 & \sigma - \beta R T_u & \lambda - \delta R T_u & 0 & 0 & 0 \\ \beta e^{-\alpha_2 \omega} V R & -(\alpha_2 + k) - q_1 Z & 0 & \beta e^{-\alpha_2 \omega} R T_u & 0 & 0 & -q_1 I_v & 0 \\ 0 & 0 & -(\alpha_3 + d) - q_2 Z & 0 & \delta e^{-\alpha_3 \omega} R T_u & 0 & -q_2 I_p & 0 \\ 0 & k & 0 & -(\alpha_4 + \sigma) & 0 & 0 & 0 & 0 \\ 0 & 0 & d & 0 & -(\alpha_5 + \lambda) & 0 & 0 & 0 \\ 0 & c I_p T_u W & c I_v T_u W & 0 & 0 & c I_v I_p T_u & 0 & 0 \\ 0 & -\rho I_p W & -\rho I_v W & 0 & 0 & -\rho I_v I_p - \alpha_6 & 0 & 0 \\ 0 & \rho I_v W & \rho I_v W & 0 & 0 & \rho I_v I_p & -\alpha_7 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & -1 \end{pmatrix}. \tag{9}$$

Then, we obtain the dynamic ODE of the system that is linearized about the equilibrium $\bar{x}_k$ by simply substituting computed $\bar{x}_k$ steady state for x in Equation (9). The linearization is necessary as it ascertain the fact that if eigenvalues of the matrix all have negative real parts, then the equilibrium $\bar{x}_k$ is locally asymptomatically stable. Therefore, with parameter values as in Tables 1 and 2, model (4) exhibits in addition to infection-free equilibrium E_0, two other physical steady states and several non-physically steady states (omitted here for brevity). More details on this aspect can be found in [3, 4].

Finally, it is important not to undermine the fact that the motivational goals of this study is the derivation of the mathematical and quantitative approach for the maximization of susceptible immune

system performance index adjudged by the benefit on $CD4^+T$ cells and CTLs concentration via optimal chemotherapy cost. Therefore, we are oblige to transform our model (4) to an optimal control problem in order to accommodate treatment functions with define objective functional.

3. Optimal Control Problem and Characterization

Here, with the application of treatment schedule, we represent our system as an optimal control problem and then establish the characteristics of the optimal control as well as show the existence of optimal control strategy.

3.1. Optimal control formulation

Taking a leap from [25] for the definition of an optimal control problem, then for a typical system of model (4), which is established base on dual delay HIV-pathogen infection and studied using dual-pair treatment functions, we seek to maximize the levels of healthy $CD4^+T$ cells as well as maximal sustainability of CTLp and CTLe. We also target at minimized systemic cost and maximal suppression of virions below detectable assay. Therefore, it becomes necessary for the introduction of chemotherapy and accompanying control functions, i.e., $h_1(t)$ and $h_2(t)$ as representing the immune boosting and viral suppressing drugs, respectively. This control functions have domain normalize at, $a_i, b_i \in [0, 1]$, $i = 1, 2$ such that if $h_i = 1,$ we have total effective chemotherapy and for $h_i = 0,$ we have off treatment situation. This is to say that model (4) is justified for $h_i = 0$.

Therefore, we seek an optimal control pair h_1^*, h_2^* such that

$$Q(h_1^*, h_2^*) = \max_{0 \le h_i \le 1} \{Q(h_1, h_2) \setminus (h_1, h_2) \in A\},$$

where $A := \{(h_1, h_2) \setminus h_i$ is Lebesgue – measurable with $a_i \le h_i \le b_i$, $t \in [t_0, t_f],$ for $i = 1, 2\}$ is the control set. Mathematically, the objective functional of the optimal control problem is formulated as:

$$Q(h_1, h_2) = \int_{t_0}^{t_f} \{T_u(t) + W(t) + Z(t) - [B_1(h_1(t))^2 + B_2(h_2(t))^2]\}dt \quad (10)$$

subject to the state system

$$\begin{aligned}
\dot{T}_u &= b_p + \sigma V + \lambda P - \alpha_1 T_u - (1 - h_1)[\beta V + \delta P]RT_u, \\
\dot{I}_\nu &= (1 - h_1)\beta e^{-\alpha_2 \omega} VRT_u - (\alpha_2 + k)I_\nu - q_1 I_\nu Z, \\
\dot{I}_p &= (1 - h_1)\delta e^{-\alpha_3 \omega} PRT_u - (\alpha_3 + d)I_p - q_2 I_p Z, \\
\dot{V} &= (1 - h_2)kI_\nu - (\alpha_4 + \sigma)V, \\
\dot{P} &= (1 - h_2)dI_p - (\alpha_5 + \lambda)P, \\
\dot{W} &= cI_\nu I_p T_u W - \rho I_\nu I_p W - \alpha_6 W, \\
\dot{Z} &= \rho I_\nu I_p W - \alpha_7 Z, \\
\dot{R} &= R_0 - R,
\end{aligned} \quad (11)$$

where virions differentiation from $CD4^+T$ cells under chemotherapy is $(1 - h_1)(\beta + \delta)$ and virions production by infected $CD4^+T$ cells under chemotherapy is given by $(1 - h_2)(k + d)$, respectively. Related mathematical models to Equations (10)-(11) can be found in [3, 9, 28].

Remark 4. The introduction of optimal function $B_{i=1,2} \geq 0$ is defined as the optimal weight factors and this accommodates the fact that benefit on cost functional is nonlinear. Otherwise, the issues of drug side-effects may not be under control, thus, the simple nonlinear controls [7, 29].

Proposition 1. *Assume there exist drug hazardous side-effect, then the inequality of the optimal weight factors* $B_{i=1,2}$ *is such that* $0 \leq a_i \leq h_i \leq b_i < 1$ *holds.*

3.2. Characterization of an optimal control

A realistic and précised formulation of an optimal control $h_i^*(t)$ requires the definition of an optimal control characteristic, i.e., the penalty terms on the constraints. To achieve this, we invoke classical Pontryagin's maximum principle [30] for which the objective functional is the Hamiltonian argument define by the Lagrangian as:

$$
\begin{aligned}
&M(T_u(t),\, I_\nu(t),\, I_p(t),\, V(t),\, P(t),\, W(t),\, Z(t),\, R(t),\, h_1(t),\\
&h_2(t),\, \eta_1(t),\, \eta_2(t),\, \eta_3(t),\, \eta_4(t),\, \eta_5(t),\, \eta_6(t),\, \eta_7(t),\, \eta_8(t))\\
&\quad = T_u(t) + W(t) + Z(t) - [B_1(h_1(t)^2) + B_2(h_2(t))^2]\\
&\qquad + \eta_1[b_p + \sigma V + \lambda P - \alpha_1 T_u - (1 - h_1)[\beta V + \delta P]RT_u]\\
&\qquad + \eta_2[(1 - h_1)\beta e^{-\alpha_2 \omega} VRT_u - (\alpha_2 + k)I_\nu - q_1 I_\nu Z]\\
&\qquad + \eta_3[(1 - h_1)\delta e^{-\alpha_3 \omega} PRT_u - (\alpha_3 + d)I_p - q_2 I_p Z]\\
&\qquad + \eta_4[(1 - h_2)kI_\nu - (\alpha_4 + \sigma)V]\\
&\qquad + \eta_5[(1 - h_2)dI_p - (\alpha_5 + \lambda)P]\\
&\qquad + \eta_6[cI_\nu I_p T_u W - \rho I_\nu I_p W - \alpha_6 W]\\
&\qquad + \eta_7[\rho I_\nu I_p W - \alpha_7 Z] + \eta_8[R_0 - R]\\
&\qquad + w_{11}(t)(b_1 - h_1) + w_{12}(t)(h_1 - a_1)\\
&\qquad + w_{21}(t)(b_2 - h_2) + w(t)(h_2 - a_2),
\end{aligned}
$$

where $w_{11}(t), w_{12}(t), w_{21}(t), w_{22}(t) \geq 0$ are penalty multipliers satisfying

$$w_{11}(t)(b_1 - h_1) = 0,\ w_{12}(t)(h_1 - a_1) = 0 \qquad \text{at the optimal } h_1^*,$$

and

$$w_{21}(t)(b_2 - h_2) = 0,\ w(t)(h_2 - a_2) = 0 \qquad \text{at the optimal } h_2^*.$$

This ensures that h_i^* remain bounded in the domain $h_i \in [0, 1]$.

The functions $\eta_j(t),\ j = 1, 2, \ldots, 8$ are the model adjoint variables, which determine the adjoint system. This adjoint system together with the state system determines the model optimality system. Furthermore, we examine all possible controls for and including boundaries of h_i^*, (i.e., $0 \leq h_i \leq 1$), $i = 1, 2$.

(i) The case of the set $\{t|0 < h_i^*(t) < 1\} : w_{ij} = 0,\ i,\ j = 1, 2$.

Pontryagin's maximum principle state that the unconstrained optimal control $h_i^*(t)$ satisfies

$$\frac{\partial M}{\partial h_1^*} = 0 \text{ and } \frac{\partial M}{\partial h_2^*} = 0.$$

Then, we find $\frac{\partial M}{\partial h_i^*} = 0,\ i = 1, 2$ and solve for h_1^* and h_2^* by setting our partial derivative of M equal to zero, i.e.,

$$\frac{\partial M}{\partial h_1^*} = -2B_1 h_1^*(t) + (\beta V + \delta P)RT_u\eta_1(t) - \beta e^{\alpha_2\omega}VRT_u\eta_2(t)$$

$$- \delta e^{-\alpha_3\omega}PRT_u\eta_3(t) - w_{11} + w_{12} = 0 \qquad \text{at } h_1^*.$$

Also,

$$\frac{\partial M}{\partial h_2^*} = -2B_1 h_2^*(t) + kI_\nu\eta_4(t) + dI_p\eta_5(t) - w_{21} + w_{22} = 0 \qquad \text{at } h_1^*.$$

Solving for the optimal controls h_i^* for $w_{ij} = 0$, we have

$$h_1^*(t) = \frac{(\beta V + \delta P)RT_u\eta_1 - \beta e^{\alpha_2\omega}VRT_u\eta_2 - \delta e^{-\alpha_3\omega}PRT_u\eta_3}{2B_1}, \tag{13}$$

and

$$h_2^*(t) = \frac{kI_v\eta_4 + dI_p\eta_5}{2\beta_1}. \tag{14}$$

To complete the characteristics of $h_i^*(t)$, we consider the boundaries for $h_i^* = 0$ and $h_i^* = 1$ as well as nonboundary cases.

(ii) The case of the set $\{t|h_i^*(t) = 0,\ i = 1, 2\}: w_{1j} \geq 0,\ w_{i2} = 0,\ i, j = 1$.

Then, the optimal control is given by

$$0 = \frac{(\beta V + \delta P)RT_u\eta_1 - \beta e^{\alpha_2\omega}VRT_u\eta_2 - \delta e^{-\alpha_3\omega}PRT_u\eta_3 - w_{1j}}{2B_1},$$

since $w_{1j} \geq 0$ the above implies that

$$\frac{(\beta V + \delta P)RT_u\eta_1 - \beta e^{\alpha_2\omega}VRT_u\eta_2 - \delta e^{-\alpha_3\omega}PRT_u\eta_3}{2B_1} \leq 0.$$

So, to ensure that h_1^* is not negative, we use the notation:

$$h_1^*(t) = \left(\frac{(\beta V + \delta P)RT_u\eta_1 - \beta e^{\alpha_2\omega}VRT_u\eta_2 - \delta e^{-\alpha_3\omega}PRT_u\eta_3}{2B_1}\right)^+ = 0,$$

i.e.,

$$h_1^*(t) = \left(\frac{(\beta V + \delta P)RT_u\eta_1 - \beta e^{\alpha_2\omega}VRT_u\eta_2 - \delta e^{-\alpha_3\omega}PRT_u\eta_3}{2B_1}\right)^+.$$

Similarly,

$$h_2^*(t) = \left(\frac{kI_v\eta_4 - dI_p\eta_5}{2\beta_2} \right)^+.$$

(iii) The case of the set $\{t|h_i^*(t) = 1,\ i = 1,\ 2\} : w_{i1} = 0,\ w_{2j} \geq 0,\ i,\ j = 2.$

The optimal control is obtain as

$$1 = \frac{(\beta V + \delta P)RT_u\eta_1 - \beta e^{\alpha_2\omega}VRT_u\eta_2 - \delta e^{-\alpha_3\omega}PRT_u\eta_3 + w_{2j}}{2B_1},$$

which implies that

$$0 \leq w_{i2} = (\beta V + \delta P)RT_u\eta_1 - \beta e^{\alpha_2\omega}VRT_u\eta_2 - \delta e^{-\alpha_3\omega}PRT_u\eta_3 - 2B_1.$$

Therefore,

$$\left\{ \left(\frac{(\beta V + \delta P)RT_u\eta_1 - \beta e^{\alpha_2\omega}VRT_u\eta_2 - \delta e^{-\alpha_3\omega}PRT_u\eta_3}{2B_1} \right) \geq 1 \right\} = h_1^*.$$

Similarly,

$$\left\{ \left(\frac{kI_v\eta_4 - dI_p\eta_5}{2\beta_2} \right) \geq 1 \right\} = h_2^*.$$

So, on this set, we must choose

$$h_1^*(t) = \min\left\{ \left(\frac{(\beta V + \delta P)RT_u\eta_1 - \beta e^{\alpha_2\omega}VRT_u\eta_2 - \delta e^{-\alpha_3\omega}PRT_u\eta_3}{2B_1} \right), 1 \right\},$$

and

$$h_2^*(t) = \min\left\{ \left(\frac{kI_v\eta_4 - dI_p\eta_5}{2\beta_2} \right), 1 \right\}.$$

Thus, we complete the characterization of the optimal controls by compatibly taking the three cases for $h_1^*(t)$ and $h_2^*(t)$ as define by the following proposition.

Proposition 2. *The optimal controls for the optimal control problem of Equation* (11) *with bounds* $0 \le a_i \le h_i^* \le b_i \ge 1$ *is completely characterized by*

$$h_1^*(t) = \min$$

$$\left\{\max\left\{a_1, \frac{1}{2B_1}\left((\beta V + \delta P)RT_u\eta_1 - \beta e^{\alpha_2\omega}VRT_u\eta_2 - \delta e^{-\alpha_3\omega}PRT_u\eta_3\right)\right\}^+, b_1\right\}, \tag{15}$$

$$h_2^*(t) = \min\left\{\max\left\{a_2, \frac{1}{2B_2}\left(kI_v\eta_4 - dI_p\eta_5\right)\right\}^+, b_2\right\}. \tag{16}$$

Remark 5. From Proposition 2, we see that control functions are define concurrently in relation to the circulating terms associated with healthy and infected $\mathrm{CD4}^+\mathrm{T}$ cells as well as virions and their adjoint variables.

The last part of this section deals with the existence of an optimal control pair for dual delay HIV-pathogen model.

3.3. Existence of optimal pair-dual controls

A critical view of Equations (10) and (11) shows that certain parameter restrictions are imposed on our system in order that the model is realistic. For instant, if $T_{\max}$ is the maximum limit of uninfected $\mathrm{CD4}^+\mathrm{T}$ cells such that if death rate at $T_{\max}$ is to be greater than the source supply rate, then an assumption of the form

$$\alpha_1 T_{\max} > b_p \tag{17}$$

holds.

The implication is that we must have a steady state population size that should be below $T_{\max}$ such that the differential invasion of $CD4^+T$ cells by infectious virions can be adequately accommodated. Moreso, population growth will slow if population size ever gets near $T_{\max}$ [31].

Furthermore, the establishment of existence of an optimal control and uniqueness proof of the optimality system requires upperbounds. Therefore, for $T_u(t) < T_{\max}$, the upperbounds on the solutions of the actively infectious state components are determined as follows:

$$\frac{d\hat{I}_\nu}{dt} = \beta e^{-\alpha_2\omega}\hat{V}RT_{(u)\max} \qquad \hat{I}_\nu(t_0) = I_{(\nu)0},$$

$$\frac{d\hat{I}_p}{dt} = \delta e^{-\alpha_3\omega}\hat{P}RT_{(u)\max} \qquad \hat{I}_p(t_0) = I_{(p)0},$$

where $\beta, \delta > 0$; $\alpha_{i=2,3} > 0$ and $\omega \geq 0$

$$\frac{d\hat{V}}{dt} = k\hat{I}_\nu \qquad \hat{V}(t_0) = V_0$$

$$\frac{d\hat{P}}{dt} = k\hat{I}_p \qquad \hat{P}(t_0) = P_0.$$

Or

$$\begin{pmatrix} \hat{I}_\nu \\ \hat{I}_p \\ \hat{V} \\ \hat{P} \end{pmatrix} = \begin{pmatrix} 0 & 0 & \beta e^{-(\alpha_2\omega)}RT_{(u)\max} & 0 \\ 0 & 0 & 0 & \delta e^{-(\alpha_3\omega)}RT_{(u)\max} \\ k & 0 & 0 & 0 \\ 0 & d & 0 & 0 \end{pmatrix} \begin{pmatrix} \hat{I}_\nu \\ \hat{I}_p \\ \hat{V} \\ \hat{P} \end{pmatrix}.$$

It becomes obvious that we have a finite time linear system with bounded coefficients and thus, the supersolutions $\hat{I}_\nu, \hat{I}_p, \hat{V}, \hat{P}$ are uniformly bounded. Therefore, we establish the existence of an optimal control for our dual-pair problem taken queue from models {([23], Theorem 2, pg. 10-11), ([30], Theorem 4.1, pg. 68-69)}, respectively.

Theorem 2. *Given Proposition* 1 *and assumption* (17), *there exists an optimal control pair* $(h_1^*, h_2^*) \in A$ *that maximizes the objective functional* $Q(h_1, h_2)$ *such that*

$$\max_{(h_1, h_2) \in A} Q(h_1, h_2) = Q(h_1^*, h_2^*). \tag{18}$$

Proof. If we recall the results of [23, 30], then we have to show that the following conditions are satisfied:

(i) The class of all control sets $h_i(t)$, $i = 1, 2$ are Lebesgue-integrable functions on $[t_0, t_f]$ with values in the admissible control sets and such that the corresponding state variables are satisfied and not empty.

(ii) The admissible control set A, is convex and closed.

(iii) The right-hand side (RHS) of the state system is continuous and bounded by a linear function of $h_{i=1,2}$ with coefficients depending on Proposition 1 and on the control variables.

(iv) The integrand of the objective functional is concave on A.

(v) There exist constants $k_1, k_2 > 0$ and $\gamma > 1$ such that the integrand $L(T_u, W, Z, h_1, h_2)$ of the objective functional satisfies

$$L(T_u, W, Z, h_1, h_2) \leq k_2 - k_1(|h_1|^2 + |h_2|^2)^{\gamma/2}.$$

Now invoking result of ([31], Theorem 9.2.1. pg. 182) we establish the existence of solution for Equation (11) with bounded coefficients and which satisfies condition (i). We note that the solutions are bounded. Then, by definition, the control set is closed and convex and thus, condition (ii) is satisfied. Since, our state system is bilinear in $h_{i=1,2}$ the RHS of Equation (11) satisfies condition (iii) and are a priori bound. Furthermore, the integrand in the functional $T_u(t) + W(t) + Z(t) - [B_1(h_1^*$

$(t))^2 + B_2(h_2^*(t))^2]$ is concave on the admissible control set. Finally, we complete the existence of an optimal control by stating that

$$\{T_u(t) + W(t) + Z(t) - [B_1(h_1^*(t))^2 + B_2(h_2^*(t))^2]\} \leq k_2 - k_1(|h_1|^2 + |h_2|^2),$$

where k_2 depends on the upper bound on T_u, W, Z and $k_1 > 0$, since $\{B_1, B_2\} > 0$. Hence, this completes the proof. □

4. Derivation of Optimality System and Uniqueness

We devote this section to the derivation of our optimality system followed by the validity of uniqueness of the optimality system.

4.1. Optimality system

Optimality system is a vital component of the optimal control problem since it observes the biological behaviour of the system upon the application of chemotherapy. The growth rate or clearance rates of state variables are determined by the optimality system.

Definition 4.1. The optimality system consists of the state system couple with the adjoint system with the initial conditions and transversality conditions together with the derived optimal control pair.

Now, the adjoint system is given by

$$\frac{d\eta_i}{dt} = \frac{\partial M}{\partial \Lambda_i},$$

where Λ_i, $i = 1, \ldots, 8$ are the state variables. The final components in the optimality system are the set of transversality conditions, which reduces and terminate the conditions on the adjoint variables. Then, for a maximization problem of the type

$$\max_{(h_1, h_2) \in A} Q(h_1, h_2) = F(T_u(t)) + \int_{t_0}^{t_f} f_0(T_u, h_1, h_2) d\upsilon,$$

subject to the system $dT_u/dt = f(t, T_u, h_1, h_2)$ and such that $T_u(t)$ belong to some target set $g(T_u(t))$, we have the following transversality conditions on the adjoint variables:

$$\eta_i(t) = \overline{\nu}F(T_u(t)) + \sum_{i=1}^{n} c_i g_i(T(t)), \tag{19}$$

where the function F is the terminal cost. Of note, our problem has no terminal cost, so $F(T_u(t)) = 0$. Also, we do not have target set here and so we have desired end result with free-state variables. Here, the summation term is zero too. This is to say that the transversality condition for the adjoint variables is

$$\eta_i(t_f) = 0,\ i = 1, \ldots, 8. \tag{20}$$

Therefore, applying Definition 4.1, and differentiating Equation (12) for η_i followed by the substitution of Equations (15) and (16) into Equation (11), we obtain the following optimality system:

$$\dot{T}_u = b_p + \sigma V + \lambda P - \alpha_1 T_u - (1 + h_1^*)[\beta V + \delta P]RT_u,$$

$$\dot{I}_\nu = (1 - h_1^*)\beta e^{-\alpha_2 \omega} VRT_u - (\alpha_2 + k)I_\nu - q_1 I_\nu Z,$$

$$\dot{I}_p = (1 - h_1^*)\delta e^{-\alpha_3 \omega} PRT_u - (\alpha_3 + d)I_p - q_2 I_p Z,$$

$$\dot{V} = (1 - h_2^*)kI_\nu - (\alpha_4 + \sigma)V,$$

$$\dot{P} = (1 - h_2^*)dI_p - (\alpha_5 + \lambda)P,$$

$$\dot{W} = cI_\nu I_p T_u W - \rho I_\nu I_p W - \alpha_6 W,$$

$$\dot{Z} = \rho I_\nu I_p W - \alpha_7 Z,$$

$$\dot{R} = R_0 - h_1^* R,$$

$$\dot{\eta}_1 = -1\{\eta_1[-\alpha_1 - (1-h_1^*(t))(\beta V + \delta P)R] + \eta_2[(1-h_1^*(t))\beta e^{-\alpha_2 \omega} VR] + \eta_3[(1-h_1^*(t))\delta e^{-\alpha_3 \omega} PR]\},$$

$$\dot{\eta}_2 = -1\{\eta_2[-(\alpha_2 + k) - q_1 Z] + \eta_4(1-h_1^*(t))k + \eta_6(cI_p T_u W - \rho I_p W) + \eta_7(\rho I_p W)\},$$

$$\dot{\eta}_3 = -1\{\eta_3[-(\alpha_3 + d) - q_2 Z] + \eta_5(1-h_2^*(t))d + \eta_6(cI_\nu T_u W - \rho I_\nu W) + \eta_7(\rho I_\nu W)\},$$

$$\dot{\eta}_4 = -1\{[\eta_1(\sigma - (1-h_1^*(t))\beta R T_u] + \eta_2[(1-h_1^*(t))\beta e^{-\alpha_2 \omega} R T_u] + \eta_4(\alpha_4 + \sigma)\},$$

$$\dot{\eta}_5 = -1\{[\eta_1(\lambda - (1-h_1^*(t))\delta R T_u] + \eta_3[(1-h_1^*(t))\delta e^{-\alpha_3 \omega} R T_u] + \eta_5(\alpha_5 + \lambda)\},$$

$$\dot{\eta}_6 = -1\{\eta_6(cI_\nu I_p T_u - \rho I_\nu I_p) - \eta_6 \alpha_6\},$$

$$\dot{\eta}_7 = -1\{\eta_2(-q_1 I_\nu) + \eta_3(-q_2 I_p) - \eta_7 \alpha_7\},$$

$$\dot{\eta}_8 = -1\Big\{\eta_1[(1-h_1^*(t))(\beta V + \delta P)T_u] + \eta_2[(1-h_1^*(t))\beta e^{-\alpha_2 \omega} V T_u] + \eta_3[(1-h_1^*(t))\delta e^{-\alpha_3 \omega} P T_u] - \eta_8 q_1\Big\}, \qquad (21)$$

where $\eta_i(t_f) = 0$, $i = 1, \ldots, 8$ and

$$h_1^*(t) = \min$$

$$\left\{\max\left\{a_1, \frac{1}{2B_1}\left((\beta V + \delta P)RT_u\eta_1 - \beta e^{\alpha_2\omega}VRT_u\eta_2 - \delta e^{-\alpha_3\omega}PRT_u\eta_3\right)\right\}^+, b_1\right\},$$

$$h_2^*(t) = \min\left\{\max\left\{a_2, \frac{1}{2B_2}\left(kI_\nu\eta_4 - dI_p\eta_5\right)\right\}^+, b_2\right\}.$$

4.2. Uniqueness of optimality system

To complete this section, we necessary have to define and prove the uniqueness of the optimality system. From the existence of optimal system, since $T_u < T_{(u)\max}$, we see that the state system have finite upperbounds. These upperbounds are needed for the uniqueness proof. The lemma below followed by a uniqueness theorem yields the desired result.

Lemma 4.1. *The function* $h^*(s) = (\min(\max(s, a, b)))$ *is Lipschitz continuous in s, where* $a < b$ *are some fixed positive constants.*

Theorem 3. *Given* t_f *as sufficiently small time interval, then bonded solutions of the optimality system re-unique.*

Proof. Let that $(T_u, I_\nu, I_p, V, P, W, Z, \eta_1, \eta_2, \eta_3, \eta_4, \eta_5, \eta_6, \eta_7, \eta_8)$ and

$(\overline{T}_u, \overline{I}_\nu, \overline{I}_p, \overline{V}, \overline{P}, \overline{W}, \overline{Z}, \overline{\eta}_1, \overline{\eta}_2, \overline{\eta}_3, \overline{\eta}_4, \overline{\eta}_5, \overline{\eta}_6, \overline{\eta}_7, \overline{\eta}_8)$ be two different solutions of our optimality system (21). Suppose

$$T_u = g^{\eta t}e,\ I_\nu = g^{\eta t}f,\ I_p = g^{\eta t}\hat{c},\ V = g^{\eta t}i,\ P = g^{\eta t}j,\ W = g^{\eta t}\hat{k},\ Z = g^{\eta t}l,$$

$$R = g^{\eta t}n,$$

and

$$\eta_1 = g^{\eta t}m,\ \eta_2 = g^{\eta t}p,\ \eta_3 = g^{\eta t}q,\ \eta_4 = g^{\eta t}r,\ \eta_5 = g^{\eta t}s,\ \eta_6 = g^{\eta t}t,$$

$$\eta_7 = g^{\eta t}u,\ \eta_8 = g^{\eta t}x,$$

$$\overline{T}_u = g^{\eta t}\bar{e},\ \bar{I}_\nu = g^{\eta t}\bar{f},\ \bar{I}_p = g^{\eta t}\hat{\bar{c}},\ \overline{V} = g^{\eta t}\bar{i},\ \overline{P} = g^{\eta t}\bar{j},\ \overline{W} = g^{\eta t}\hat{\bar{k}},\ \overline{Z} = g^{\eta t}\bar{l},$$

$$\overline{R} = g^{\eta t}\overline{n},$$

$$\overline{\eta}_1 = g^{\eta t}\overline{m},\ \overline{\eta}_2 = g^{\eta t}\overline{p},\ \overline{\eta}_3 = g^{\eta t}\overline{q},\ \overline{\eta}_4 = g^{\eta t}\overline{r},\ \overline{\eta}_5 = g^{\eta t}\overline{s},\ \overline{\eta}_6 = g^{\eta t}\overline{t},\ \overline{\eta}_7$$

$$= g^{\eta t}\overline{u},\ \overline{\eta}_8 = g^{\eta t}\overline{x},$$

where $\eta > 0$ is to be chosen.

From Equation (15) and (16), if we substitute the above variables into the two different solutions, then the optimal pair solution become:

$$h_1^*(t) = \min\left\{\max\left\{a_1, \frac{1}{2B_1}\left((\beta i + \delta j)nem - \beta e^{\alpha_2\omega}i(nep) - \delta e^{-\alpha_3\omega}j(neq)\right)\right\}^+, b_1\right\};$$

$$h_2^*(t) = \min\left\{\max\left\{a_2, \frac{1}{2B_2}\left(k(rf) - d(cs)\right)\right\}^+, b_2\right\},$$

and

$$\overline{h}_1^*(t) = \min\left\{\max\left\{a_1, \frac{1}{2B_1}\left((\beta\bar{i} + \delta\bar{j})\overline{nem} - \beta e^{\alpha_2\omega}\bar{i}(\overline{nep}) - \delta e^{-\alpha_3\omega}\bar{j}(\overline{neq})\right)\right\}^+, b_1\right\};$$

$$\overline{h}_2^*(t) = \min\left\{\max\left\{a_2, \frac{1}{2B_2}\left(k(\bar{r}\bar{f}) - d(\overline{cs})\right)\right\}^+, b_2\right\}.$$

Now, we substitute $T_u = g^{\eta t}e$, and all corresponding terms into first ODEs of Equation (21) and differentiate to get

$$e' + \eta e = b_p + \sigma g^{\eta t} i + \lambda g^{\eta t} j - \alpha_1 g^{\eta t} e - (1 - h_1^*(t))[\beta g^{\eta t} i + \delta g^{\eta t} j] g^{\eta t}(ne),$$

$$f' + \eta f = (1 - h_1^*(t))\beta e^{-\alpha_2 \omega} g^{\eta t} i(ne) - (\alpha_2 + k) g^{\eta t} f - q_1 g^{\eta t}(lf),$$

$$c' + \eta c = (1 - h_1^*(t))\delta e^{-\alpha_3 \omega} g^{\eta t} j(ne) - (\alpha_3 + k) g^{\eta t} c - q_2 g^{\eta t}(lc),$$

$$i' + \eta i = (1 - h_2^*(t))\hat{k} g^{\eta t} f - (\alpha_4 + \sigma) g^{\eta t} i,$$

$$j' + \eta j = (1 - h_2^*(t)) d g^{\eta t} \hat{c} - (\alpha_5 + \lambda) g^{\eta t} j,$$

$$\hat{k}' + \eta \hat{k} = c g^{\eta t}(f\hat{c}e\hat{k}) - \rho g^{\eta t}(f\hat{c}\hat{k}) - \alpha_6 g^{\eta t} \hat{k},$$

$$l' + \eta l = \rho g^{\eta t}(f\hat{c}\hat{k}) - \alpha_7 g^{\eta t} l,$$

$$n' + \eta n = R_0 - h_1^* g^{\eta t} n,$$

$$\begin{aligned} m' + \eta m = -1\{ & g^{\eta t} m[-\alpha_1 - (1 - h_1^*(t)) g^{\eta t}(\beta i + \delta j) g^{\eta t} n] + g^{\eta t} p[(1 - h_1^*(t)) \\ & \beta e^{-\alpha_2 \omega} g^{\eta t}(ni)] \\ & + g^{\eta t} \hat{q}[(1 - h_1^*(t))\delta e^{-\alpha_3 \omega} g^{\eta t} n\hat{q}]\}, \end{aligned}$$

$$\begin{aligned} p' + \eta p = -1\{ & g^{\eta t} p[-(\alpha_2 + k) - q_2 g^{\eta t} l] + g^{\eta t} r[(1 - h_2^*(t))\hat{k}] \\ & + g^{\eta t} t[c g^{\eta t}(\hat{c}e\hat{k}) - \rho g^{\eta t}(\hat{c}\hat{k})] + g^{\eta t} u[\rho g^{\eta t}(\hat{c}\hat{k})]\}, \end{aligned} \tag{22}$$

$$\begin{aligned} \hat{q}' + \eta \hat{q} = -1\{ & g^{\eta t} \hat{q}[(\alpha_3 + d) - q_2 g^{\eta t} l] + g^{\eta t} s(1 - h_1^*(t))\hat{d}] + g^{\eta t} t[c g^{\eta t}(fe\hat{k}) \\ & - \rho g^{\eta t}(\hat{c}\hat{k})] + g^{\eta t} u[\rho g^{\eta t}(f\hat{k})]\}, \end{aligned}$$

$$\begin{aligned} r' + \eta r = -1\{ & g^{\eta t} m[(\sigma - (1 - h_1^*(t))\beta g^{\eta t}(ne)] + g^{\eta t} p[(1 - h_1^*(t))\beta e^{-\alpha_2 \omega} g^{\eta t}(ne)] \\ & + g^{\eta t} r(\alpha_4 + \sigma)\}, \end{aligned}$$

$$s' + \eta s = -1\{g^{\eta t} m[(\lambda - (1 - h_1^*(t))\delta g^{\eta t}(ne)] + g^{\eta t}\hat{q}[(1 - h_1^*(t))\delta e^{-\alpha_3 \omega} g^{\eta t}(ne)] + g^{\eta t} s(\alpha_5 + \lambda)\},$$

$$t' + \eta t = -1\{g^{\eta t} t[(cg^{\eta t}(\hat{c}fe) - \rho g^{\eta t}(\hat{c}f)] - g^{\eta t} t\alpha_6\},$$

$$u' + \eta u = -1\{g^{\eta t} p[(- g^{\eta t} q_1 f)] + g^{\eta t}\hat{q}(- g^{\eta t} q_2 \hat{c}) - g^{\eta t} u\alpha_7\},$$

$$x' + \eta x = -1\{g^{\eta t} m[(1 - h_1^*(t))g^{\eta t}(\beta i + \delta j)g^{\eta t} e] + g^{\eta t} p[(1 - h_1^*(t))\beta e^{-\alpha_2 \omega} g^{\eta t}(ei)] + g^{\eta t}\hat{q}[(1 - h_1^*(t))\delta e^{-\alpha_3 \omega} g^{\eta t}(ej)] - g^{\eta t} x q_1\}.$$

Next, we subtract the equations $\overline{T}_u$ from T_u, $\overline{I}_\nu$ from I_ν, …, $\overline{R}$ from R, $\overline{\eta}_1$ from η_1, …, and $\overline{\eta}_8$ from η_8 and then multiply the result obtained by appropriate difference of functions and integrates from t_0 to t_f. Finally, we sum the sixteen integral equations and using estimation approach, to derive the uniqueness of optimality system. By Lemma 4.1, we have

$$\left|h_1^*(t) - \overline{h}_1^*\right| \le \frac{1}{2B_1}\left|(me - \overline{m}\,\overline{e}) + (\hat{k}t - \bar{\hat{k}}\bar{t}) + (ul - \overline{u}\,\overline{l})\right|,$$

and

$$\left|h_2^*(t) - \overline{h}_2^*\right| \le \frac{1}{2B_2}\left|(pf + q\nu + ri + sj + nx) - (\overline{p}\overline{f} + \overline{q}\,\overline{\nu} + \overline{r}\bar{i} + \overline{s}\bar{j} + \overline{n}\,\overline{x})\right|.$$

For the first case of $T_u(t)$, we perform the estimate (using $h_1^* - \overline{h}_1^*$ estimate), i.e.,

$$\frac{1}{2}(e - \bar{e})^2(t_f) + \eta_1 \int_{t_0}^{t_f} (e - \bar{e})^2 dt$$

$$\le \int_{t_0}^{t_f} \alpha_1 |e - \bar{e}| dt + [\int_{t}^{t_f} \left|h_1^* e - \overline{h}_1^* e\right| |e - \bar{e}| dt] + g^{\eta t} \int_{t_0}^{t_f} \left|(i + j) - (\bar{i} + \bar{j})\right| |e - \bar{e}| dt$$

$$\leq \psi_1 \int_{t_0}^{t_f} [|e-\bar{e}|^2 + |m-\overline{m}|^2 + \left|\hat{k}-\bar{\hat{k}}\right|^2 + |t-\bar{t}|^2 + \left|l-\bar{l}\right|^2 + |u-\overline{u}|^2]dt$$

$$+ \psi_2 g^{\eta t_f} \int_{t_0}^{t_f} [|e-\bar{e}|^2 + |m-\overline{m}|^2 + \left|\hat{k}-\bar{\hat{k}}\right|^2 + |t-\bar{t}|^2 + \left|l-\bar{l}\right|^2 + |u-\overline{u}|^2]dt,$$

where ψ_1 and ψ_2 are constants determined upon the coefficients and bounds on state and adjoints variables. Combining the sixteen estimates, we obtain as follows:

$$\frac{1}{2}(e-\bar{e})^2(t_f) + \frac{1}{2}(f-\bar{f})^2(t_f) + \ldots + \frac{1}{2}(n-\overline{n})^2(t_f) + \frac{1}{2}(m-\overline{m})^2(t_0)$$

$$+ \frac{1}{2}(p-\overline{p})^2(t_0) + \ldots + \frac{1}{2}(x-\overline{x})^2(t_0)$$

$$+ \eta \int_{t_0}^{t_f} \left[(e-\bar{e})^2 + (f-\bar{f})^2 + \ldots + (n-\overline{n})^2 + (m-\overline{m})^2 + (p-\overline{p})^2 + \ldots + (x-\overline{x})^2\right]dt,$$

$$\leq (\psi_1 + \psi_2 e^{3\eta t_f}) \int_{t_0}^{t_f} \left[(e-\bar{e})^2 + (f-\bar{f})^2 + \ldots + (n-\overline{n})^2 + (m-\overline{m})^2 + (p-\overline{p})^2\right.$$

$$\left. + \ldots + (x-\overline{x})^2\right]dt,$$

holds for all $t_0 = 0$. Therefore, from the result above, we inferred that

$$(\eta - \tilde{\psi}; + \tilde{\psi}_2 e^{3\eta t_f}) \int_{t_0}^{t_f} \left[(e-\bar{e})^2 + (f-\bar{f})^2 + \ldots + (n-\overline{n})^2 + (m-\overline{m})^2 + (p-\overline{p})^2\right.$$

$$\left. + \ldots + (x-\overline{x})^2\right]dt \leq 0,$$

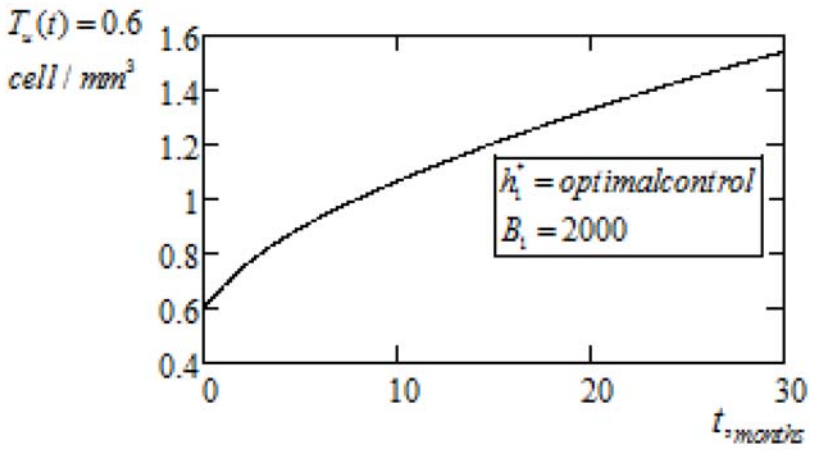
where $\tilde{\psi}_1 + \tilde{\psi}_2$ are functions define by the coefficients and bounds on $e, f, \ldots, x$. For simplicity, we choose η such that $\eta > \tilde{\psi}_1 + \tilde{\psi}_2$ and $t_f < \frac{1}{3\eta} \ln(\frac{\eta - \psi_1}{\psi_2})$, then $e = \bar{e}$, $f = \bar{f}$, $\ldots$, $x = \bar{x}$. Hence, for sufficiently small time, the solution is unique.

For related results on uniqueness of optimality system, readers are advised to consult [25, 32, 33]. The mathematical implication of uniqueness for small time interval is a two-point boundary value problem due to its opposite time orientation and state equations, which have initial and final time conditions. The optimal controls h_1^* and h_2^* are characterized by the unique solution of the optimality system. Furthermore, from epidemiological point of view of Theorem 3, if $\eta > B_1 + B_2$ and $t_f < \frac{1}{3\eta}\ln(\frac{\eta - B_1}{B_2})$ such that $B_2 \lhd 0$, then infection is below detectable limit of clinical assay. Ironically, if $t_f > \frac{1}{3\eta}\ln(\frac{\eta - B_1}{B_2})$ such that $\eta < B_1 + B_2$, then prevalence of infection is bound to occur and could be globally asymptomatically stable.

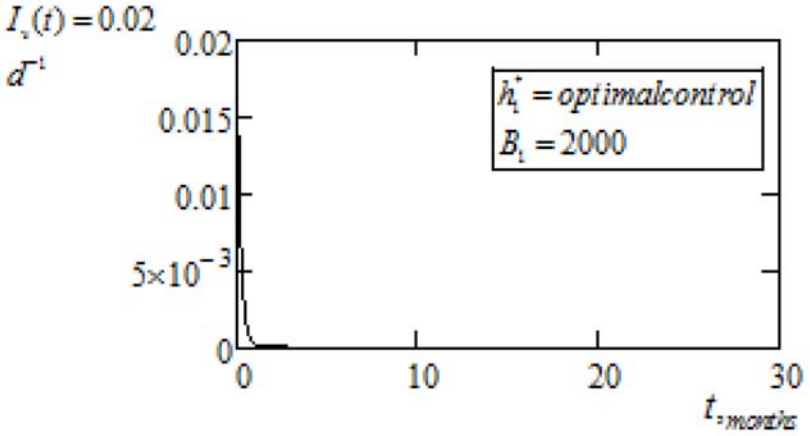
5. Numerical Computation of Optimality System

In this section, we numerically validate our derived optimality system. Here, the optimality system (21) and its control functions (10), (15) and (16) are solved using initial conditions of Tables 1 and 2 facilitated using Runge-Kutta of order 4 in a Mathcad surrounding. Of note, the simulations of Equations (10), (15), and (16) provide us with option of ascertaining the cost of treatment.

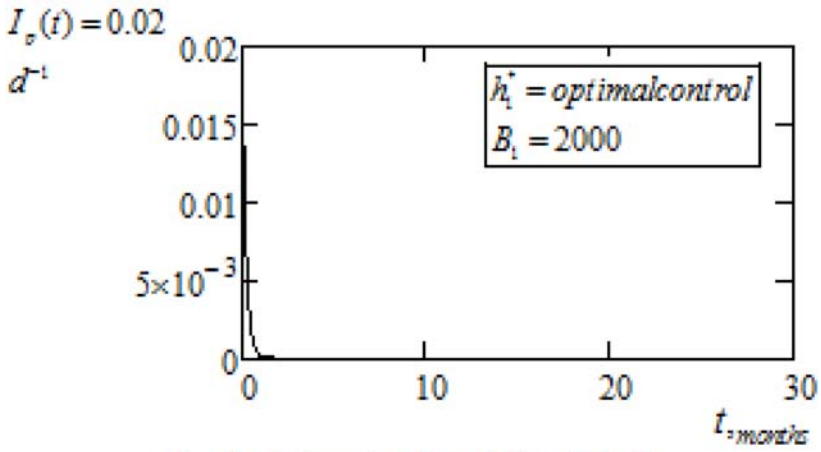
With optimal weight factors (B_1, B_2) and bounds (a_i, b_i), $i = 1, 2$ on controls, several treatment schedules can be generated with varying time interval, which can be regulated to achieve convergence. If we let $a_1 = 0$, $b_1 = 0.2$, $a_2 = 0.2$, $b_2 = 0.9$, which balance the optimal weight factors $B_1 = 2000$, $B_2 = 25$, then from [7], we illustrate the application of dual-pair treatment on infectious dual delay HIV-pathogen for as depicted by Figure 2(a)-(h) below:



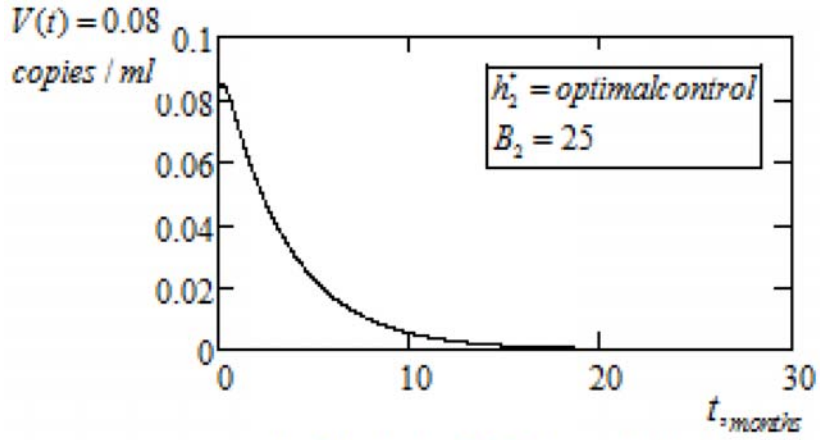
a) Simulation of uninfected CD4+ T cells with $b_p = 0.05 mm^3 d^{-1}$



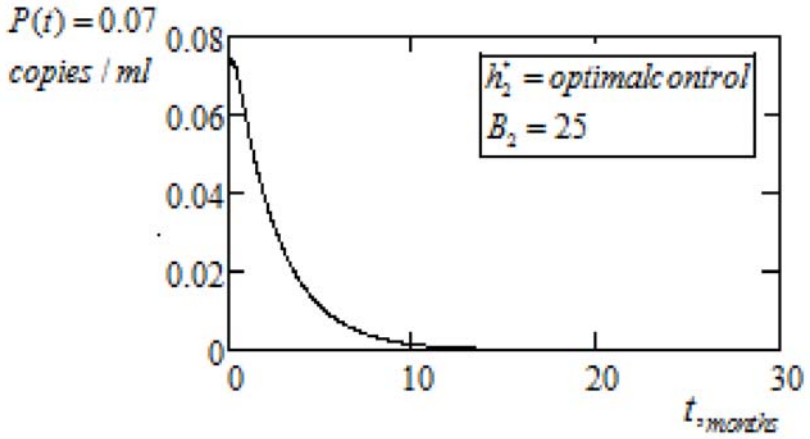
b) Simulation of HI-virus infected T cells with $\sigma = 0.2 mm^3$



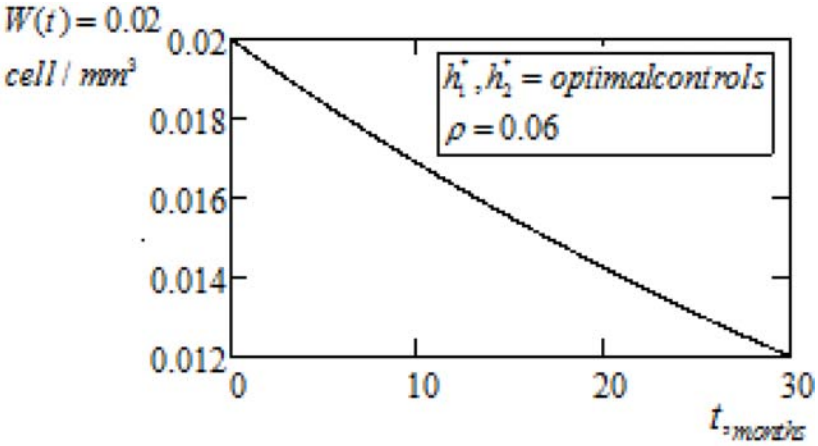
c) Simulation of pathogen infected Tcells with $\lambda = 0.04 mm^3$



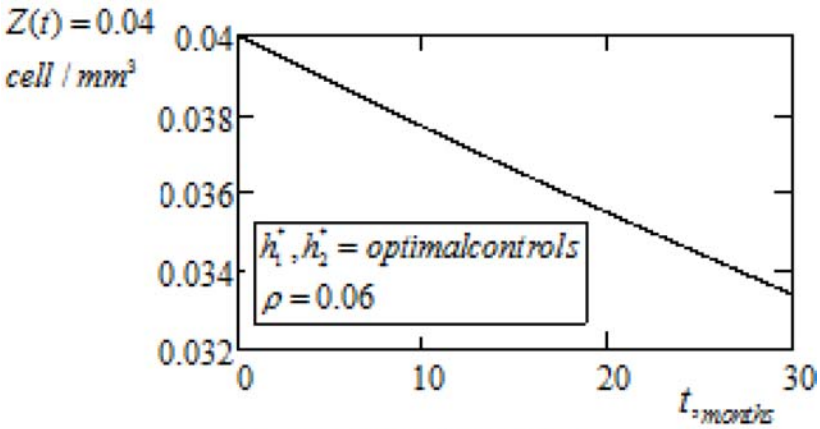
d) Simulation of infectious viral load with $\beta = 0.5 mm^3 d^{-1}$



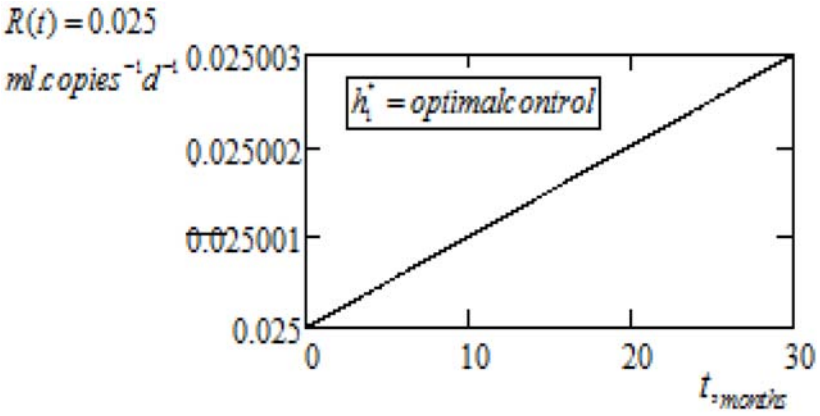
e) Simulation of infectious pathogen with $\delta = 0.5 mm^3 d^{-1}$



f) Simulation of CTLp with $c = 0.005 mm^3 cell^{-2} d^{-1}$



g) Simulation of CTLe with $q_1, q_2 = 0.05 mm^3 d^{-1}$



h) Simulation of intrinsic virulence with $R_0 = 10^{-7} copies ml d^{-1}$

Figure 2(a)-(h). Graphical simulations of pair-dual treatment functions form dual delayed HIV-pathogen infections with h_1^* and h_2^*.

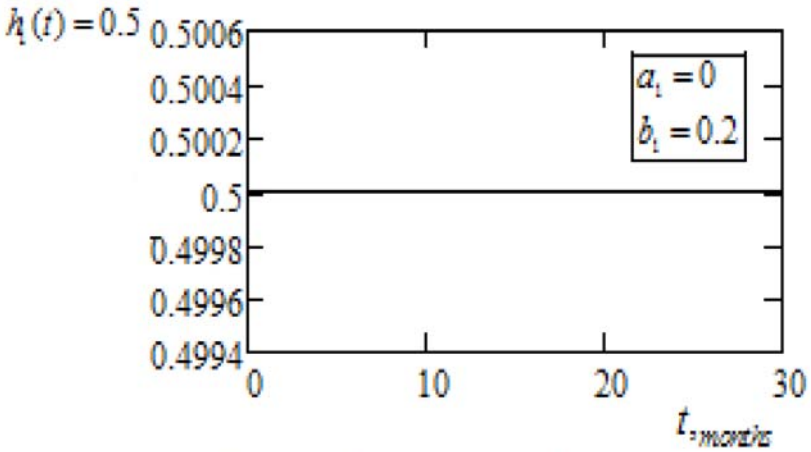
From Figure 2(a)-(c), we studied the biological changes of both healthy and virions infected $CD4^+T$ cells, subjected to $h_1^*(t)$ treatment function. In Figure 2(a), we investigate the level of healthy $CD4^+T$ cells concentration following the introduction of dual-pair treatment functions and time delay lag on dual delay HIV-pathogen infections. The graph shows a smooth convex-like rapid increase for healthy $CD4^+T$ cells with $0.6 \le T_u(t) \le 1.541\text{cell/mm}^3$ time interval $t_f \le 30$ months. In Figure 2(b) & (c), we depict the rapid elimination of viral load infected $CD4^+T$ cells and pathogen infected $CD4^+T$ cells following the commencement of highly toxic multiple chemotherapies in the presence of boosted precursors and effectors of CTLs (= CTLp and CTLe). Both infected T-cells $(I_v(t),\ I_p(t))$ exhibits positive response to treatment functions with $I_v(t) \le 6.911 \times 10^{-8}$ while $I_p(t) \le 1.562 \times 10^{-9}$ decline at early $1^{\text{st}} - 3^{\text{rd}}$ months of adherent to treatment conditions.

The biological behaviours of infectious virions (viral load and pathogen) are investigated with $h_2^*(t)$ as treatment function. Figure 2(d) depicts a concave-like initial decline of infectious viral load and gradually approaches zero elimination with value $V(t) \le 1.721 \times 10^{-5}$ copies/ml at $16 \le t_f \le 18$ months. Figure 2(e) exhibit similar structural and biological behaviour for infectious pathogen under similar onset toxic treatment conditions with elimination value at $P(t) \le 4.279 \times 10^{-7}$ copies/ml for $11 \le t_f \le 13$ months.

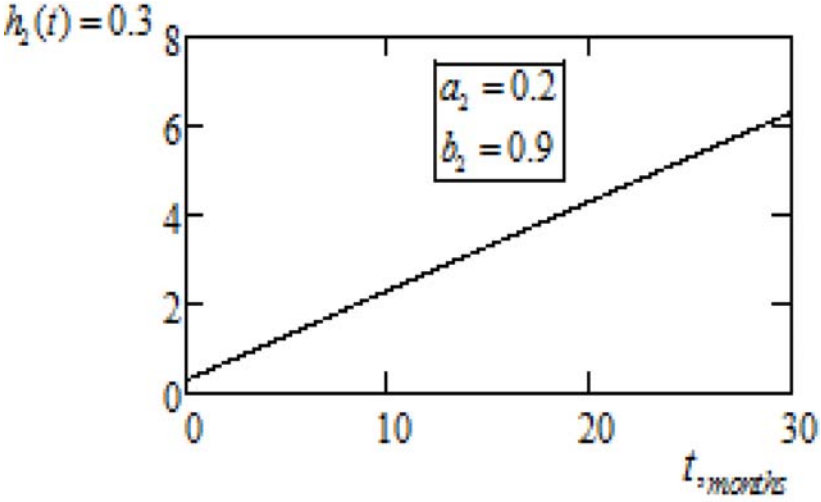
The crucial role of subdivided CTLs (CTLp and CTLe) are represented by Figure 2(f) & (g), respectively. Figure 2(f) exhibits the biological changes of the immune memory production T-helper, which is dependent on the rate of concentration of virions present at a given time interval. The precursors of CTLp shows linear decline after $t_f \le 30$

months. This defines its active role in the early suppression and eventual elimination of both infected $CD4^+T$ cells and virions with value $W(t) \leq 0.012\text{cell/mm}^3$. On a similar note, Figure 2(g) represents the active role of effectors of CTLe in clearing both infected $CD4^+T$ cells and infectious virions with value declining to $Z(t) \leq 0.033\text{cell/mm}^3$. The aggressiveness of infectious virions is investigated as presented by Figure 2(h). Here, following the cogent application of dual-pair treatment conditions, intrinsic virulence index indicates insignificant increase with $R(t) \leq 3 \times 10^{-6}\text{ml.copies}^{-1}\text{d}^{-1}$ after $t_f \leq 30$ months. Other graphical representations omitted for brevity are the corresponding adjoint variables graphs to Figure 2(a)-(h).

Furthermore, we ascertain the quantifiability of each optimal control pair of chemotherapies by simulating as in Figure 3(a)-(b), the chemotherapy required for treatment. Accounting for drug severities, treatment functions were placed under optimal weight factors $(B_i)_{i=1,2}$ with defined lower and upper bounds $(a_i, b_i)_{i=1,2}$, respectively.



a) Simulation of optimal control function on RTI for $I_u(t), I_v(t), I_p(t)$



b) Simulation of optimal control function on PIs for $V(t), P(t)$

Figure 3(a)-(b). Graphical simulations of optimal control pair with $B_1 = 2000$, $B_2 = 25$.

Of note, Figure 3(a)-(b) shows intriguing smooth linear dual-pair-like characteristics typical of optimal dynamics. The amount of RTI drug is defined by $0.5 \le h_1^*(t) \le 0.5001$, which is significantly small. On the other hand, more of PIs is required to combat virions dual HIV-pathogen with value at $0.3 \le h_2^*(t) \le 6.3$ for all $t_f \le 30$ months, respectively.

Finally, we investigate our objective functional, which clearly define the optimal control pair in relation to healthy and infected organs as well as chemotherapies applied. This succinct explanation is represented by Figure 4 below:

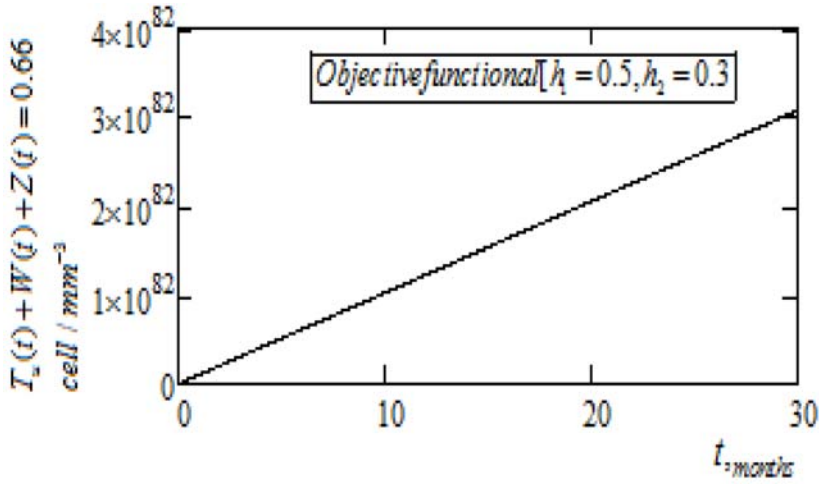


Figure 4. Simulation of objective functional for pair-dual treatment with $B_1 = 2000$, $B_2 = 25$.

The smooth linear inclination depicts the overall commercial value of dual-pair optimal control required to maximize healthy $CD4^+T$ cells and sustain positively, the dual immune responses (CTLp and CTLe), respectively. We see that for treatment duration of $t_f \le 30$ months, the overall chemotherapy cost is at $Q[h_1, h_2] \le 3.073 \times 10^{82}$.

6. Discussion

In line with clinical ethics of scientific investigation for infectious diseases prevention approach as was carefully highlighted in the literature of this paper, the present study mathematically seek to address the complexity surrounding the emergence of dual HIV-pathogen infectivity. Using ODEs, the study had formulated as an extended version of models [2, 21], an articulated 8-dimensional nonlinear delay-differential dual HIV-pathogen dynamic model. Not only did the present model incorporated time delay lag (intracellular delay) as its novelty but in addition to dual chemotherapy treatment, the dual combination of precursors and effectors of CTLs as pair state components and as pair treatment functions informed the uniqueness of this model. Moreso, the explicit behavioural changes of viral load infected $CD4^{+}T$ cells and pathogen infected T-cells were clinically uncovered and as well, allows the investigation of the extent to which virions aggressiveness could be managed.

To achieve this desired goal, the model was presented as an optimal control problem with classical Pontryagin's maximum principle adopted for its analysis. This led to the establishment of the positivity of state variables, and conducted stability analysis of the state variables. We also investigated the existence and uniqueness of optimal control strategies and finally, derived the model optimality system. The model equally showed that using linearization method, the matrix of the state components all have negative real part and hence, the equilibrium state were locally asymptotically stable. A result that is consistent with the experimental findings of models [3, 4].

Validation of the derived model was numerically demonstrated using Runge-Kutta of order 4, in a Mathcad surrounding. Therefore, we had predominantly sought to the best possible accuracy, the solution for dual-pair treatment of dual delayed HIV-pathogen infections. The results from

numerical simulations clearly indicated tremendous maximization of healthy $CD4^+T$ cells under current articulated treatment conditions. Of note, Figure 2(a) showed increase in $T_u(t)$ from $0.6 \rightarrow 1.541 \text{cell/mm}^3$, a value far more positive when compared to that of pilot our model [2], where $0.25 \leq T_u(t) \leq 0.558 \text{mm}^3$ for all $t_f \leq 30$ months. It is also note that the seeming smooth parabolic inclination of healthy $CD4^+T$ cells of the present model indicated far reaching outstanding model when compared to the undulating and unstable outcome of healthy T-cells achieved by model [21].

From Figure 2(b) & (c), the time taken for the elimination of both viral load infected cells and pathogen infected cells were far smaller compared to those of model [2]. Also, both virions infected cells were eliminated at much earlier time intervals, i.e., $1 \leq t_f \leq 3$ months for $I_v(t)$ and $1 \leq t_f \leq 2$ months for $I_p(t)$ as against time intervals of $1 \leq t_f \leq 24$ months for $I_v(t)$ and $1 \leq t_f \leq 11$ months for $I_p(t)$ of model [2]. In a similar trend, the eradication of infectious viral load and pathogen, were faster (see Figures 2(d) & (e) with $V(t)$ at $t_f \leq 18$ months and $P(t)$ at $t_f \leq 13$ months when compared to time taken by models [2, 23, 26]. On contradiction, from model [21], viral load was only suppressed after third month but was never eliminated as was the case in this present study.

We as well presented in this study, an articulated and explicit role of both precursors and effectors of CTLs as seen in Figure 2(f) & (g), respectively. Both figures indicated sharp linear decline, which are consistent when compared to those of models [21, 35]. Obviously, these decreases are directly correlated to the coherent dual-pair treatment efficacy. Moreso, these figures depicts is the dynamic representation of the quantified aggressiveness of both virions under novel treatment conditions, a situation that is clearly defined only by this present

investigation. Thus, we see from Figure 2(h), insignificantly quasi-homeostatic virions aggressiveness as a vindicatory effort of introduced dual-pair treatment functions. Of interest, the distinct nature of this study is seen with the numerical representations of included intrinsic virulence index, which were only discussed at the formulation stage of models [21, 22]. Furthermore, in fulfilling of study set goal, optimal maximization treatment cost are discussed by Figures 3 and 4. Figure 3(a)-(b) demonstrated the amount of chemotherapies required to achieve the desired results. Precisely, under clinical lower and upper bounds on optimal weight factors, reduced amount of drugs were involved with PIs needed more. Finally, Figure 4 illustrated the commercial cost of chemotherapies to maximize both healthy $CD4^+T$ cells and precursors and effectors of cytotoxic T-lymphocytes.

7. Conclusion

We had studied a dual delay HIV-pathogen infection model with pair immune systems (precursors and effectors) responses and delay intracellular in the presence of intrinsic virulence index as presented by model (4). With the alignment of dual role of CTLp and CTLe as treatment functions, the derived 8-dimensional mathematical model accounted for the dynamic optimal control of dual-pair treatment functions for dual delay HIV-pathogen infections. This extended model allowed the mirroring of the biological interface of dual HIV-pathogen infections and the evaluation of the effectiveness of dual-pair treatment functions in terms of dynamics of state variables. The implementation of classical analysis led to optimum maximization of healthy $CD4^+T$ cells and maximal sustainability of both precursors and effectors of CTLs. Also, the dependent and independent role of CTLp and CTLe defined the qualitative and quantitative crucial role of CTLs in maximizing healthy $CD4^+T$ cells and the rapid elimination of I_v, I_p cells and infectious virions.

Furthermore, under set novel treatment conditions, virions infected cells and infectious virions were concurrently eliminated at early time intervals of $1 \leq \{I_v(t),\ I_p(t)\} \leq 3$ months and $1 \leq \{V(t),\ P(t)\} \leq 13$ months following cogent application of chemotherapies at set-point. Results also validated maximal systemic cost of chemotherapy and the overall commercial benefit on drugs acquisition. Notably, result of this study not only collaborated with the experimental finding of models [2, 21, 23, 25] but further achieved sharper and coincides outcome. The study is therefore, an admirable intellectual proceeding that justified its investigation and is equivocally recommended for other related infectious diseases.

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