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OPTIMAL CONTROL MODEL FOR IMMUNE EFFECTORS RESPONSE AND MULTIPLE CHEMOTHERAPY TREATMENT (MCT) OF DUAL DELAYED HIV - PATHOGEN INFECTIONS

Research

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CONFLICTS OF INTEREST
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ABSTRACT
In tackling the persistent menace of the deadly human immunodeficiency virus (HIV) and its accompanying acquired immunodeficiency syndrome (AIDS), some notably mathematical models have been formulated. In this present study, a number of compatible models were studied. The result of which led to the formulation of a classical 5-Dimensional delay-differential dynamic equations, principally primed with the investigation of the methodological application of multiple chemotherapy treatment (MCT) in the presence of delay intracellular and cell-mediated immune effectors response on the interplay of dual delayed HIV-pathogen infections and the T-lymphocytes cells. The model was presented as an optimal control problem and analyses conducted using classical numerical methods – Pontryagin's minimum principle. The method demanded for the verification of positivity of state variables and boundedness of solution; as well as the establishment of model existence of optimal control pair for MCT and the system dynamic optimality solution. Using in-built Runge-Kutter of order of precision 4 in a Mathcad platform, the resulting analyses were subjected to numerical verification. Numerical simulations indicated that maximization of uninfected T-lymphocytes cells is dynamic under drug validity period. Importantly, the model established the fact that upperbounds on treatment optimal weight factors and presence of delay intracellular are crucial to the maximization of healthy $CD4^+$ T cells, significant reduction of virions and suppression of infected $CD4^+$ T cells. Furthermore, the rapid response of virions and infected cells to multiple chemotherapy treatment is emphatically attributed to the enormous role of boosted immune effectors response. The study therefore, advocate for a more accurate model that extensively define the role of the immune effectors response.

KEYWORDS: Dual-delayed-HIV-pathogen-infection, multiple-chemotherapy-treatment, immune-effectors-response, time-delay, delay-differential-equation, optimal-control-pair, clinical-upper-bound

INTRODUCTION
The lentivirus activities of the dreaded human immunodeficiency virus (HIV) with no clear medical cure and which often led to acquired immunodeficiency syndrome (AIDS) has been further compounded by submerging new cases of parasitoid-pathogen infectivity. The situation has in the last two decades, left research scientists with no other option than to research for possible preventive and suppressing measures.

The understanding of the dynamics, transmission and methodological application of chemotherapy treatments has been through mathematical modeling. Thus, there are quite knowledgeable and resourceful litera-

tures on the proceedings and eradication of HIV infection. Therefore, in relation to the scope of this present study, we shall take precedence to those studied in relation to the present investigation. For instance, the model [1], investigated the problem of optimal control of HIV-infection dynamics. The paper considered and related this problem to that of a trajectory – tracking problem in cosmonautics, which cannot be solved without control theory. The investigation establishes the usefulness of application of optimal control in treatment of HIV-infection.

The model [2] studied the optimal control of an HIV immunology using two treatment factors reserve transcriptase inhibitors and protease inhibitors (RTI and PIs), without accounting for intracellular delay and the behavioral tendency of immune effectors response. The study focuses on the methodological and drug efficacy. Result showed that drugs with higher weight factor leads to early tapping off of treatment. We recommend readers to find more details in [2, 4, 5, 6, 7] for optimal control problems on HIV infection, each with varying models using single treatment factor and closely related objective functional. These models were without consideration for either the biological behavior of intracellular delay or the effects of immune effectors response.

In the model [8], two optimal treatments of HIV infection was investigated. The model explored optimal control of drug treatment of HIV, using two controls, which measured the efficiency of RTI and PIs respectively. Result showed that decrease in viral load is dependent on the amount of drug administered. The study as well, had ignored the implication of intracellular delay, probably with the assumption of instantaneous virus infection process.

More significantly, is the study by [9], which was formulated a set of mathematical model for the dynamics of HIV-1 infection with intracellular delay and cell-mediated immune response. The investigation incorporated both cytotoxic T-lymphocytes (CTLs) and intracellular delay into the model. In addition to the stability analysis explored by the model, the study investigated the positive role of CTLs in maintaining the level of healthy cells as well as, controlled the level of viral load. The optimization of this model led to the improved model by [10], which presented a delay-differential model with optimal control with the incorporation of two treatment controls on RTI and PIs respectively. The numerical results from the optimal treatment strategies indicated reduction of viral load and increase the concentration of uninfected $CD4^+$ T cell count.

Basically, intracellular delay represents the definite time interval required by infected cells to replicate infectious virions upon viral transmission. Whereas, immune effector response is an embodiment of antibodies, cytokines, natural killer cells, B cells and T-lymphocytes cells responsible for the defense and attach of virus-infected cells. Capitalizing on the above definitions and invoking models [4, 9, 10], this present paper formulate a mathematical model aimed at investigating the methodological application of multiple chemotherapy treatment (MCT) of dual delayed HIV – parasitoid pathogen infections in the presence of enhanced immune effectors response. Therefore, the novelty of this model is the classical and comprehensive combination of multiple HIV treatment factors (RTI and PIs) under delay intracellular and immune effectors response, formulated as an optimal control treatment of dual HIV-parasitoid pathogen. Finally, in addition to the methodological approach, the model focuses on the establishment of multiple- dimensional benefit of the aforementioned treatment factors in tackling the menace of the diverse new cases of multiple HIV infectivity.

Explicitly, the present investigation is framed around five sections with section 1, covering the introductory aspect. Section 2 is devoted to the material and methods of the model, which accounts for the model formulation with intracellular delay, as well as establishes model positivity and boundedness of solutions. The introduction of optimal control strategy in the analysis of the model is presented in section 3. Covered in section 4, are a number of numerical illustrations and the discussion of the results that follows. Finally, we draw a succinct conclusion and recommendations of the study in section 5. The entire work is thought to give insight into the significant of optimal control to multiple chemotherapy treatment of dual HIV-parasitoid pathogen infection in the presence of intracellular delay and immune effectors response.

Material and methods

We adopt in this section, the presentation of the model formulation, designed to include dual HIV- pathogen virions interaction with immune system ($CD4^+$ T cells) in the presence of multiple chemotherapy treatment with intracellular delay and immune effector response. Since model state variables represents living organisms, it becomes necessary to establish the non-negativity and also, show that the model solutions are bounded.

Problem statement and model formulation

In formulating the model equation and presenting the problem statement of this present study, we shall recall three major mathematical models, which had considered single HIV infection (the last two) with intracellular delay and cell-mediated immune response [4, 9, 10].

From [9], the dynamics of this model is derived as:

$$\frac{dx}{dt} = s - dx(t) - kv(t)x(t)$$

,

$$\frac{dy}{dt} = ke^{-\delta\tau}v(t-\tau)x(t-\tau) - \delta y(t) - py(t)z(t)$$

,

$$\frac{dv}{dt} = N\delta y(t) - \mu v(t)$$

,

$$\frac{dz}{dt} = cy(t)z(t) - bz(t)$$

,

where $x(t), y(t), v(t)$ and $z(t)$ denotes the concentrations of uninfected cells, infected cells and virus and cytotoxic T - lymphocytes (CTLs) respectively.

From model (1), s - represent production of susceptible cells, which die at a rate d . Susceptible becomes infected by viral load at the rate k , while infected cells die at a rate δ with p , representing the rate at which CTLs kills infected cells. Free virus is produced by infected cells at a rate $N\delta$ and decay at a rate μ , with N , as the number of free virus produced by infected cells. The activation of CTLs response is given by c and decay in the absence of stimulus at a rate b . Time taken by infected cells to produce virions (i.e. intracellular delay) is given as τ .

The novelty of model [10] is the introduction of two controls u_1 and u_2 , which accounted for the evaluation of efficiency of the treatment factors – reverse transcriptase inhibitors and protease inhibitors (RTI and PIs). This inclusion modified model (1) to become:

$$\frac{dx}{dt} = s - dx(t) - (1-u_1(t))kv(t)x(t)$$

,

$$\frac{dy}{dt} = (1-u_1(t))ke^{-\delta\tau}v(t-\tau)x(t-\tau) - \delta y(t) - py(t)z(t)$$

, (2)

$$\frac{dv}{dt} = \left(1-u_2(t)\right)N\delta y(t) - \mu v(t)$$

,

$$\frac{dz}{dt} = cy(t)z(t) - bz(t)$$

.

Deducing from models (1) and (2) in formulating the model for our dual delay HIV-Pathogen infections incorporating two control measures on the multiple treatment factors, we invoke our earlier model [4], which was governed by

$$\frac{dU_T}{dt} = \frac{b}{1+V+P} + gU_T\left(1 - \frac{U_T + I_T}{U_{\max}}\right) - \alpha_1 U_T - r(t)[h_1 VU_T + h_2 PU_T]$$

$$\frac{dI_T}{dt} = r(t)[h_1 VU_T + h_2 PU_T] - \left(z_v + z_p\right)\alpha_2 I_T \quad (3)$$

$$\frac{dV}{dt} = z_v\alpha_2 I_T - \alpha_3 VU_T$$

$$\frac{dP}{dt} = z_p \alpha_2 I_T - \alpha_4 P U_T$$

Analyzing these three models, we note that model (1), treated single infection using single treatment factor in the presence of intracellular delay and cell-mediated immune response.
Also, no impose control measures on the toxicity of the drug. In model (2), observing all the parameters and conditions of model (1), we incorporated two control measures u_1 and u_2 was incorporated as treatment factors. Here, infection was single under dual chemotherapy treatment. On the other hand, model (3) was formulated to investigate dual HIV-pathogen infection, using single control measure as single treatment factor.
Thus, the above critical review of models (1)-(3) forms the inspirational background of this present study. Therefore, adopting model (3) and incorporating models (1) and (2), we formulate a novel delay differential equation that describe dual HIV-pathogen infection on host target cells ($CD4^+$ T cells), distorted by two treatment factors (as control measures) and which accounts for system intracellular delay and the critical functioning of the immune effectors response. Furthermore, by letting $P(t)$ denote the concentration of free pathogen and $M(t)$ representing the concentration of CTLs, such that the linear dependent former of $M(t)$ is given by $f(\mathrm{U}_T, \mathrm{I}_T, \mathrm{V}, \mathrm{P}, \mathrm{M}) = cI_T(t)$, then the physiological derivation from the modifications of models (1)-(3) and as aided by fig. 1 below, is governed by the following equations:

$$\begin{aligned}
\frac{dU_T}{dt} &= \frac{b}{1+V+P} + gU_T\left(1 - \frac{U_T + I_T}{U_{\max}}\right) - \alpha_1 U_T - (1-r_1(t))[h_1 V + h_2 P]U_T \\
\frac{dI_T}{dt} &= (1-r_1(t))\,\mathrm{e}^{-\alpha_2 \tau}\mathrm{U}_T(\mathrm{t}-\tau)[h_1 V(t-\tau) - h_2 P(t-\tau)] - \left(z_v + z_p\right)\alpha_2 I_T - qI_T M \\
\frac{dV}{dt} &= (1-r_2(t))z_v \alpha_2 I_T - \alpha_3 V \\
\frac{dP}{dt} &= (1-r_2(t))z_p \alpha_2 I_T - \alpha_4 P
\end{aligned} \tag{4}$$

,

$$\frac{dM}{dt} = cI_T M - dM$$

,

with initial conditions: $U_T(0) = U_{(T)0}, I_T(0) = I_{(T)0}, V(0) = V_0, P(0) = P_0$ and $M(0) = M_0$ at $t = t_0$ and satisfying the biological state variables and parameter values as describe by tables (1 & 2) below. Model (4) is the mathematical equation of the system under consideration by this present study.

With close affinity of model (3) and model (4), the detail description of these models can be deduce from that of model (4) as follows: from the first equation, the first term $b/1+V+P$ - define the natural source of uninfected $CD4^+$ T cells differentiated respect to the invasion of external virions, g is the growth rate (per day) of $CD4^+$ T cells, having a logistic term $\left(1 - \frac{U_T + I_T}{U_{\max}}\right)$. Therefore, U_T can never be larger than $U_{\max}$. The magnitude of loss of infected U_T due to V and P is given as $h_1 V U_T$ and $h_2 P U_T$ respectively. The variable U_T die naturally at a rate α_1, while $(1-r_1(t))$ is the infection rate in the presence of drug control measure $r_1(t)$.

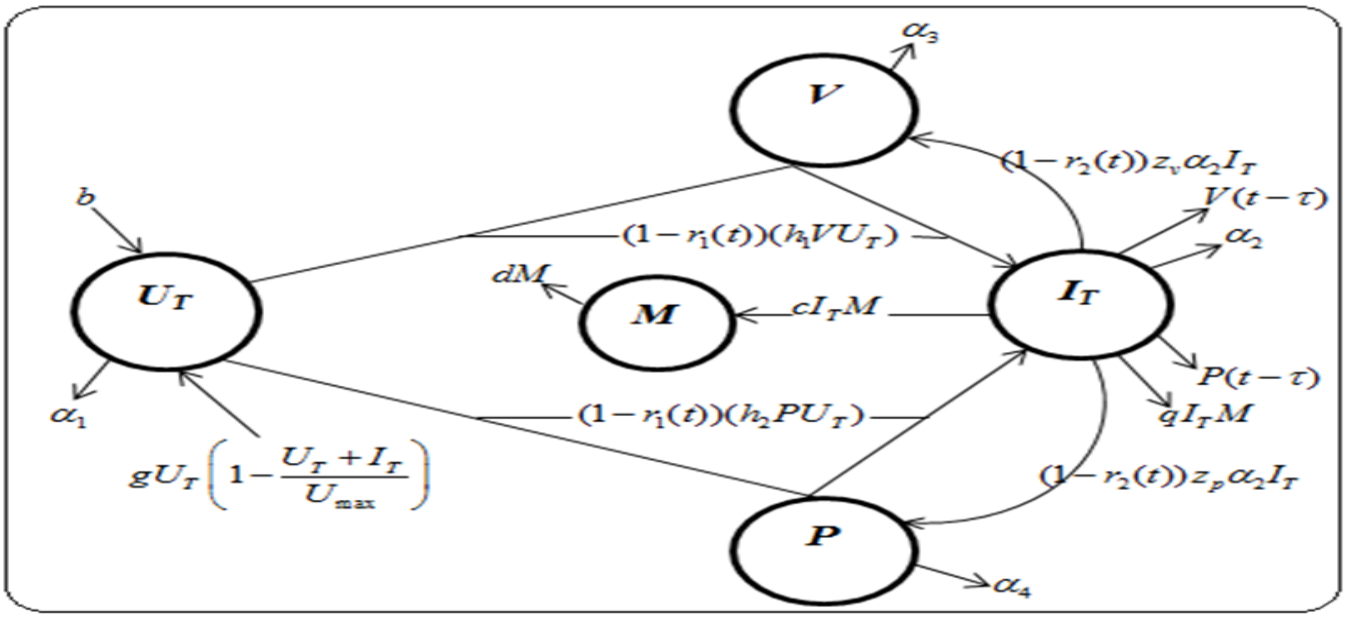


Fig. 1: Schematic representation of dual HIV-pathogen infection with delay intracellular and immune effectors response.

From the second equation, the terms different from that of first equation are: the product of the exponential term, reflecting death rate and time delay affecting the flow of infected $CD4^+$ T cells by both viral load and parasitoid-pathogen. Infected T cells are cleared at the rate $\alpha_2 I_T$, of which the circle is sustained by the rate of virions replication z_v and z_p respectively. Contributing to the elimination of infected cells is the strength of lytic components (CTLs) denoted by $qI_T M$.

In the third and fourth equations, the term $(1-r_2(t))$ denotes the effect of control measure on PIs represented by $z_v\alpha_2 I_T$ and $z_p\alpha_2 I_T$ with each having $\alpha_3 V$ and $\alpha_4 P$ as the death rate of free viral load and pathogen respectively. Finally, the amount of immune effectors response produced by $CD4^+$ T cells due to the rate of infection is define by $cI_T M$, where c is the activation of response by CTLs on viral antigens. The last term, dM is the immune effectors response loss rate due to its interaction with infected cells.

Variables	Dependent variables		
	Definition	**Initial values**	**Units**
U_T	Uninfected T-lymphocytes cells population	0.5	*cells/mm*^{3}
I_T	Infected T-lymphocytes cells population	0.1	-
V	Infectious viral load population	0.2	*mm*^{3}
P	Infectious pathogen population	0.1	*mm*^{3}
M	Immune effectors response	10	*mm*^{3}*day*$^{-1}$

Table1: Values used forstate variables of model (4)

Parame-ters	Parameters and constants		
	Definition	**Values**	**Units**
b_1	Natural source of uninfected T-lymph cells rate	0.5	cell/mm^3.day
α_1	Natural death rate of uninfected T-lymph cells	0.03	day^{-1}
α_2	Death rate of infected T-lymphocytes cells	0.32	day^{-1}
α_3	Death rate of free viral load, V	0.4	day^{-1}
α_4	Death rate of free parasitoid-pathogen, P	0.5	day^{-1}
g	Growth rate of CD4$^+$ T cells	0.04	day^{-1}
h_1	Rate CD4$^+$ T cells becomes infected by viral load, V	0.044	mm^{3}virions^{-1} day^{-1}
h_2	Rate CD4$^+$ T cells becomes infected by parasitoid-pathogen,P	0.016	mm^{3}virions^{-1} day^{-1}
z_V	Replication rate of free viral load by infected CD4$^+$ T cells	28	-
z_P	Replication rate of free pathogen by infected CD4$^+$ T cells	16	-
$r_1(t)$	Optimal control measure for U_T and I_T	$r_1 \in [0,1)$	day^{-1}
$r_2(t)$	Optimal control measure for V and P	$r_2 \in [0,1)$	day^{-1}
τ	Time delay	0.5	day
c	Immune effectors response activation rate	0.2	mm^3.day^{-1}
q	Rate of death of infected T-lymph cells induced by immune effectors	0.05	mm^{3}day^{-1}
d	Death rate of CTLs effectors	0.03	day^{-1}
U_{max}	Maximum level of T-lymphocytes cells population	0.8	cell/mm^3.day

Table2: Summary of parameter values for model (4)

Positivity and boundedness of solution

For the simple fact that the key components of model (4) are the state variables representing delay differential equations and denoting living organisms', it becomes necessary to verify the non-negativity of these state variables and also, show that the model has definite solutions.

Suppose $H = C([-\tau, 0]), \Re^5$ be the Banach space of continuous mapping in the interval $[-\tau, 0]$ into $\Re^5$ equipped with the sup-norm (topology of uniform convergence). Invoking the fundamental theory of functional differential equations (FDEs) from [12], there exist unique solutions $\left(u_T(t), i_T(t), v(t), p(t), m(t)\right)$ to model (4) and having initial conditions

$$\left(u_T(t), i_T(t), v(t), p(t), m(t)\right) \in H \quad . (5)$$

Biologically, these initial functions $u_T(\theta), i_T(\theta), v(\theta), p(\theta)$ and $m(\theta)$ are assumed to be non-negative, i.e.

$$u_T(\theta) \geq 0, i_T(\theta) \geq 0, v(\theta) \geq 0, p(\theta) \geq 0, m(\theta) \geq 0 \text{ , for } \theta \in [-\tau, \theta] \quad .(6)$$

Then, the positivity and boundedness of solutions of model (4) with initial functions satisfying equations (5) and (6) is clearly established by the following theorem:

Theorem 1

Let $\left(u_T(t), i_T(t), v(t), p(t), m(t)\right)$ be the solution of model (4) satisfying conditions (5) and (6). Then $u_T(\theta), i_T(\theta), v(\theta), p(\theta)$ and $m(\theta)$ are all non-negative and bounded for all $t \geq 0$ at which the solution exists.

Proof

Clearly, from model (4), we have

$$u_T(t) = u_T(0) e^{-\int_{t_0}^{t_f} \left(\alpha_1 + g\left(1 - \frac{u_T(\xi) + i_T(\xi)}{u_{\max}}\right) + (1 - r_1(t))(h_1 v(\xi) - h_2 p(\xi)) \right) d\xi}$$

$$+ \int_{t_0}^{t_f} \frac{b}{1 + v + p} e^{-\int_{\eta}^{t_f} \left(\alpha_1 + g\left(1 - \frac{u_T(\xi) + i_T(\xi)}{u_{\max}}\right) + (1 - r_1(t))(h_1 v(\xi) - h_1 p(\xi)) \right) d\xi} d\eta$$

,

$$i_T(t) = i_T(0) e^{-\int_{t_0}^{t_f} \left((z_v + z_p)\alpha_1 + qm(\xi) \right) d\xi}$$

$$+ \int_{t_0}^{t_f} (1 - r_1(t)) u_T(\eta - \tau)[h_1 v(\eta - \tau) - h_2 p(\eta - \tau)] e^{-\alpha_2} e^{-\int_{\eta}^{t_f} \left((z_v + z_p)\alpha_2 + qm(\xi) \right) d\xi} d\eta$$

,

$$v(t) = v(0) e^{-\alpha_3(t)} + \int_{t_0}^{t_f} (1 - r_2(t))\, z_v\, \alpha_2 i_T(\eta) e^{-\alpha_3(t-\eta)} d\eta$$

,

$$p(t) = p(0) e^{-\alpha_4(t)} + \int_{t_0}^{t_f} (1 - r_2(t))\, z_p\, \alpha_2 i_T(\eta) e^{-\alpha_4(t-\eta)} d\eta$$

and

$$m(t) = m(0)e^{\int_{t_0}^{t_f}(ci_T(\xi)-b)d\xi}$$

.

Positivity immediately follows from the above integral forms and (5) and (6).
For boundedness of the solution, we define

$$Q(t) = c(z_v + z_p)e^{-\alpha_2\tau}u_T(t) + c(z_v + z_p)i_T(t+\tau) + \frac{c}{2}\big(v(t+\tau)p(t+\tau)\big) + (z_v + z_p)qm(t+\tau)$$

and $s = \min\{\alpha_1, \alpha_2/2, \alpha_3, \alpha_4, d\}$. By non-negativity of the solution, it follows that

$$\frac{d}{dt}[Q(t)] = c(z_v + z_p)e^{-\alpha_2\tau}[\frac{b}{1+v(t)+p(t)} + gu_T(1 - \frac{u_T(t)+i_T(t)}{u_{\max}(t)}) - \alpha_1 u_T(t) - (h_1 v(t).h_2 p(t))u_T(t)]$$

$$+c(z_v + z_p)(h_1.h_2)e^{-\alpha_2\tau}v(t)p(t)u_T(t) - \alpha_2 c(z_v + z_p)i_T(t+\tau)$$

$$-c(z_v + z_p)qi_T(t+\tau)m(t+\tau) + \frac{\alpha_2 c(z_v + z_p)}{2}i_T(t+\tau)$$

$$-\frac{c(\alpha_3 + \alpha_4)}{2}v(t+\tau)p(t+\tau) + c(z_v + z_p)qi_T(t+\tau)m(t+\tau)$$

$$-(z_v + z_p)qdm(t+\tau)$$

$$= c(z_v + z_p)e^{-\alpha_2\tau}\frac{b}{1+v(t)+p(t)} - c\alpha_1(z_v + z_p)e^{-\alpha_2\tau}u_T(t) - \frac{\alpha_2}{2}c(z_v + z_p)i_T(t+\tau)$$

$$-\frac{c(\alpha_3 + \alpha_4)}{2}v(t+\tau)p(t+\tau) - (z_v + z_p)qdm(t+\tau)$$

$$< c(z_v + z_p)\frac{b}{1+v(t)+p(t)}e^{-\alpha_2\tau} - sQ(t)$$

.

This implies that $Q(t)$ is bounded and so are $u_T(t), i_T(t), v(t), p(t)$ and $m(t)$. Hence, this completes the proof. □

Remark 1 It follows from Thm.1, that in addition to conditions (5) and (6):

If either, $i_T(0) > 0$ or $v(0) > 0$, $p(0) > 0$ then $i_T(t), v(t), p(t)$ and $m(t)$ are actually positive.

The boundedness established in Thm. 1, ensures that the solution exists for all $t \geq 0$.

Now, we verify in our next section, the inclusion of two control measures, which determine the efficacy of the multiple chemotherapies. This is achievable by presenting the model as an optimal control problem.

Optimal control problems for MCT

From model (4), the functions $r_1(t)$ and $r_2(t)$ had been introduced as optimal treatment controls on the effects multiple drugs has on dual delay HIV-parasitoid pathogen and infected cells. Therefore, model (4) can be presented as an optimal control problem with the introduction of an objective functional that maximizes

$$Z(r_1, r_2) = \int_{t_0}^{t_f}\{U_T(t) + M(t) - [K_1(r_1(t))^2 + K_2(r_2(t))^2]\}dt \tag{7}$$

where, the positive constants $K_i \le 1, i = 1,2$ are the "optimal weight factors" base on the optimal benefit on $CD4^+$ T cells concentration and which determines drug efficacy r_1, r_2 respectively [3, 4, 6, 9].

It becomes obvious that our control functions $r_1(t)$ and $r_2(t)$ is bounded Lebesgue integrable functions. The control $r_2(t)$ represents the efficacy of chemotherapy in inhibiting viral load and pathogen production, such that replication of these virions under chemotherapy is $(1-r_2(t)(z_v + z_p)\alpha_2$. This implies that if $r_2 = 1$, then infection is inhibited at 100% and if $r_2 = 0$, there no infection inhibition and disease is endemic. Furthermore, the control $r_1(t)$ denotes the efficacy of chemotherapy blocking new infection. Therefore, infection rate in the presence of chemotherapy is given as $(1-r_1(t))(h_1 + h_2)$. Thus, if $r_1 = 0$ due to any constraint, then infection is bound to be endemic. On the other hand, if $r_1 = 1$ then maximal chemotherapy is used and we say that infection is evidently under control i.e. maximal use of chemotherapy $= (r_{i=1,2})^2$ [3, 8]. The following proposition then holds:

Proposition 1

Assume there exist drug hazardous side effect, then, the inequality of the optimal weight factors $K_i, i = 1,2$ is such that $0 \le x_i \le K_i(t) \le y_i < 1 \quad i = 1,2$ holds.

Then, following the analysis and the above proposition, we see that optimal control problem is concern with the maximization of uninfected $CD4^+$ T cells concentration, maximize immune effectors response by CTLs, decrease/suppression of both viral load and parasitoid-pathogen, while in the process aimed at minimizing systemic cost. Therefore, from equation (7), we seek an optimal control pair (r_1^*, r_2^*) satisfying

$$\max_{0 \le r_i \le 1} Z(r_1, r_2) = Z(r_1^*, r_2^*)$$

such that

$$Z(r_1^*, r_2^*) = \max\{Z(r_1, r_2) : (r_1, r_2) \in A\} \tag{8}$$

where A is the control set defined by

$$A = \{r = (r_1, r_2) : r_i \ \ measurable, x_i \le r_i(t) \le y_i, t \in [t_0, t_f], i = 1,2\}$$

.

Remark 2 The introduction of optimal function $K_i \ge 0, i = 1,2$ defined as the optimal weight factors follows from the fact that the benefit on cost functional is non-linear. Hence, simple non-linear controls are introduced on the cost indicators [3, 4].

Existence of an optimal control pair for MCT

From model (4), we observe that certain parameter restrictions are imposed on the model in order to ensure that the model is realistic. For instance, if death rate at $U_{\max}$ is to be greater than the source supply rate then an assumption of the form

$$\alpha_1 U_{\max} > b \tag{9}$$

holds. To this effect, we must have a steady state population size that should be below $U_{\max}$ in order for the $CD4^+$ T cells population to expand when stimulated by the dual infections. Moreso, if the population ever gets near $U_{\max}$ growth should slow [13].

Furthermore, the existence of an optimal control and uniqueness proof of the optimality system requires explicit upperbounds. So, using $U_T(t) < U_{\max}$, upper bounds on the solutions of the state system are determined, thus:

$$\frac{d\hat{I}_T}{dt} = [h_1\hat{V}(t-\tau) + h_2\hat{P}(t-\tau)]U_{\max}, \qquad \hat{I}_T(t_0) = I_{(T)0}$$

$$\frac{d\hat{V}}{dt} = z_v\alpha_2\hat{I}_T, \qquad \hat{V}(t_0) = V_0$$

$$\frac{d\hat{P}}{dt} = z_p\alpha_2\hat{I}_T, \qquad \hat{P}(t_0) = V_0 \qquad \text{where } h_1, h_2, z_v, z_p > 0$$

or

$$\begin{pmatrix} \hat{I}_T \\ \hat{V} \\ \hat{P} \end{pmatrix} = \begin{pmatrix} 0 & h_1(t-\tau)U_{\max} & h_1(t-\tau)U_{\max} \\ z_v\alpha_2 & 0 & 0 \\ z_p\alpha_2 & 0 & 0 \end{pmatrix} \begin{pmatrix} \hat{I}_T \\ \hat{V} \\ \hat{P} \end{pmatrix}.$$

We see at once linear system in finite time with bounded coefficients, i.e. the supersolutions $\hat{I}_T, \hat{V}, \hat{P}$ are uniformly bounded.

At this point, we recall the result by ([14], Thm. 4.1, pg. 68-69) for the determination of existence of an optimal control of our structured problem.

Theorem 2

Under proposition 1 and equation (9), there exists an optimal control pair $(r_1^*, r_2^*) \in A$ that maximizes the objective functional $Z(r_1, r_2)$ such that

$$\max_{(r_1,r_2)\in A} Z(r_1, r_2) = Z(r_1^*, r_2^*) \qquad (10)$$

Proof

Applying the result of [14] for the verification of existence of optimal control pair, we at once check that the following conditions are satisfied:

The set of controls $r_i(t), i = 1, 2$ are Lebesgue-integrable in the interval $[t_0, t_f]$ and corresponding state variables is nonempty.

The admissible control set A, is convex and closed.

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

The integrand of the objective functional is concave on A.

There exist constants $C_1, C_2 > 0$ and $\beta > 1$ such that the integrand $L(U_T, M, r_1, r_2)$ of the objective

funtional satisfies

$$L(U_T, M, r_1, r_2) \le C_2 - C_1(/r_1/^2 + /r_2/^2)^{\beta/2}$$

.

In verifying these conditions, we invoke the result of ([15], Thm. 9.2.1, pg. 182), which establishes the existence of solution of model (4) with bounded coefficients and satisfies condition (i). We note that the solutions are bounded. Then, by definition, the control set is closed and convex, which satisfies condition (ii). Since our state system is bilinear in $r_i, i = 1,2$, the RHS of model (4) satisfies condition (iii), using the boundedness of the solutions. Moreso, the integrand of the objective functional $U_T(t) + M(t) - [K_1(r_1(t))^2 + K_2(r_2(t))^2]$ is concave on the control set A . Lastly, the completeness of the existence of solution is the fact that

$$U_T(t) + M(t) - [K_1(r_1(t))^2 + K_2(r_2(t))^2] \le C_2 - C_1(/r_1/^2 + /r_2/^2)$$

where C_2 depends on the upper bound on U_T and M with $C_1 > 0$, since $K_1, K_2 > 0$. Then, the proof of existence is completed. □

Optimal control strategy

Here, we denote this subsection to the derivation of the necessary conditions for an optimal control pair with delay intracellular. Applying Pontryagin's minimum principle with delay, we invoke [16], which provided necessary conditions for an optimal control problem. The principle redefined model (4), equations (7) and (8) into a problem of maximizing an Hamiltonian, H with

$$\begin{aligned} H(t, u_T, i_T, v, p, m, u_\tau, v_\tau, p_\tau, r_1, r_2, \lambda) &= K_1(r_1)^2 + K_2(r_2)^2 - u_T - m \\ &+ \lambda_1[\frac{b}{1+v+p} + g u_T(1 - \frac{u_T + i_T}{u_{\max}}) - \alpha_1 u_T - (1 - r_1)(h_1 v + h_2 p) u_T] \\ &+ \lambda_2[(1 - r_1)e^{-\alpha_2 \tau} u_T \tau(h_1 v_\tau - h_2 p_\tau) - (z_v + z_p)\alpha_2 i_T - q i_T m] \\ &+ \lambda_3[z_v \alpha_2 i_T - \alpha_3 v] + \lambda_4[z_p \alpha_2 i_T - \alpha_4 p] + \lambda_5[c i_T m - d m] \end{aligned} \tag{11}$$

.

This leads to the following theorem.

Theorem 3

Given optimal controls r_1^*, r_2^* and solutions $u_T^*, i_T^*, v^*, p^*, m^*$ of the corresponding model (4), then there exists adjoint variables $\lambda_1, \lambda_2, \lambda_3, \lambda_4$ and λ_5 satisfying

$$\lambda_1'(t) = 1 + \lambda_1(t)[\alpha_1 + g(1 - \frac{i_T^*(t)}{u^*_{\max}(t)}) + (1 - r_1^*(t))(h_1 v^*(t) + h_2 p^*(t))]$$

$$+ \chi_{[t_0, t_f - \tau]}(t)\lambda_2(t + \tau)(r_1^*(t + \tau) - 1)e^{-\alpha_2 \tau}(h_1 v^*(t) + h_2 p^*(t))$$

$$\lambda_2'(t) = \lambda_1(t)[g u_T^*(t)(1 - \frac{u_T^*(t)}{u^*_{\max}(t)})] + \lambda_2(t)[(z_v + z_p)\alpha_2 - q m^*(t)]$$

$$+ (1 - r_2^*(t))\lambda_3(t) z_v \alpha_2 + (1 - r_2^*(t))\lambda_4(t) z_p \alpha_2 + \lambda_5(t) c m^*(t)$$

$$\lambda_3'(t) = \lambda_1(t)[\frac{b}{(1+v^*(t)+p^*(t))^2} + (1-r_1^*(t)h_1u_T^*(t)] + \lambda_3(t)\alpha_3$$
$$+\chi_{[t_0,t_f-\tau]}(t)\lambda_2(t+\tau)(r_1^*(t+\tau)-1)e^{-\alpha_2\tau}(h_1u_T^*(t))$$
$$\lambda_4'(t) = \lambda_1(t)[\frac{b}{(1+v^*(t)+p^*(t))^2} + (1-r_1^*(t))h_2u_T^*(t)] + \lambda_4(t)\alpha_4$$
$$+\chi_{[t_0,t_f-\tau]}(t)\lambda_2(t+\tau)(r_1^*(t+\tau)-1)e^{-\alpha_2\tau}(h_2u_T^*(t))$$
$$\lambda_5'(t) = 1 + qi_T^*(t)\lambda_2(t) + \lambda_4(t)(d - ci_T^*(t)) \quad , \tag{12}$$

with transversality conditions $\lambda_i(t_f) = 0, i = 1,..,5$. Furthermore, the optimal control is given by

$$r_1^*(t) = \min\left\{y_1, \max[x_1, \frac{h_1+h_2}{K_1}[\lambda_2(t)e^{-\alpha_2\tau}u_T^*(t-\tau)(h_1v^*(t-\tau)+h_2p^*(t-\tau))\right.$$
$$\left.-\lambda_1(t)(v^*(t)+p^*(t))u_T^*(t)]]\right\}$$
$$r_2^*(t) = \min\left\{y_2, \max[x_2, \frac{1}{K_2}[\lambda_3(t)z_v\alpha_2i_T^*(t) + \lambda_4(t)z_p\alpha_2i_T^*(t)]]\right\} \tag{13}$$

Proof

The adjoint equations and transversality conditions can be obtained by using Pontryagin's minimum principle with delay in state [16] such that

$$\lambda_1'(t) = -\frac{\partial L}{\partial u_T}(t) - \chi_{[t_0,t_f-\tau]}(t)\frac{\partial L}{\partial u_{(T)\tau}}(t+\tau) \quad , \quad \lambda_1(t_f) = 0$$
$$\lambda_2'(t) = -\frac{\partial L}{\partial i_T}(t) \quad , \quad \lambda_2(t_f) = 0$$
$$\lambda_3'(t) = -\frac{\partial L}{\partial v}(t) - \chi_{[t_0,t_f-\tau]}(t)\frac{\partial L}{\partial v_\tau}(t+\tau) \quad , \quad \lambda_3(t_f) = 0$$
$$\lambda_4'(t) = -\frac{\partial L}{\partial p}(t) - \chi_{[t_0,t_f-\tau]}(t)\frac{\partial L}{\partial p_\tau}(t+\tau) \quad , \quad \lambda_4(t_f) = 0$$
$$\lambda_5'(t) = -\frac{\partial L}{\partial m}(t) \quad , \quad \lambda_5(t_f) = 0 \quad . \tag{14}$$

The optimal controls r_1^* and r_2^* can then be solved from the optimality conditions

$$\frac{\partial L}{\partial r_1}(t) = 0 \quad , \quad \frac{\partial L}{\partial r_2}(t) = 0 \tag{15}$$

That is

$$\left.\begin{aligned}\frac{\partial L}{\partial r_1}(t) &= K_1 r_1(t) + [(h_1 v(t) - h_2 p(t))u_T(t)]\lambda_1(t) = 0 \\ \frac{\partial L}{\partial r_2}(t) &= K_2 r_2(t) + z_v \alpha_2 i_T(t)\lambda_3(t) + z_p \alpha_2 i_T(t)\lambda_4(t) = 0\end{aligned}\right\} \quad (16)$$

Then, by bounds in A of the controls, it is easy to obtain the compact forms of r_1^* and r_2^* as in equation (13) respectively. □

Therefore, by definition, optimality system is an embodiment of the state system couple with the adjoint system with the initial and transversality conditions together with the derived optimal control pair. Thus, if we substitute r_1^* and r_2^* into model (4) and equation (12), we obtain the following optimality system:

$$\frac{dU_T^*(t)}{dt} = \frac{b}{1+V+P} + gU_T\left(1 - \frac{U_T + I_T}{U_{\max}}\right) - \alpha_1 U_T - (1 - r_1^*(t))[h_1 V + h_2 P]U_T$$

$$\frac{dI_T^*(t)}{dt} = (1 - r_1^*(t))\,\mathrm{e}^{-\alpha_2 \tau}\mathrm{U}_T(\mathrm{t}-\tau)[h_1 V(t-\tau) - h_2 P(t-\tau)] - \left(z_v + z_p\right)\alpha_2 I_T - qI_T M$$

$$\frac{dV^*(t)}{dt} = (1 - r_2^*(t))z_v \alpha_2 I_T - \alpha_3 V$$

$$\frac{dP^*(t)}{dt} = (1 - r_2^*(t))z_p \alpha_2 I_T - \alpha_4 P \quad ,$$

$$\frac{dM^*(t)}{dt} = cI_T M - dM \quad ,$$

$$\frac{d\lambda_1(t)}{dt} = 1 + \lambda_1(t)[\alpha_1 + g(1 - \frac{i_T^*(t)}{u^*_{\max}(t)}) + (1 - r_1^*(t))(h_1 v^*(t) + h_2 p^*(t))]$$

$$+\chi_{[t_0, t_f - \tau]}(t)\lambda_2(t+\tau)(r_1^*(t+\tau) - 1)e^{-\alpha_2 \tau}(h_1 v^*(t) + h_2 p^*(t))$$

$$\frac{d\lambda_2(t)}{dt} = \lambda_1(t)[gu_T^*(t)(1 - \frac{u_T^*(t)}{u^*_{\max}(t)})] + \lambda_2(t)[(z_v + z_p)\alpha_2 - qm^*(t)]$$

$$+(1 - r_2^*(t))\lambda_3(t)z_v \alpha_2 + (1 - r_2^*(t))\lambda_4(t)z_p \alpha_2 + \lambda_5(t)cm^*(t)$$

$$\frac{d\lambda_3(t)}{dt} = \lambda_1(t)[\frac{b}{(1 + v^*(t) + p^*(t))^2} + (1 - r_1^*(t)h_1 u_T^*(t)] + \lambda_3(t)\alpha_3$$

$$+\chi_{[t_0, t_f - \tau]}(t)\lambda_2(t+\tau)(r_1^*(t+\tau) - 1)e^{-\alpha_2 \tau}(h_1 u_T^*(t))$$

$$\frac{d\lambda_4(t)}{dt} = \lambda_1(t)[\frac{b}{(1 + v^*(t) + p^*(t))^2} + (1 - r_1^*(t))h_2 u_T^*(t)] + \lambda_4(t)\alpha_4$$

$$+\chi_{[t_0, t_f - \tau]}(t)\lambda_2(t+\tau)(r_1^*(t+\tau) - 1)e^{-\alpha_2 \tau}(h_2 u_T^*(t))$$

$$\frac{d\lambda_5(t)}{dt} = 1 + qi_T^*(t)\lambda_2(t) + \lambda_4(t)(d - ci_T^*(t))$$

,

where

$$r_1^*(t) = \min\left\{y_1, \max[x_1, \frac{h_1+h_2}{K_1}[\lambda_2(t)e^{-\alpha_2\tau}u_T^*(t-\tau)(h_1v^*(t-\tau) + h_2p^*(t-\tau))\right.$$

$$\left.-\lambda_1(t)(v^*(t) + p^*(t))u_T^*(t)]]\right\}$$

$$r_2^*(t) = \min\left\{y_2, \max[x_2, \frac{1}{K_2}[\lambda_3(t)z_v\alpha_2 i_T^*(t) + \lambda_4(t)z_p\alpha_2 i_T^*(t)]]\right\}$$

with $\lambda_i(t_f) = 0, i = 1,..,5$. (17)

It therefore follows that the controls are dependent on the adjoints $\lambda_1, \lambda_2, \lambda_3$ and λ_4 , since those adjoints corresponds to the state variables U_T, I_T, V and P of which the first four state equations of model (4) contains the terms. Finally, we leave the derivation of uniqueness of optimal control system to our readers as it can be obtained by standard results in [2, 14]. On this note, our next phase is the simulations of some illustrations using the derived optimality control system of equation (17).

Numerical simulations and discussion

In this section, we describe a numerical method that solves the optimality system of equation (17) followed by the discussion of the outcome.

Numerical simulations

The computer program, which involves the application of in-built Runge-Kutter of order of precision 4, in a Mathcad surface requires the definition of the convertible key variables and parameters. So that if we let combinations of weight factors (K_1, K_2) have upperbounds $0 \le x_i \le K_i(t) \le y_i < 1$, for all $i = 1,2$ in the controls, then one can generate several treatment schedules for varying time periods. For the purpose of clarity, we demonstrate a case of two different values of $K_{i=1,2}$ for $t_f \le 30$ months of treatment schedules as shown in fig. 2(a-e) and fig. 3(a-b) respectively. From fig. 2(a-e), we utilized tables (1 & 2) with the infusion of $K_1 = 2000, K_2 = 25, x_1 = 0, y_1 = 0.2, x_2 = 0.2$ and $y_2 = 0.8$, for $T = 30$ and $n = 1000$.

For all the simulations, let $\{U_T, I_T, V, P, M\} \equiv \{H_1,.., H_5\}$ and $\{\lambda_1,.., \lambda_5\} \equiv \{H_6,.., H_{10}\}$, such that if $H_1,.., H_5$ are defined by state variable of table 1, then values for $(H_6,.., H_{10}) := (0.5 \quad 0.2 \quad 0.2 \quad 0.1 \quad 10)^T$.

Remark 3: It is important to note that (i) for brevity, the graphical representations of the penalty conditions are omitted; (ii) due to drug variation in strength, the upper bound y_1 of r_1 control is much smaller than upper bound y_2 of r_2 control [7], since $r_1 = 0.5$ and $r_2 = 0.3$ respectively.
The following simulations are then performed:

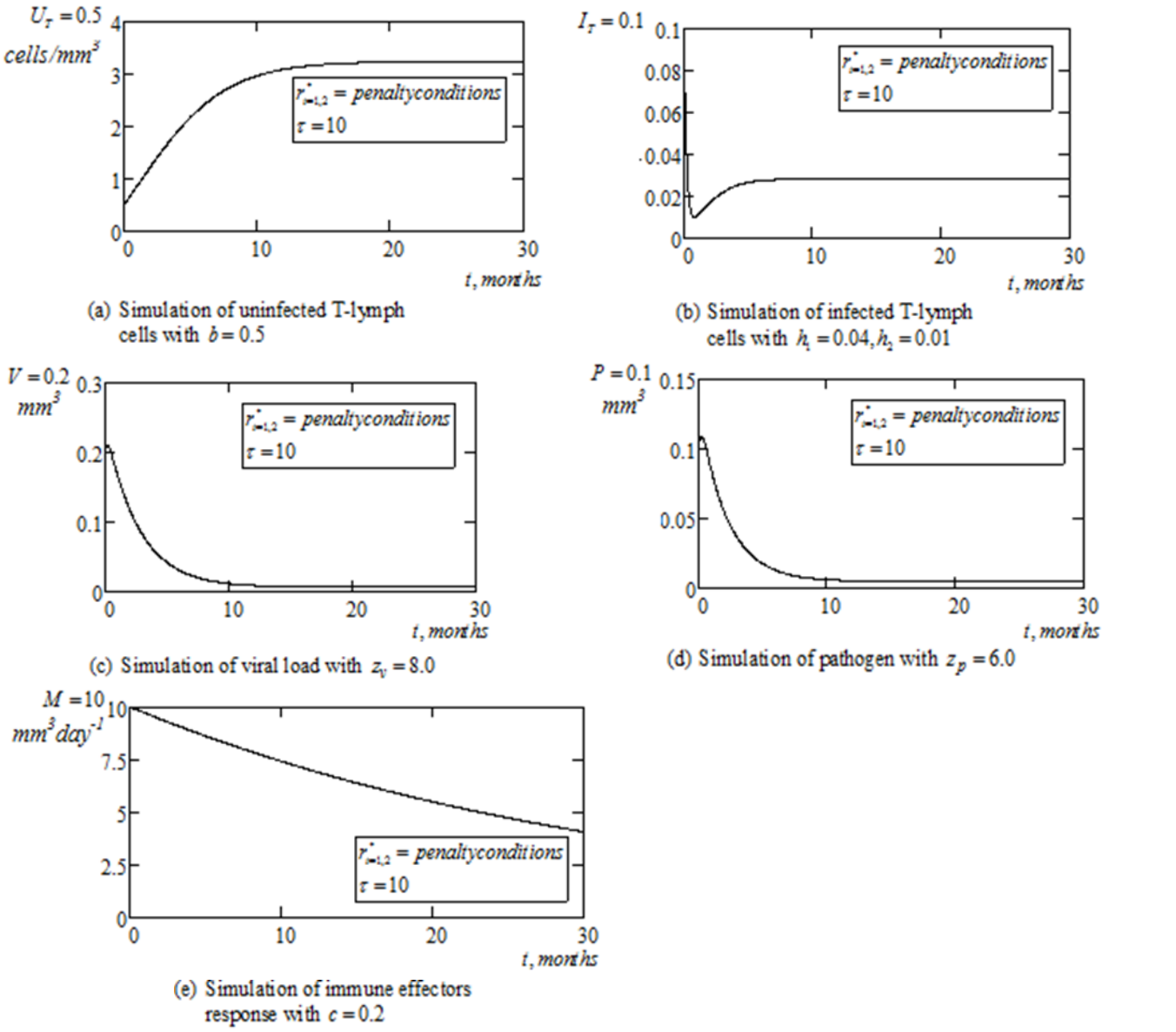


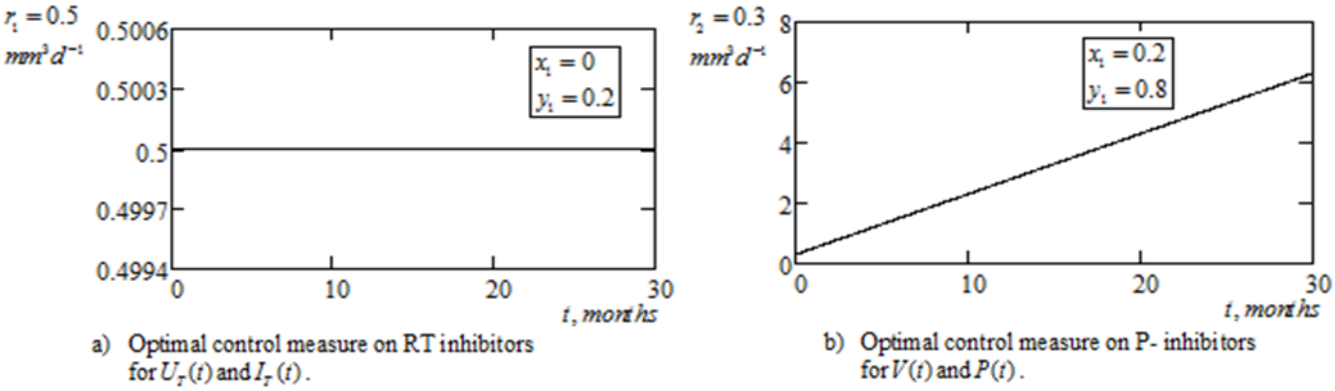
Fig. 2(a-e) Graphical representation of MCT for dual delayed HIV- pathogen infection with immune response.

From fig. 2(a), observing tables (1 & 2), we investigate the concentration of uninfected T-lymphocytes cells population as a consequence of the application of optimal control measures on RTI depicted by $r_1^*(t)$ of equation (17), which subjected to intracellular delay in the presence of boosted immune effectors response $M(t) = 10 mm^3 d^{-1}$. The illustration shows significant growth in healthy CD4$^+$ T cells following consistent treatment for $t \le 30$ i.e. $U_T(t)$ increases from $0.5 \to 3.245 cell mm^3$. Fig. 2(b) exhibits tremendous decline/ suppression of infected CD4$^+$ T cells under similar observed conditions of fig. 2(a). Explicitly, we observe here, sharp decline in the early 2 months of chemotherapy i.e. $I_T(t) = 0.1 \to 0.01$ and then submerged to stability

from the 8th month through the duration of treatment schedule i.e. $I_T(t) = 0.01 \rightarrow 0.025$.
In fig. 2(c), the amount of viral load concentration is observe to exhibit gradual decline following initial application of drug with high toxicity value i.e. viral load decreases in the manner $V(t) = 0.2 \rightarrow 6.642 \times 10^{-3}\, mm^3$ after 12 months. Obviously, this later value shows the stability and persistent level of viral load for $t_f \leq 30$ months of PIs chemotherapy. Similarly, under same condition, fig. 2(d) depicts a drastic reduction in parasitoid-pathogen. We see $P(t)$ declining from $(0.1 \rightarrow 4.776 \times 10^{-3})mm^3$ at $t_f = 11$ months and then attain stability at $12 \leq t_f \leq 30$ months with value $P(t) = 4.976 \times 10^{-3}\, mm^3$.

Finally, from fig. 2(e), we investigate the crucial contribution of the presence of immune effectors response as boosted by the application of multiple chemotherapies (RTI and PIs). Obviously, the gradual decline of the immune effectors response from $M(t) = 10 \rightarrow 4.087 mm^3 d^{-1}$ is attributed to its active role in causing gradual de-replication and significant suppression of dual delayed HIV-pathogen viruses as well as the clearance rate factor. Intuitively, this is a clear affirmation of the fact that the amount of immune effectors response present at any period of time is significantly dependent on the concentration of virions in the immune system. Therefore, the higher the virions present, the readily activation of the presence of immune effectors response.

Furthermore, the evaluation of systemic cost of chemotherapy administration is as depicted by figures 3 (a-b) below:



a) Optimal control measure on RT inhibitors for $U_T(t)$ and $I_T(t)$.

b) Optimal control measure on P- inhibitors for $V(t)$ and $P(t)$.

Fig. 3(a-b) Graphical simulations of optimal control pair for multiple chemotherapies treatment with penalty conditions, L1 = 2000 and L2 = 25

Critical view of figures 3(a-b) shows the graphical representation of the outcome of cost benefits considered as systemic cost on model (4). Fig. 3(a) depicts the instantaneous increment of the application of RTI chemotherapy under well-defined upper bound that allows reducible amount of overall use of drug i.e. $0.5 \leq r_1^* \leq 0.501$, for $t_f \leq 30$ months. On the other hand, due to varying strength for varying chemotherapies, fig 3(b) representing PIs chemotherapy shows that $6.0 d^{-1}$ is required for blockage and suppression of new infection replication and inhabitation of viral load and pathogen production. Therefore, for a dynamic system of model (4), the varying amount of PIs required for the sustainability of low level virology, is in the range of $0.3 \leq r_1^*(t) \leq 6.3 d^{-1}$.

Discussion

The present study had used ordinary differential equation to formulate a 5-Dimensional mathematical delay-differential model for the investigation of dual delay HIV-parasitoid pathogen infection. Intracellular delay and immune effectors response was incorporated to dual treatment factors (RTI and PIs) to investigate the biological and physiological behavioral interplay of dual HIV infectivity on the immune system ($CD4^+$ T cells). The study explored classical numerical methods, which allows the application of Pontryagin's minimum principle in the analysis of the optimality control system. Knowledgeable, is the imposition of optimal control measures and penalty conditions on treatment factors and the state variables. The conduct of numerical simulation follows suit. Results of the analysis as depicted by figures 2(a-e) and 3(a-b) indicated that for the application of multiple chemotherapeutical treatment on dual delayed HIV-pathogen infections, optimal chemotherapy is dynamic in the sense that treatment is adjustable over a defined period of time preferably, initiating treatment with strong dosing schedule. More visibly, results of simulation portrait to the fact that the benefits on cost are independent of prolonged drugs administration.

Explicitly, from fig. 2(a-e), results of the numerical simulations further showed that maximization of uninfected $CD4^+$ T cells concentration is a function of the clinical upperbounds on RTI and PIs as defined by $r^*_{i=1,2}$ and the critical role of boosted immune effectors response in the immune system. Vital in the slow and determination of the rate of infected cells is the incorporation of the delay intracellular, which allows for the concentration of chemotherapy when virions were still at latent stage. More satisfactorily, is the stability of both viral load and parasitoid-pathogen on prolong chemotherapies administration, which suggest that toxicity of chemotherapies are paramount at treatment set-point and therefore, suppression of infected cells is independent of prolonged therapy application. However, systemic cost is more visible and lessened on prolong chemotherapy administration.

Furthermore, results of fig. 3(a-b), also indicated that infection rate triggers a corresponding quantity of immune effectors response reproduced (as defense mechanism), which kills off infected cells. More specifically, the drop in the level of immune effectors response were a clear indication of enhance decline in virions infection rate. Then, suffice to say that the present result not only agreed with notable existing studies (as contained in the literature) but is an enhancement of those models by [4, 9, 10]. Therefore, it is arguably accepted (as depicted by fig. 3(b)) that the high amount of PIs that is required were a clear indication to the fact that reduction and suppression of infected cells is a function of high toxicity of PIs required early enough to cause de-replication of new viral load and parasitoid-pathogen viruses.

CONCLUSION

Following the extensive analyses and modifications of a number of compactible models, this present paper using ordinary differential equations, formulated a 5-Dimensional delay differential equation, which accounted for the dynamic behavior of dual delayed HIV –pathogen infections on T-lymphocytes cells distorted by multiple chemotherapy treatment with the incorporation of delay intracellular and interface by immune effectors response. The model, which was presented as an optimal control problem, explored classical numerical methods in the analysis and numerical illustrations conducted.

The results of the simulations indicated that maximization of uninfected T-lymphocytes as a consequence of multiple chemotherapy application on dual delayed HIV-pathogen infectivity is a dynamic one and admissible within defined drugs validity time interval. Moreso, the concentration of healthy $CD4^+$ T cells is a function of clinical upperbounds on RTI and PIs and the emphatic role of enhanced immune effectors response. Observably, the rapid decline in infected cells is arguably as a result of the introduction of delay intracellular to the model.

Finally, reduction in the amount of immune effectors suggests the positive response of virions to multiple chemotherapies and agreed to the fact that the concentration of immune effectors response present at any period (as defense mechanism) is dependent on the amount of virions infiltrating the immune systems at that same time interval. Thus, the model studied here is admirably simple and therefore, recommends extension of the investigation to incorporate a more involving model of the immune effectors response.

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