Applied Mathematics and Physics, 2017, Vol. 5, No. 2, 61-76
Available online at http://pubs.sciepub.com/amp/5/2/5

DOI:10.12691/amp-5-2-5

Optimal Control Model for Pair Chemotherapy Treatment with Time-delay Immunity in Dual HIV-Infectivity

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Abstract The seeming incurable status of HIV/AIDS and its associated virus infectivity had continuously led to series of scientific research, geared towards the amelioration of the increasing trend of the deadly disease. In this paper, a system of ordinary differential equations was used for the formulation of a 4-Dimensional mathematical dynamic HIV-pathogen model. The model was presented as optimal control problem, which accounted for the methodological pair chemotherapy treatment, with treatment factors clinically sandwiched in two temporal time-delay immunity chambers. The methodology of the model involved dual state infectious variables, pair treatment factors - reverse transcriptase inhibitors and protease inhibitors (RTI and PI), with immune system cells as vectors. The study explored numerical methods with analysis conducted using classical Pontryagin's Maximum Principle. We proved that the model variables have non-negative solutions and as well, established the existence and uniqueness of the optimal control strategy, which led to the derivation of the model optimal dynamic solution. Numerical computations of the model explored Runge-Kutter of order of precision 4 in a Mathcad environment. The result demonstrated novel precision, which not only agreeing with known existing models but also showed that the higher the amount of optimal weight factor, the earlier, efficient, faster and less amount of chemotherapies required for the maximization of healthy $CD4^+$ T cell count concentration. Furthermore, sustainability of declined infectivity and significant minimization of optimal cost was a function of prolong treatment schedule with drug validity period accounted for. Therefore, the study which could be readily adopted for other infectious diseases, suggests further investigations with more interplay of multiple control functions.

Keywords: *time-delay-immunity, dual-HIV-infectivity, chemotherapy-treatment, optimal-weight-factor, vasodilatation, methodological-pair- treatment*

Cite This Article: Bassey E. Bassey, "Optimal Control Model for Pair Chemotherapy Treatment with Time-delay Immunity in Dual HIV-Infectivity." *Applied Mathematics and Physics*, vol. 5, no. 2 (2017): 61-76. doi: 10.12691/amp-5-2-5.

1. Introduction

The continuous insurmountable challenges posed by lack of précised cure for the human immunodeficiency virus (HIV), vice averse the acquired immunodeficiency syndrome (AIDS) has led to series of mathematical and optimal control models, not just on the dynamics of its infection but of diverse interest, are the dynamics of varying applications of chemotherapies and its associated treatments proceedings.

Following new diverse multi-facets of HIV and its associated infections, a number of models on the best practice of chemotherapy application have been formulated. Immunotherapy administration during the early stage of the disease progression is most beneficial for raising $CD4^+$ T cell count [1]. However, understanding the interactions of the multi-facets infections on host $CD4^+$ T cells can best be outlined by estimation of the parameters associated with the progression of the immunotherapies. The quantitative method by which we analyze this whole lot of progression is visible through application of optimal control theory.

Mathematical models of [2,3,4], studied optimal control problems of HIV infection in varying modeling approach, using single treatment with similar objective functional. The model [4], investigated the optimal therapeutic control modeling, using linear optimal state evaluator in a feedback therapy to minimize the effect of measurement error, with the aid of immune system response model as explored in [5,6].

In [2], immunotherapy of HIV-1 infection with the application of cytokine interleukin-2 (IL-2), was investigated with model using immune boosting response to fight HIV infection. Optimal control strategy was deployed in the analysis of the mechanism of the immune viral dynamics. The model observed that loss rate of plasma virus is dependent on the $CD4^+$ T cell count, which represent the capacity of immune system to clear the virus. Survey on early optimal control application to biological problems was studied by [7]; while the depiction of optimal control as an organizing principle for natural immune system

behavior and its application on HIV treatment was studied by [8,9].

The studies [10,11,12], investigated body biological systems in the defense against pathogen via the introduction of inflammation and vasodilatation, causing blood coagulation that slow the spread of infection to other parts of body, as well as raising alarm for more complete response. Examined by [13], was the dynamics of infection by HIV, as well as therapies that minimize viral load, restore adaptive immunity and utilization of minimal dosage of anti-HIV drugs. The study observed the never cured infection status and therefore, requires continuous treatment to keep the condition in remission.

Other relevant optimal control mathematical models on the dynamics of interactions of chemotherapies on viral load and the immune system could be found in [14-24]. The model [25], applied stochastic optimal control theory to develop protocol for the treatment of human diseases and which also accounted for time dependent uncertainties of the model.

In this present model, motivated by [1,2,3], we formulate, using ordinary differential equations, a 4-Dimensional dynamic HIV-pathogen model, presented as an optimal control problem. The novelty of the model, accounts for the methodological pair treatment of dual HIV-pathogen infectivity with treatment factors clinically sandwiched in a two temporal time-delay immunity chambers. The methodology of the model is the constituent of two infectious state variables (viral load and parasitoid-pathogen); two chemotherapies – reverse transcriptase inhibitors (RTI), as immune boosting and protease inhibitors (PI), as immune suppressing therapy; and the host – immune system cells. The method explores the use of numerical methods; skew to optimal control strategy with analysis conducted using Pontryagin's Maximum Principle.

The entire model is composed of the introductory aspect as in section 1. Definition of model mathematical statement and design of the optimal control problem are absorbed in section 2. Section 3, is devoted to the existence and uniqueness of the optimal control pair treatment in the presence of latent chambers. Numerical simulations as well as model illustrations and discussion were designated for section 4. Finally, in section 5, we summarized the work, following the observatory conclusion and remarks base on model formulation, extensive analysis and illustrations thereof.

2. Material and Methods

We shall devote this section to the complete definition of the mathematical statement and model formulation of the study; as well as the design for the optimal control problem of the model.

2.1. The Mathematical Statement and Model Formulation

With intending simplicity, we presuppose the formulation of the present model as constituted by host victim – $CD4^+$ T cells having interaction with two infectious variables – viral load and parasitoid-pathogen, in the presence of two distorting treatment factors – reverse transcriptase inhibitors (RTI) and protease inhibitors (PI) under two ameliorating time-delay latent chambers. The definitions of the model dynamics is aided by the schematic structure as presented by Figure 1, below:

From Figure 1 below, we see that the model is defined around four subgroups leading to a 4 - Dimensional dual HIV dynamic model. Suppose we let the concentration of the subgroups represent the population understudy with unit volume, mm^3, then, by the inscription of Figure 1, we derive the following definitions: T_u - uninfected $CD4^+$ T cell count, T_i - infected $CD4^+$ T cells (by both viruses - viral load and parasitoid-pathogen), I_T - infected $CD4^+$ T cells receiving treatment and A_p - full-blown AIDS population, represent the biological interaction of the variables with $G_i, i=1,2$, sandwiched in between T_u, T_i and I_T, as two latent time-delay immunity chambers.

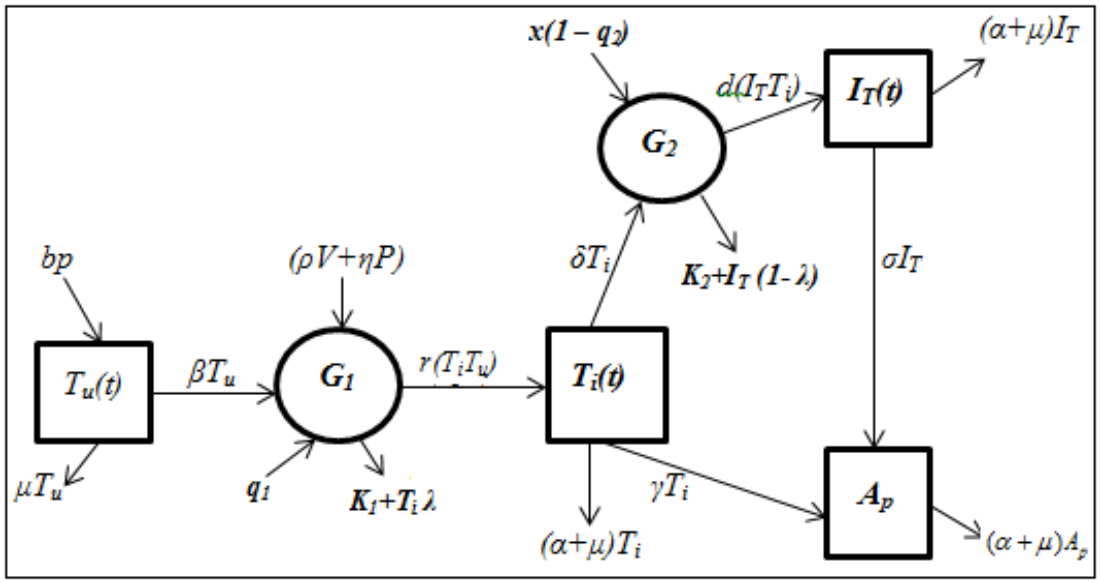


Figure 1. Schematic HIV-pathogen infection dynamics with two time-delay latent chambers

The dynamic physiology of the model is then represented by the following differential derivations:

$$\frac{dT_u}{dt} = b_p - \beta T_u - G_1 T_u - r(\mathrm{T}_i \mathrm{T}_u) - \mu T_u \qquad (2.1)$$

where, $G_1 = \frac{q_1(\rho \mathrm{V} + \eta \mathrm{P})}{K_1 + T_i \lambda}$. Then, equation (2.1) can be written as

$$\frac{dT_u}{dt} = b_p - \beta T_u - \frac{q_1(\rho V + \eta P)T_u}{K_1 + T_i \lambda} - r(T_i T_u) - \mu T_u \qquad (2.2)$$

As the T-cells becomes infected, the epidemiological interaction is given by

$$\begin{aligned} \frac{dT_i}{dt} &= \beta T_u + G_1 T_i + r(\mathrm{T}_i \mathrm{T}_u) \\ &\quad - (\delta + \gamma + \alpha + \mu) T_i - G_2 T_i - d(\mathrm{I}_T \mathrm{T}_i) \end{aligned} \qquad (2.3)$$

where $G_2 = \frac{x(1-q_2)}{K_2 + I_T(1-\lambda)}$ and with G_1 known, equation (2.3), is derived as:

$$\begin{aligned} \frac{dT_i}{dt} &= \beta T_u + \frac{q_1(\rho V + \eta P)T_i}{K_1 + T_i \lambda} + r(T_i T_u) \\ &\quad - (\delta + \gamma + \alpha + \mu) T_i - \frac{x(1-q_2)T_i}{K_2 + I_T(1-\lambda)} - d(I_T T_i) \end{aligned} \qquad (2.4)$$

Applying G_2, as treatment chamber to the infected T-cells, we have,

$$\frac{dI_T}{dt} = \delta T_i + \frac{x(1-q_2)I_T}{K_2 + I_T(1-\lambda)} + d(I_T T_i) - (\sigma + \alpha + \mu) I_T. \qquad (2.5)$$

Finally, acute blown AIDS due to lack of treatment application and gradual maturity from cells exposed to treatment lead to the derivation,

$$\frac{dA_p}{dt} = \gamma T_i + \sigma I_T - (\alpha + \mu)\mathrm{A}_p \qquad (2.6)$$

with all initial conditions given as:

$$T_u(0) = T_{(\mathrm{u})0}, \mathrm{T}_i(0) = T_{(\mathrm{i})0}, \mathrm{I}_T(0) = I_{(\mathrm{T})0}, \mathrm{A}_p(0) = A_{(\mathrm{p})0}$$

and satisfying the biological variables and parameters values as define in Table 1 below:

Table 1. Variables and parameters for optimal control pair treatment

Dependent variables	**Initial values**
T_u Uninfected CD4$^+$ T cells count	$0.6mm^{-3}$
T_i Infected CD4$^+$ T cells by viruses	$0.2mm^{-3}$
I_T Infected CD4$^+$ T cells receiving treatment	$0.15mm^{-3}$
A_p Full-blown AIDS population	$0.05mm^{-3}$
Parameters and Constants	Values
b_p natural source term for uninfected CD4$^+$ T cells	$10mm^{-3}d^{-1}$
μ natural death rate of uninfected CD4$^+$ T cells	$0.02d^{-1}$
α death rate of infected CD4$^+$ T cells	$0.7d^{-1}$
β probability of T_u cells becoming infected by viruses	$5d^{-1}$
ρ rate CD4$^+$ T cells becoming infected by free virus, V	$2.5d^{-1}$
η rate of CD4$^+$ T cells becoming infected by pathogen, P	$1.0mm^3d^{-1}$
K_1 half saturation constant for T_u	$5mm^3d^{-1}$
K_2 half saturation constant for T_i	$30d^{-1}$
λ latent period for T_i cells	$0.6mm^{-3}d^{-1}$
$(1-\lambda)$ latent period for I_T cells	$0.4mm^{-3}d^{-1}$
r rate at which T_u cells become latently infected	$0.04d^{-1}$
d rate at which T_i cells become actively infectious, I_T	$0.42d^{-1}$
δ probability of active infectious receiving treatment	0.5
γ probability of T_i cells becoming full-blown AIDS	2.0
σ probability of I_T cells becoming full-blown AIDS	0.004
x input rate of external viral other than T- cells	$2d^{-1}$
q_1 immune boosting control function for CD4+ T cells	0.02
$(1-q_2)$ immune suppressing control function for CD4+ T cells	0.5
ϕ_1 optimal weight factor on q_1 for viruses (V,P) at T_iT_u	12
ϕ_2 optimal weight factor on $(1-q_2)$ for viruses (V,P) at I_TT_i	3

Therefore, the basic model equation derived as in equations (2.2), (2.4), and (2.5) and (2.6), are as summarized in Table 2 below:

Table 2. Epidemiological derivatives of the system model

variable	Derivatives	Eqn. no.
T_u	$\frac{dT_u}{dt} = b_p - \beta T_u - \frac{q_1(\rho \mathrm{V} + \eta \mathrm{P})T_u}{K_1 + T_i\lambda} - r(\mathrm{T_i T_u}) - \mu T_u$	(2.2)
T_i	$\frac{dT_i}{dt} = \beta T_u + \frac{q_1(\rho \mathrm{V} + \eta \mathrm{P})T_i}{K_1 + T_i\lambda} + r(\mathrm{T_i T_u}) - (\delta + \gamma + \alpha + \mu)T_i - \frac{x(1-q_2)T_i}{K_2 + I_T(1-\lambda)} - d(\mathrm{I_T T_i})$	(2.4)
I_T	$\frac{dI_T}{dt} = \delta T_i + \frac{x(1-q_2)I_T}{K_2 + I_T(1-\lambda)} + d(I_T T_i) - (\sigma + \alpha + \mu)I_T$	(2.5)
A_p	$\frac{dA_p}{dt} = \gamma T_i + \sigma I_T - (\alpha + \mu)\mathrm{A}_p$	(2.6)

Equations (2.2), (2.4), (2.5) and (2.6), constitute the model equations and its state space is given by

$$\mathbb{R}^4_+ = \left\{(t_u, t_i, \mathrm{i}_T, \mathrm{a}_p) \in \mathbb{R}^4 : t_u \geq 0, t_i \geq 0, \mathrm{i}_T \geq 0, \mathrm{a}_p \geq 0, \right\} \quad (2.5')$$

Thus, equations (2.2), (2.4), (2.5) and (2.6), with the condition (2.5'), is the standard model for the diagnosis of two infectious variables with multiple (two) treatment factors, enhanced by two latency time-delay immunity chambers $G_i, i = 1,2$. These chambers are the passive and active temporal delay reservoirs and not epidemiological transmission outlets. It serves as the temporal delay treatment compartments adequately enough to accommodate the asymptomatic stage of viruses infectivity, children yet to develop active infectious stage (at passive chamber, G_1); enable study of viremia levels, early stigmatization and the impoverished society (at the active chamber, G_2), [26,27].

The epidemiological description of equations (2.2), (2.4), (2.5) and (2.6), are viewed from the fact that, in equation (2.2), $b_p - \beta T_u$ is the source/proliferation of uninfected CD4$^+$ T cells, $-q_1(\rho V + \eta P)T_u / K_1 + T_i\lambda - r(T_i T_u)$, is the proliferation of latently infected CD4$^+$ T cells at asymptomatic stage under immune boosting chemotherapy q_1 and having limiting factors $-(\rho + \eta) - r$, $-r(T_i T_u)$ is the gross loss by infection due to viruses. The death rate here is the natural death given by $-\mu T_u$.

In equation (2.4), the proliferated uninfected CD4$^+$ T cells become the source for latently infected T-cells following its interaction with viruses and are given by $\beta T_u + q_1(\rho V + \eta P)T_i / K_1 + T_i\lambda + r(T_i T_u)$. The sum of infection transmission, death rate due to infection and natural loss rate are given by $-(\delta + \gamma + \alpha + \mu)T_i$. The term $-x(1-q_2)T_i / K_2 + I_T(1-\lambda)$ is the probability at which progressing latently infected CD4$^+$ T cells that become actively infectious T-cells are subjected to suppressing chemotherapy treatment and having $-d(I_T T_i)$ as rate of treatment while becoming actively infectious.

Similarly, in equation (2.5), the first term $\delta T_i + x(1-q_2)I_T / K_2 + I_T(1-\lambda)$ accounts for the amount of actively infectious CD4$^+$ T cells that are been subjected to suppressing chemotherapy, occasioned by external source of infection, x and having treatment rate of $d(I_T T_i)$ as the third term. The last term defined the sum transmission rate of active infected CD4$^+$ T-cells to full blown AIDS, infection clearance rate due to chronism and occasioned natural death rate.

Finally, from equation (2.6), the first term γT_i, denote progression of latent infected T-cells that transmit to full-blown AIDS with only immune boosting chemotherapy treatment, while the second term σI_T - accounts for the actively infected T-cells that were exposed to dual treatment but gradually transmitted to full-blown AIDS. The model life-cycle terminates following death rate due to chronic infection as well as natural death rate designated by $-(\alpha + \mu)A_p$.

2.2. An Optimal Control Problem

If we decide to take into account the epidemiological dynamics of infections, then the optimal values of the control variables $q_i, i = 1,2$ (optimal control treatments), can be estimated by transmutation of the system model (2.2), (2.4), (2.5) and (2.6), as an optimal control problem. This goal is achieved by the introduction of objective functional, which maximize the control system define by

$$F(q_1, q_2) = \int_{t_0}^{t_f} \left[T_u - (\phi_1(q_1(\mathrm{t}))^2 + \phi_2(q_2(t))^2) \right] dt \quad (2.7)$$

where $\phi_i, i = 1,2$ represents the optimal "weight factors" on the optimal cost ascertained by the optimal benefit based on the CD4$^+$ T cells count concentration and which determines the toxicity of treatment control functions q_1, q_2, respectively [9]. Thus, equation (2.7), is said to be characterized by the optimal control pair q_1^*, q_2^*, define by the limit

$$\max_{0 \leq q_i \leq 1} F(q_1, q_2) = F(q_1^*, q_2^*).$$

We at once observe from the above expression, that

$$F(q_1^*, q_2^*) = \{F(q_1, q_2) \,|\, (q_1, q_2) \in S\}$$

where,

$$S = \left\{ \begin{matrix} (q_1, q_2) \mid q_i measurable, \\ b_i \le q_i \le c_i, t \in [t_0, t_f], i = 1, 2 \end{matrix} \right\},$$

is considered admissibility limit of the model measurable function. Therefore, infection is bound to be endemic if $q_i = 0$, due to insufficient chemotherapy and if $q_i = 1$, representing maximal use of chemotherapy, infection is bound to be under control. Thus, maximal cost of chemotherapy is given by $(q_i)^2$ and the following proposition holds.

Proposition 1.

Assume there exist drug hazardous side effect, then, the inequality of the introduced optimal weight factors $\phi_i, i = 1, 2$ such that $0 \le b_i \le \phi_i(t) \le c_i < 1, i = 1, 2$ holds.

Next, we show using the following theorem, that the model variables, which represent the human immune system are all compactible and non-negative integers.

Theorem 1.

Given the model equations (2.2), (2.4), (2.5) and (2.6), let

$$\omega = \left\{ \begin{matrix} (t_{(u)}, i_{(VP)}, i_{(T)}, a_{(vp)} \in \mathbb{R}_+^4 : t_{(u)}(0) > 0, \\ i_{(VP)}(0) > 0, i_{(T)}(0) > 0, a_{(vp)}(0) > 0 \end{matrix} \right\}.$$

Then, the positivity of the solution $\left\{ (t_{(u)}(t), i_{(VP)}(t), i_{(T)}(t), a_{(vp)}(t) \right\}$ of the system (2.2), (2.4), (2.5) and (2.6), are guarantee and are compactible for all $t \ge 0$ [28].

Proof.

Consider the model equations (2.2), (2.4), (2.5) and (2.6), we differentiate each equation with respect to their variables, i.e.

From equation (2.2), we have

$$\frac{dT_u}{dt} = b_p - \beta T_u - \frac{q_1(\rho \mathrm{V} + \eta \mathrm{P})T_u}{K_1 + T_i \lambda} - r(\mathrm{T}_i \mathrm{T}_u) - \mu T_u.$$

Differentiating with respect to T_u, we have

$$\frac{dT_{(u)}}{dt} \ge -(\beta + \mu)T_{(u)}, \frac{dT_{(u)}}{dt} + (\beta + \mu)T_{(u)} \ge 0.$$

The inequality here, means that T_u is finite and positive or $T_u = +\infty$, since $t \ge 0$, (from the theorem).

Finding the integrating factor,

$$IF = e^{\int (\beta + \mu) dt} = e^{(\beta + \mu)t}.$$

Multiplying by the integrating factor, we have

$$e^{(\beta + \mu)t} \left\{ T_u' + (\beta + \mu)T_u \right\} \ge 0.$$

Rewrite the left hand side of the equation

$$\frac{d}{dt} \left(e^{(\beta + \mu)t} T_u \right) \ge 0.$$

Integrating both sides leads to

$$e^{(\beta + \mu)t} T_u(t) = C.$$

Divide through by the integrating factor, we have

$$T_u(\mathrm{t}) = \mathrm{C} e^{(\beta + \mu)t}.$$

Applying the initial conditions: at

$$t = 0, \mathrm{T}_u(t) = T_u(0). \mathrm{T}_u(0) \ge C$$

$$T_u(t) \ge T_u(0) e^{(\beta + \mu)t} \ge 0, t \ge 0.$$

When $t \to \infty, \mathrm{T}_u(t) \ge 0$.

Therefore,

$$T_u(t) \ge 0.$$

From equation (2.4), we set

$$\frac{dT_i}{dt} = \beta T_u + \frac{q_1(\rho \mathrm{V} + \eta \mathrm{P})T_i}{K_1 + T_i \lambda} + r(\mathrm{T}_i \mathrm{T}_u)$$

$$-(\delta + \gamma + \alpha + \mu)T_i - \frac{x(1 - q_2)T_i}{K_2 + I_T(1 - \lambda)} - d(\mathrm{I}_T \mathrm{T}_i).$$

$$\frac{dI_{(vp)}}{dt} \ge -(\delta + \gamma + \alpha + \mu) I_{(vp)}.$$

Integrating both sides, we have

$$\int \frac{dI_{(vp)}}{I_{(vp)}} \ge \int -(\delta + \gamma + \alpha + \mu) dt.$$

Taking integrating factor, $IF = e^{-(\delta + \gamma + \alpha + \mu)t}$ we, have

$$I_{(vp)}(t) \ge I_{(vp)}(0) e^{-(\delta + \gamma + \alpha + \mu)t} \ge 0, t \ge 0.$$

Applying initial conditions: at

$$t = 0, \mathrm{I}_{vp}(t) \ge I_{vp}(0).$$

When $t \to \infty, \mathrm{I}_{vp}(t) \ge 0$.

Taking on equation (2.5), we have,

$$\frac{dI_T}{dt} = \delta T_i + \frac{x(1 - q_2)I_T}{K_2 + I_T(1 - \lambda)} + d(I_T T_i) - (\sigma + \alpha + \mu)I_T$$

$$\frac{dI_T}{dt} \ge -(\sigma + \alpha + \mu) I_T$$

$$\frac{dI_T}{I_T} \ge -(\sigma + \alpha + \mu) dt$$

$$\int \frac{dI_T}{I_T} \ge -\int (\sigma + \alpha + \mu) dt.$$

Therefore,

$$I_T(t) \ge I_T(0) e^{-(\sigma + \alpha + \mu)t} \ge 0, t \ge 0.$$

Finally, from equation (2.6), we have,

$$\frac{dA_p}{dt} = \gamma T_i + \sigma I_T - (\alpha + \mu) \mathrm{A}_p$$

$$\frac{dA_{(vp)}}{dt} \ge -(\alpha + \mu) A_{(vp)}$$

$$\frac{dA_{(vp)}}{A_{(vp)}} \ge -(\alpha + \mu) dt$$

$$\int \frac{dA_{(vp)}}{A_{(vp)}} \geq -\int (+\alpha+\mu)\,dt.$$

Therefore,

$$A_{(vp)}(t) \geq A_{(vp)}(0)e^{-(\alpha+\mu)t} \geq 0, t \geq 0.$$

Hence, model variables are all non-negative and this complete the proof.

3. Existence and Uniqueness of Optimal Control Pair Treatment with Latent Chambers

In section two, we have proved that the variables of model are non-negative and compactible. Next, we justify the existence and uniqueness of optimal control pair chemotherapy treatment for the model in the presence of two temporal latency chambers. Here lies the novelty of the present model formulation.

3.1. Existence of Optimality Control Pair

The existence of the model system consisting of two infectious variables under optimal control pair and clinically administered via two control latent chambers can be prove by juxtaposing the boundedness of the solution of the system, given a finite time interval. Since we consider the boundedness of the solution, then there exists super-solution $\overline{T}_u, \overline{I}_{(vp)}, \overline{I}_T$, and $\overline{A}_{(vp)}$ satisfying

$$\begin{aligned} &\frac{d\overline{T}_u}{dt} = b_p - \frac{[q_1(t)]\overline{T}_u}{K_1+\overline{T}_i}, \frac{d\overline{T}_i}{dt} = \frac{[q_1(t)]\overline{T}_i}{K_1+\overline{T}_i} - \frac{x\overline{T}_i}{K_2+\overline{I}_T} \\ &\frac{d\overline{I}_T}{dt} = \frac{x\overline{T}_i}{K_2+\overline{I}_T}, \frac{d\overline{A}_p}{dt} = \gamma\overline{T}_i + \sigma\overline{I}_T \end{aligned} \quad (2.8)$$

which are bounded on a finite time interval. The existence is therefore established by applying results from ([1], Th. 2.1, p. 4-5; [29], Th. 4.1, p. 68-69).

Theorem 2 Consider the optimal control problem with system equations (2.2), (2.4), (2.5) and (2.6). Then using proposition 1, there exists an optimal control pair $\vec{q}^{\,*} = (q_1^*, q_2^*) \in S$, such that

$$\max_{(q_1,q_2)\in S} F(q_1,q_2) = F(q_1^*, q_2^*)$$

maximizes the objective functional $F(q_1,q_2)$.

Proof. We prove by showing that the following conditions hold:

i. All the initial conditions with the controls q_1 and q_2 such that q_i, i=1,2 is a Lebesgue-integrable function on $[t_0,t_f]$ with values in the admissible control set S, such that the state system is satisfied and not empty.
ii. The admissible control set S, is closed and convex.
iii. The right hand side (RHS) of the state system is continuous, is bounded above by a sum of the bounded control and the state variables; and can be written as a linear function of q_i, i = 1, 2 with coefficients depending on assumption 1 and on the state variables.
iv. The integrand of the objective functional is concave on the admissible S, of the control set.
v. There exists consistence $c_1, c_2 > 0$ and $\beta > 1$, such that the integrand $L(T_u, q_1, q_2)$ of the objective functional satisfies

$$L(T_u, q_1, q_2) \leq c_2 - c_1(|q_1|^2 + |q_2|^2)^{\beta/2}.$$

To verifying these conditions, we invoke an existence result of [[30], Thm. 9.2.1], for the existence of the state system (2.2), (2.4), (2.5) and (2.6), with bounded coefficients, which gives condition (i). We note that the solutions are bounded. By definition, our control set is closed and convex, and then, satisfies condition (ii). Since our state system is bilinear in q_1, q_2, the RHS of (2.2), (2.4), (2.5) and (2.6), satisfies condition (iii), using the boundedness of the solutions. In addition, the integrand of the objective functional $T_u - (\phi_1(q_1(t))^2 + \phi_2(q_2(t))^2)$ is concave on the admissible control set S. Finally, the completeness of the existence of solution of the optimal control is the fact that

$$T_u - \left[\phi_1(q_1(t))^2 + \phi_2(q_2(t))^2\right] \leq c_2 - c_1\left(|q_1|^2 + |q_2|^2\right)$$

where c_2 depends on the upper bound on T_u, and $c_1 > 0$ since $\phi_1, \phi_2 > 0$. Then this completes the proof.

Now, since we have shown that solution of optimal control problem of the system exist, we then have to derive the optimality control strategy of the system.

3.2. Model Optimality Control Strategy

In sub-section 3.1, we had established the existence of the model optimality control pair, aimed at the maximization of the objective functional (2.7), subject to model equations (2.2), (2.4), (2.5) and (2.6). Then, we now define the system optimality control strategy. We proceed by driving the necessary conditions for the optimal control strategy using the Pontryagin's Maximum Principle define by the Lagrangian:

$$\begin{aligned} L = {} & [T_u - (\phi_1 q_1^2 + \phi_2 q_2^2)] + \ell_1[b_p - \beta T_u(t) \\ & - \frac{q_1(\rho V(t) + \eta P(t))T_u(t)}{K_1 + T_i(t)\lambda} - r(T_i(t)T_u(t)) - \mu T_u(t)] \\ & + \ell_2[\beta T_u(t) + \frac{q_1(\rho V(t) + \eta P(t))T_i(t)}{K_1 + T_i(t)\lambda} + r(T_i(t)T_u(t)) \\ & - (\delta + \gamma + \alpha + \mu)T_i(t) - \frac{x(1-q_2)T_i(t)}{K_2 + I_T(1-\lambda)} - d(I_T(t)T_i(t))] \\ & + \ell_3[\delta T_i(t) + \frac{x(1-q_2)T_i(t)}{K_2 + I_T(1-\lambda)} + d(I_T(t)T_i(t)) \\ & - (\sigma + \alpha + \mu)I_T(t)] + \ell_4[\gamma T_i(t) + \sigma I_T(t) - (\alpha+\mu)A_p(t)] \\ & + z_{11}(t)(c_1 - q_1) + z_{12}(t)(q_1 - b_1) \\ & + z_{21}(t)(c_2 - q_2) + z_{22}(t)(q_2 - b_2) \end{aligned}$$

where $z_{11}(t), z_{12}(t), z_{21}(t), z_{22}(t) \geq 0$ is penalty multiplier satisfying $z_{11}(t)(c_1 - q_1) = 0, z_{12}(t)(q_1 - b_1) = 0$ at the optimal q_1* and $z_{21}(t)(c_2 - q_2) = 0, z_{22}(t)(q_2 - b_2) = 0$ at the optimal q_2*

Theorem 3.

Let q_1^*, q_2^* be the optimal control and having the solutions $T_u^*, T_i^*, I_T^*, A_p^*$, for the corresponding basic model (2.2), (2.4), (2.5) and (2.6). Then, there exist adjoint variables $\ell_1, \ell_2, \ell_3, \ell_4$ satisfying

$$\ell_1' = -1 + \ell_1[\beta + \frac{k_1 q_1(\rho V + \eta P)}{K_1 + T_i^*(t)\lambda} - rT_i^*(t) - \mu] - \ell_2[\beta + rT_i^*(t)]$$

$$\ell_2' = \ell_1[T_u^*(t)] - \ell_2[\frac{k_1 q_1(\rho V + \eta P)}{K_1 + T_i^*(t)\lambda} + r(T_u^*(t)) - (\delta + \gamma + \alpha + \mu) - \frac{k_2 x(1-q_2)}{K_2 + I_T^*(t)(1-\lambda)} - d(I_T^*)] + \ell_3[\delta + d(I_T^*)] + \ell_4\gamma$$

$$\ell_3' = \ell_3[\frac{k_2 x(1-q_2)}{K_2 + I_T^*(t)(1-\lambda)} + d(T_i^*(t)) - (\sigma + \alpha + \mu)] + \ell_4\sigma$$

$$\ell_4' = -1 + \ell_4(\alpha + \mu)$$

and having $\ell_i(t_f) = 0, i = 1,..,4$, as transversality conditions. In addition,

$$q_1*(t) = \min\left\{\max\left\{b_1, \frac{1}{2\phi_1}\left(\ell_1 T_u*(t)\right)\right\}, c_1\right\}$$

$$q_2*(t) = \min\left\{\max\left\{b_2, \left(\frac{\ell_2 + \ell_3 + \ell_4}{2\phi_2} \times \frac{\left(T_i^*(t) + I_T^*(t) + A_p^*(t)\right)}{\left(K_1 + K_2\right)\left[\begin{matrix} T_i^*(t) + I_T^*(t) \\ + A_p^*(t) \end{matrix}\right]}\right)\right\}, c_2\right\}.$$

Proof.

From the above given Lagrangian, we differentiate w.r.t. T_u, T_i, I_T, A_p, for the using the Pontryagin's Maximum Principle [31], to obtain the standard adjoint equations and the transversality conditions. The preceding adjoint variable of the system is obtained as:

$$\ell_1' = -\frac{\partial L}{\partial T_u} = -1 + \ell_1[\beta + \frac{k_1 q_1(\rho V + \eta P)}{K_1 + T_i^*(t)\lambda} - rT_i^*(t) - \mu] - \ell_2[\beta + rT_i^*(t)] \quad (2.9)$$

$$\ell_2' = -\frac{\partial L}{\partial T_i} = \ell_1[T_u^*(t)] - \ell_2[\frac{k_1 q_1(\rho V + \eta P)}{K_1 + T_i^*(t)\lambda} + r(T_u^*(t)) - (\delta + \gamma + \alpha + \mu) - \frac{k_2 x(1-q_2)}{K_2 + I_T^*(t)(1-\lambda)} - d(I_T^*)] + \ell_3[\delta + d(I_T^*)] + \ell_4\gamma \quad (2.10)$$

$$\ell_3' = -\frac{\partial L}{\partial I_T} = \ell_3[\frac{k_2 x(1-q_2)}{K_2 + I_T^*(t)(1-\lambda)} + d(T_i^*(t)) - (\sigma + \alpha + \mu)] + \ell_4\sigma \quad (2.11)$$

$$\ell_4' = -\frac{\partial L}{\partial A_p} = -1 + \ell_4(\alpha + \mu). \quad (2.12)$$

The result that follows is the optimality equation of the system [32] derived as:

$$\frac{\partial L}{\partial q_1} = -2\phi_1 q_1^*(t) + \ell_1 T_u^* - z_{11}(t) + z_{12}(t) = 0 \text{ at } q_1^*$$

$$\frac{\partial L}{\partial q_2} = -2\phi_2 q_2^*(t) + (\ell_2 + \ell_3 + \ell_4)\left[-\frac{T_i^*(t) + I_T^*(t) + A_p^*(t)}{(K_1 + K_2)[T_i^*(t) + I_T^*(t) + A_p^*(t)]}\right] - z_{21}(t) + z_{22}(t) = 0 \text{ at } q_2^*.$$

Therefore, the optimality control q_1^*, q_2^* are obtain as

$$q_1^*(t) = \frac{1}{2\phi_1}\left[\ell_1 T_u^*(t) - z_{11}(t) + z_{12}(t)\right] \quad (2.13)$$

$$q_2^*(t). = \frac{1}{2\phi_2}\left[\begin{matrix} -\left(\ell_2 + \ell_3 + \ell_4\right) \\ \times \dfrac{T_i^*(t) + I_T^*(t) + A_p^*(t)}{(K_1 + K_2)[T_i^*(t) + I_T^*(t) + A_p^*(t)]} \\ -z_{21}(t) + z_{22}(t) \end{matrix}\right] \quad (2.14)$$

It thus follows from the point of the boundedness on the control that,

$$q_1^* = \begin{cases} \frac{1}{2\phi_1}\ell_1 T_u^*(t) & if \quad b_1 < \frac{1}{2\phi_1}\ell_1 T_u(t) < c_1 \\ b_1 & if \quad \frac{1}{2\phi_1}\ell_1 T_u^*(t) \leq b_1 \\ c_1 & if \quad \frac{1}{2\phi_1}\ell_1 T_u^*(t) \geq c_1 \end{cases}.$$

i.e. q_1^* is compactly notated as

$$q_1* = \min\left\{\max\left\{b_1, \frac{1}{2\phi_1}\left(\ell_1 T_u^*(t)\right)\right\}, c_1\right\}.$$

In a similar approach,

$$q_2^* = \begin{cases} -\left(\dfrac{\left(\ell_2+\ell_3+\ell_4\right)}{2\varphi_2} \times \dfrac{T_i^*(t)+I_T{}^*(t)+A_p{}^*(t)}{(K_1+K_2)[T_i^*(t)+I_T{}^*(t)+A_p{}^*(t)]} \right) \\ \quad if\ b_2 < -\left(\dfrac{\left(\ell_2+\ell_3+\ell_4\right)}{2\varphi_2} \times \dfrac{T_i^*(t)+I_T{}^*(t)+A_p{}^*(t)}{(K_1+K_2)\begin{bmatrix} T_i^*(t)+I_T{}^*(t) \\ +A_p{}^*(t) \end{bmatrix}} \right) < c_2 \\ b_2 \\ \quad if\ -\left(\dfrac{\left(\ell_2+\ell_3+\ell_4\right)}{2\varphi_2} \times \dfrac{T_i^*(t)+I_T{}^*(t)+A_p{}^*(t)}{(K_1+K_2)\begin{bmatrix} T_i^*(t)+I_T{}^*(t) \\ +A_p{}^*(t) \end{bmatrix}} \right) \le b_2 \\ c_2 \\ \quad if\ -\left(\dfrac{\left(\ell_2+\ell_3+\ell_4\right)}{2\varphi_2} \times \dfrac{T_i^*(t)+I_T{}^*(t)+A_p{}^*(t)}{(K_1+K_2)\begin{bmatrix} T_i^*(t)+I_T{}^*(t) \\ +A_p{}^*(t) \end{bmatrix}} \right) \ge c_2 \end{cases}$$

with compact form as:

$$q_2{}^* = \min\left\{\max\left\{b_2, -\left(\dfrac{\left(\ell_2+\ell_3+\ell_4\right)}{2\varphi_2} \dfrac{T_i^*(t)+I_T{}^*(t)+A_p{}^*(t)}{(K_1+K_2)\begin{bmatrix} T_i^*(t)+I_T{}^*(t) \\ +A_p{}^*(t) \end{bmatrix}} \right)\right\}, c_2\right\}.$$

By definition, optimization control system is a constituents of the state system couple with the adjoint system with the initial and transversality conditions together with the characterization of the optimal control pair,

$$q_1{}^* = \min\left\{\max\left\{b_1, \frac{1}{2\phi_1}\left(\ell_1 T_u{}^*(t)\right)\right\}, c_1\right\} \quad (2.15)$$

$$q_2{}^* = \min\left\{\max\left\{b_2, -\left(\dfrac{\left(\ell_2+\ell_3+\ell_4\right)}{2\varphi_2} \cdot \dfrac{T_i^*(t)+I_T{}^*(t)+A_p{}^*(t)}{(K_1+K_2)\begin{bmatrix} T_i^*(t) \\ +I_T{}^*(t) \\ +A_p{}^*(t) \end{bmatrix}} \right)\right\}, c_2\right\}. \quad (2.16)$$

Hence, a complete representation of the optimality system is derived by substituting equations (2.15) and (2.16) into the original model equations (2.2), (2.4), (2.5) and (2.6), as seen below:

$$\frac{dT_u(t)}{dt} = b_p - \beta T_u(t) - \frac{\min\left\{\max\left\{b_1, \frac{1}{2\phi_1}\left(\ell_1 T_u(t)\right)\right\}, c_1\right\}(\rho V + \eta P)T_u(t)}{K_1 + T_i(t)\lambda} - r(T_i(t)T_u(t)) - \mu T_u(t)$$

$$\frac{dT_i(t)}{dt} = \beta T_u(t) + \frac{\left(\min\left\{\max\left\{b_1, \frac{1}{2\phi_1}\left(\ell_1 T_u(t)\right)\right\}, c_1\right\} \times (\rho V + \eta P)T_i(t)\right)}{K_1 + T_i(t)\lambda} + r(T_i(t)T_u(t)) - (\delta + \gamma + \alpha + \mu)T_i(t) - \frac{x\left[1 - \min\left\{\max\left\{b_2, -\left(\dfrac{\left(\ell_2+\ell_3+\ell_4\right)}{2\phi_2} \dfrac{T_i(t)+I_T(t)+A_p(t)}{(K_1+K_2)\begin{bmatrix} T_i(t) \\ +I_T(t) \\ +A_p(t) \end{bmatrix}} \right)\right\}, c_2\right\}\right]T_i(t)}{K_2 + I_T(t)(1-\lambda)} - d(I_T(t)T_i(t))$$

$$\frac{dI_T(t)}{dt} = \delta T_i(t) + \frac{x\left[1 - \min\left\{\max\left\{b_2, -\left(\dfrac{\left(\ell_2+\ell_3+\ell_4\right)}{2\phi_2} \cdot \dfrac{\begin{pmatrix} T_i(t)+I_T(t) \\ +A_p(t) \end{pmatrix}}{\begin{pmatrix} K_1 \\ +K_2 \end{pmatrix}\begin{bmatrix} T_i(t) \\ +I_T(t) \\ +A_p(t) \end{bmatrix}} \right)\right\}, c_2\right\}\right]I_T(t)}{K_2 + I_T(t)(1-\lambda)} + d(I_T(t)T_i(t)) - (\sigma + \alpha + \mu)I_T(t)$$

$$\frac{dA_p}{dt} = \gamma T_i + \sigma I_T - (\alpha + \mu)\mathrm{A}_p$$

$$\ell_1{}' = -1 + \ell_1[\beta + \frac{k_1\left[\min\left\{\max\left\{b_1, \frac{1}{2\phi_1}\left(\ell_1 T_u(t)\right)\right\}, c_1\right\}\right](\rho V + \eta P)}{K_1 + T_i(t)\lambda} - rT_i(t) - \mu] - \ell_2[\beta + rT_i(t)]$$

$$\ell_2{}' = \ell_1[T_u(t)]$$

$$-\ell_2[\frac{k_1\left[\min\left\{\max\left\{b_1,\frac{1}{2\phi_1}\left(\ell_1 T_u(t)\right)\right\},c_1\right\}\right](\rho V+\eta P)}{K_1+T_i(t)\lambda}$$

$$+r(T_u(t))-(\delta+\gamma+\alpha+\mu)$$

$$\frac{k_2 x\left[1-\min\left\{\max\left\{b_2,-\left(\frac{(\ell_2+\ell_3+\ell_4)}{2\phi_2}\frac{T_i(t)+I_T(t)+A_p(t)}{(K_1+K_2)\begin{bmatrix}T_i(t)\\+I_T(t)\\+A_p(t)\end{bmatrix}}\right)\right\},c_2\right\}\right]}{K_2+I_T(t)(1-\lambda)}$$

$$-d(I_T(t))]+\ell_3[\delta+d(I_T(t))]+\ell_4\gamma$$

$$\ell_3{}' = \ell_3\times$$

$$[\frac{k_2 x\left[1-\min\left\{\max\left\{b_2,-\left(\frac{(\ell_2+\ell_3+\ell_4)}{2\phi_2}\cdot\frac{\left(\begin{matrix}T_i(t)+I_T(t)\\+A_p(t)\end{matrix}\right)}{\left(\begin{matrix}K_1\\+K_2\end{matrix}\right)\begin{bmatrix}T_i(t)\\+I_T(t)\\+A_p(t)\end{bmatrix}}\right)\right\},c_2\right\}\right]}{K_2+I_T(t)(1-\lambda)} \quad (2.17)$$

$$+d(T_i(t))-(\sigma+\alpha+\mu)]+\ell_4\sigma$$

$$\ell_4{}' = -1+\ell_4(\alpha+\mu)$$

where, $\ell_1(t_f)=\ell_2(t_f)=\ell_3(t_f)=\ell_4(t_f)=0$ and $T_u(0)=T_{(u)0}$, $T_i(0)=T_{(i)0}$, $I_T(0)=I_{(T)0}$, and

$$A_p(0)=A_{(p)0}..$$

3.3. Uniqueness of Optimality Control Strategy

We had started our proof with the showing of the positivity of the model variables, followed by the existence of the model optimal control strategy. Then, we need to show that the control strategy is unique. Lemma 1 below, leads to the explicit proof of the theorem, which ascribes the uniqueness of the control strategy.

Lemma 1. The function $q^*(\upsilon)=(\min(\max(\upsilon,b),c))$ is Lipschitz continuous in υ, where $b<c$ are some fixed positive constants.

Theorem 4. Given the final time t_f sufficiently small, then, the bounded solutions of the optimality system are unique [1,3].

Proof. If $\left(T_u,T_i,I_T,A_p,\ell_1,\ell_2,\ell_3,\ell_3\right)$ and

$$(\overline{T}_u,\overline{T}_i,\overline{I}_T,\overline{A}_p,\overline{\ell}_1,\overline{\ell}_2,\overline{\ell}_3,\overline{\ell}_3)$$

are two separate solutions of the optimization system (2.17), then, we define as follows: let $T_u=e^{\ell t}g$, $T_i=e^{\ell t}m$, $I_T=e^{\ell t}n$, $A_p=e^{\ell t}v$, $\ell_1=e^{\ell t}u$, $\ell_2=e^{\ell t}y$, $\ell_3=e^{\ell t}l$, $\ell_4=e^{\ell t}k$ and $\overline{T}_u=e^{\ell t}\overline{g}$, $\overline{T}_i=e^{\ell t}\overline{m}$, $\overline{I}_T=e^{\ell t}\overline{n}$, $\overline{A}_p=e^{\ell t}\overline{v}$, $\overline{\ell}_1=e^{\ell t}\overline{u}$, $\overline{\ell}_2=e^{\ell t}\overline{y}$, $\overline{\ell}_3=e^{\ell t}\overline{l}$, $\overline{\ell}_4=e^{\ell t}\overline{k}$, where $\ell>0$ is to be chosen. Furthermore, we let

$$q_1{}^*(t)=\min\left\{\max\left\{b_1,\frac{1}{2\phi_1}(ug)\right\},c_1\right\}$$

$$q_2{}^*(t)$$

$$=\min\left\{\max\left\{b_2,-\left(\frac{(y+l+k)}{2\phi_2}\times\frac{m+n+v}{(K_1+K_2)\left[e^{\ell t}m+e^{\ell t}n+e^{\ell t}v\right]}\right)\right\},c_2\right\}$$

and

$$\overline{q}_1{}^*(t)=\min\left\{\max\left\{b_1,\frac{1}{2\phi_1}(\overline{ug})\right\},c_1\right\}$$

$$\overline{q}_2{}^*(t)$$

$$=\min\left\{\max\left\{b_2,-\left(\frac{(\overline{y}+\overline{l}+\overline{k})}{2\phi_2}\times\frac{\overline{m}+\overline{n}+\overline{v}}{(K_1+K_2)[e^{\ell t}\overline{m}+e^{\ell t}\overline{n}+e^{\ell t}\overline{v}]}\right)\right\},c_2\right\}.$$

If we consider each of the terms of the equations (2.17), such that we substitute each of the corresponding system solution i.e. $T_u=e^{\ell t}g$ into the first equation and differentiate, we have,

$$g'+\ell g=b_p-\beta e^{\ell t}g$$

$$-\frac{\min\left\{\max\left\{b_1,\frac{1}{2\phi_1}(ug)\right\},c_1\right\}(\rho V+\eta P)g}{K_1+e^{\ell t}m\lambda} \quad (2.18)$$

$$-re^{\ell t}(mg)-\mu e^{\ell t}g$$

Similarly, for $T_i=e^{\ell t}m$ and putting also, the expressions for $I_T.,\ell_1,..,\ell_4$ into their respective ODE's, of equation (2.17), we have as follows:

$$m'+\ell m=\beta e^{\ell t}g+\frac{\min\left\{\max\left\{b_1,\frac{1}{2\phi_1}(ug)\right\},c_1\right\}(\rho V+\eta P)g}{K_1+e^{\ell t}m\lambda}$$

$$+re^{\ell t}(mg)-(\delta+\gamma+\alpha+\mu)e^{\ell t}m-$$

$$\frac{x\left[1-\min\left\{\max\left\{b_2,-\left(\frac{(y+l+k)}{2\phi_2}\cdot\frac{e^{\ell t}(m+n+v)}{\left[\begin{matrix}(K_1+K_2)\\e^{\ell t}[m+n+v]\end{matrix}\right]}\right)\right\},c_2\right\}\right]m}{K_2+e^{\ell t}n(1-\lambda)} \quad (2.19)$$

$$-de^{\ell t}(nm)$$

$$n'+\ell n=\delta e^{\ell t}m$$

$$+\frac{x\left[1-\min\left\{\max\left\{b_2,-\left(\frac{\frac{(y+l+k)}{2\phi_2}}{\frac{e^{\ell t}(m+n+v)}{(K_1+K_2)e^{\ell t}[m+n+v]}}\right)\right\},c_2\right\}\right]n}{K_2+e^{\ell t}n(1-\lambda)} \quad (2.20)$$

$$+de^{\ell t}(nm)-(\sigma+\alpha+\mu)e^{\ell t}n$$

$$v'+\ell v=\gamma e^{\ell t}m+\sigma e^{\ell t}n-(\alpha+\mu)e^{\ell t}v \quad (2.21)$$

$$-u'+\ell u$$

$$=e^{\ell t}-u[\beta+\frac{k_1\left[\min\left\{\max\left\{b_1,\frac{1}{2\phi_1}(ug)\right\},c_1\right\}\right](\rho V+\eta P)}{K_1+e^{\ell t}m\lambda} \quad (2.22)$$

$$-re^{\ell t}m-\mu]-e^{\ell t}y[\beta+re^{\ell t}m]$$

$$-y'+\ell y=-u[e^{\ell t}g]$$

$$-e^{\ell t}y[\frac{k_1\left[\min\left\{\max\left\{b_1,\frac{1}{2\phi_1}(ug)\right\},c_1\right\}\right](\rho V+\eta P)}{K_1+e^{\ell t}m\lambda}$$

$$+re^{\ell t}m-(\delta+\gamma+\alpha+\mu) \quad (2.23)$$

$$-\frac{k_2x\left[1-\min\left\{\max\left\{b_2,-\left(\frac{\frac{(y+l+k)}{2\phi_2}}{\frac{e^{\ell t}(m+n+v)}{\left[\begin{matrix}(K_1+K_2)\\e^{\ell t}[m+n+v]\end{matrix}\right]}}\right)\right\},c_2\right\}\right]}{K_2+e^{\ell t}n(1-\lambda)}$$

$$-de^{\ell t}n]+e^{\ell t}l[\delta+de^{\ell t}n]+\gamma e^{\ell t}v$$

$$-l'+\ell l$$

$$=-l[\frac{k_2x\left[1-\min\left\{\max\left\{b_2,-\left(\frac{\frac{(y+l+k)}{2\phi_2}}{\frac{e^{\ell t}(m+n+v)}{\left(\begin{matrix}(K_1+K_2)e^{\ell t}\\\times[m+n+v]\end{matrix}\right)}}\right)\right\},c_2\right\}\right]}{K_2+e^{\ell t}n(1-\lambda)} \quad (2.24)$$

$$+de^{\ell t}m-(\sigma+\alpha+\mu)]+\sigma e^{\ell t}k$$

$$-k'+\ell k=e^{\ell t}-k[(\alpha+\mu)]. \quad (2.25)$$

We then proceed to carefully subtract solutions of T_u from $\overline{T}_u$ and progress same for the rest of other state solutions. The obtained results for each are multiplied by appropriate difference of functions and integrated from t_0 to t_f. Finally, we collate all the eight integral equations and by estimation approach, we derive the uniqueness of the model.

Using lemma 1, the first result is obtain as

$$\left|q_1^*(t)-\overline{q}_1^*(t)\right|\le\frac{1}{2\phi_1}\left|ug-\overline{ug}\right|$$

and

$$\left|q_2^*(t)-\overline{q}_2^*(t)\right|$$

$$\le\left|\frac{1}{2\phi_2}\left[\begin{matrix}\frac{(y+l+k)(m+n+v)}{(K_1+K_2)e^{\ell t}[m+n+v]}\\-\frac{(\overline{y}-\overline{l}-\overline{k})(\overline{m}+\overline{n}+\overline{v})}{(K_1+K_2)e^{\ell t}[\overline{m}+\overline{n}+\overline{v}]}\end{matrix}\right]\right|$$

$$\left|q_2^*(t)-\overline{q}_2^*(t)\right|$$

$$\le\left|\frac{1}{2\phi_2}\left[\begin{matrix}\frac{(y+l+k)(m+n+v)}{(K_1+K_2)e^{\ell t}[m+n+v]}\\-\frac{(\overline{y}-\overline{l}-\overline{k})(\overline{m}+\overline{n}+\overline{v})}{(K_1+K_2)e^{\ell t}[\overline{m}+\overline{n}+\overline{v}]}\end{matrix}\right]\right|$$

$$\le\frac{1}{2\phi_2}\left|\frac{\left\{\begin{matrix}(K_1+K_2)[(y+l+k)(m+n+v)\\-(\overline{y}-\overline{l}-\overline{k})(\overline{m}+\overline{n}+\overline{v})]\\+e^{\ell t}\left[(y+l+k)-(\overline{y}+\overline{l}+\overline{k})\right]\end{matrix}\right\}}{\begin{matrix}[(K_1+K_2)e^{\ell t}(m+n+v)]\\[(K_1+K_2)e^{\ell t}(\overline{m}+\overline{n}+\overline{v})]\end{matrix}}\right|.$$

As an illustration of the estimation process, we consider a particular solution of the optimal control i.e. using $\left|q_1^*-\overline{q}_1^*\right|$ estimate for the case of $T_u(t)$. We thus have,

$$\frac{1}{2}(g-\overline{g})^2(t_f)+\ell\int_{t_0}^{t_f}(g-\overline{g})^2dt$$

$$\le\int_{t_0}^{t_f}\left|\begin{matrix}\frac{(\rho V+\eta P)(m+n+v)}{K_1+e^{\lambda t}(m+n+v)}\\-\frac{(\rho V+\eta P)(\overline{m}+\overline{n}+\overline{v})}{K_1+e^{\lambda t}(\overline{m}+\overline{n}+\overline{v})}\end{matrix}\right|\left|g-\overline{g}\right|dt$$

$$+\int_{t_0}^{t_f}\mu\left|g-\overline{g}\right|dt$$

$$+\tau_1\int_{t_0}^{t_f}e^{\lambda t}\left|m-\overline{m}\right|\left|g-\overline{g}\right|dt$$

$$+\tau_2\int_{t_0}^{t_f}e^{\lambda t}\left|n-\overline{n}\right|\left|g-\overline{g}\right|dt$$

$$+\tau_3\int_{t_0}^{t_f}e^{\lambda t}\left|v-\overline{v}\right|\left|g-\overline{g}\right|dt$$

$$+\int_{t_0}^{t_f}\left|q_1^*g-\overline{q}_1^*\overline{g}\right|\left|g-\overline{g}\right|dt.$$

$$\le Q_1\int_{t_0}^{t_f}\left[\begin{matrix}\left|g-\overline{g}\right|^2+\left|m-\overline{m}\right|^2+\left|n-\overline{n}\right|^2\\+\left|v-\overline{v}\right|^2+\left|u-\overline{u}\right|^2\end{matrix}\right]dt$$

$$+Q_2e^{\ell t_f}\int_{t_0}^{t_f}\left[\begin{matrix}\left|g-\overline{g}\right|^2+\left|m-\overline{m}\right|^2\\+\left|n-\overline{n}\right|^2+\left|v-\overline{v}\right|^2\end{matrix}\right]dt,$$

where, the constants Q_1 and Q_2 are coefficient dependent and on bounds of the state and adjoints. The results of the combination of the eight estimates are as follows:

$$\frac{1}{2}(g-\bar{g})^2(t_f)+\frac{1}{2}(m-\bar{m})^2(t_f)+\frac{1}{2}(n-\bar{n})^2(t_f)$$
$$+\frac{1}{2}(v-\bar{v})^2(t_f)+\frac{1}{2}(u-\bar{u})^2(t_0)$$
$$+\frac{1}{2}(y-\bar{y})^2(t_0)+\frac{1}{2}(l-\bar{l})^2(t_0)+\frac{1}{2}(k-\bar{k})^2(t_0)$$
$$+\ell\int_{t_0}^{t_f}\begin{bmatrix}(g-\bar{g})^2+(m-\bar{m})^2+(n-\bar{n})^2+(v-\bar{v})^2\\+(u-\bar{u})^2+(y-\bar{y})^2+(l-\bar{l})^2+(k-\bar{k})^2\end{bmatrix}dt.$$

For a more simplify result, we let $t_0=0$, and the expression becomes:

$$\leq\left(\tilde{Q}_1+\tilde{Q}_2e^{3\ell t}\right)\int_0^{t_f}\begin{bmatrix}(g-\bar{g})^2+(m-\bar{m})^2+(n-\bar{n})^2\\+(v-\bar{v})^2+(u-\bar{u})^2+(y-\bar{y})^2\\+(l-\bar{l})^2+(k-\bar{k})^2\end{bmatrix}dt.$$

Clearly, it is observed from the above expression that

$$\left(\ell-Q_1-Q_2e^{3\ell t}\right)\int_0^{t_f}\begin{bmatrix}(g-\bar{g})^2+(m-\bar{m})^2\\+(n-\bar{n})^2+(v-\bar{v})^2+(u-\bar{u})^2\\+(y-\bar{y})^2+(l-\bar{l})^2+(k-\bar{k})^2\end{bmatrix}dt\leq 0,$$

where Q_1, Q_2 are functions dependent on the coefficients and bounds of $g, m, n, \mathrm{v}, u, y, l, k$.

Hence, for any value of (ℓ), such that $\ell > Q_1+Q_2$ and for all $t_f < \frac{1}{3\ell}\ln\left(\frac{\ell-Q_1}{Q_2}\right)$, then $g=\bar{g}$, $m=\bar{m}$, $n=\bar{n}$, $v=\bar{v}$, $u=\bar{u}, y=\bar{y}, l=\bar{l}, k=\bar{k}$. Therefore, the solution is unique for sufficiently small time.

We refer to [1,3], for related uniqueness proofs under relatively small time interval. The result here affirm most existing results on the basis that small time interval is often a two-point boundary value problem, following from system opposite time orientation and state initial condition with adjoint equations exhibiting final time conditions. More importantly, we deduce from the proof of Thm. 4 that for a model of pair chemotherapy treatment with time-delay immunity chamber, if $\ell < Q_1+Q_2$ for all $t_f < \frac{1}{3\ell}\ln\left(\frac{\ell-Q_1}{Q_2}\right)$ such that $Q_2 \lhd 0$ then, infection is eliminated. On the other hand, if $t_f > \frac{1}{3\ell}\ln\left(\frac{\ell-Q_1}{Q_2}\right)$ such that for $\ell < Q_1+Q_2$ then, infection is endemic and global.

4. Numerical Simulation and Discussion

In line with our theoretical derivations of the system model typically represented by the dynamic optimal control equations (2.17), we illustrate the model using RK4 in Mathcad software application in the following subsection.

4.1. Numerical Simulation

In simulating our model, we consider the parameter values as in Table 1, above, amid predominant parameters such as: $d=0.42$, $\sigma=0.04$, $\gamma=2.0$, $x=2$ and under the transversality conditions ($\ell_1=0.4$, $\ell_2=0.2$, $\ell_3=0.2$, $\ell_4=0.1$). We also regulated the system control function at $q_1=0.02$ and $q_2=0.5$, with each having a normalizing optimal weight factor $\phi_1=12$ and $\phi_2=3$, for all the various compartments of the initial simulations as represented by Figure 2(a-e) below. Here, we present the result analysis, without figures of the conditions for brevity.

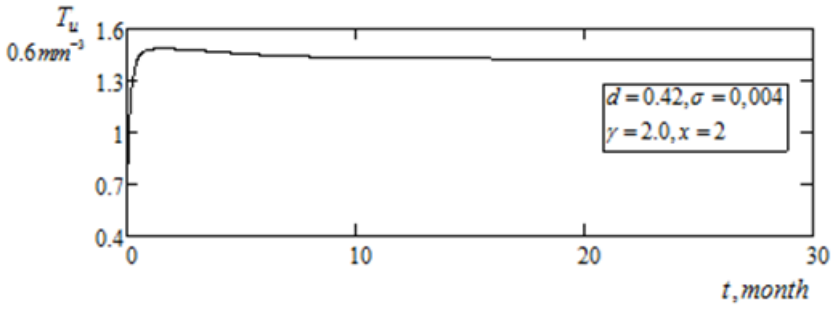
From Figure 2 (a), we visibly observed sharp increase in the susceptible $CD4^+$ T cells to an apex of $1.489mm^{-3}$, at the first two months, following consistent population natural source and consequence of dual application of chemotherapy treatment under dual temporal-delay immunity chambers $G_i, i=1,2$. A slight decline was observed from the third month, with attainment of stability i.e. $T_u(t)=1.485mm^{-3}$, from the seventh month and through duration of 30 months of chemotherapy regulation period.

From Figure 2 (b), at asymptomatic stage, the latently infected $CD4^+$ T cells exhibit some increase $(0.2\rightarrow 2.536)mm^{-3}$ at the third month. Consistent application of boosting chemotherapy (RTI), and the effect of the administration of suppressing chemotherapy (PI), saw accelerated decline of infection, which gradually stabilized after 22 months of drug schedule to as low as $0.4mm^{-3}$.

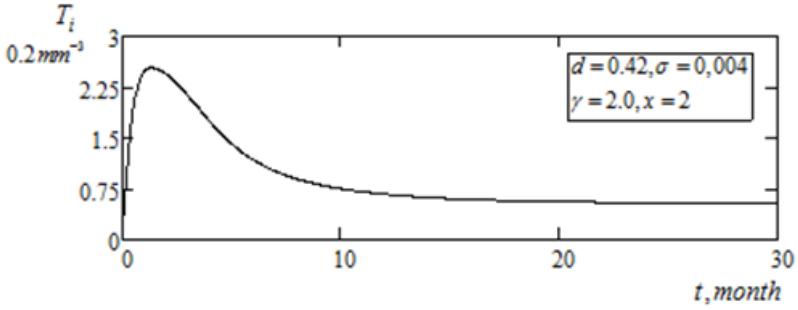
Figure 2 (c), represents simulation of acute infectious T-cells population, which is observed to exhibit initial spurring increase under first application of only immune boosting chemotherapy. The inclusion of suppressing treatment schedule under G_2 chamber, leads to the control of the growth of the infectious population stabilizing at $32.093mm^{-3}$.

It is seen from Figure 2 (d), that acute full-blown AIDS population exhibited sharp initial growth due to proliferation from latently infected that were not exposed to immune suppressing chemotherapy. Here, AIDS population was highest $(0.05\rightarrow 5.842)mm^{-3}$ at the third month. Consistent subjection of the infectious T-cells at the third compartment to suppressing chemotherapy (PI), had some tremendous control effect on acute AIDS population, as infected T-cell decline to as low as $A_p(t)=1.8mm^{-3}$, after 20 months of drug schedule.

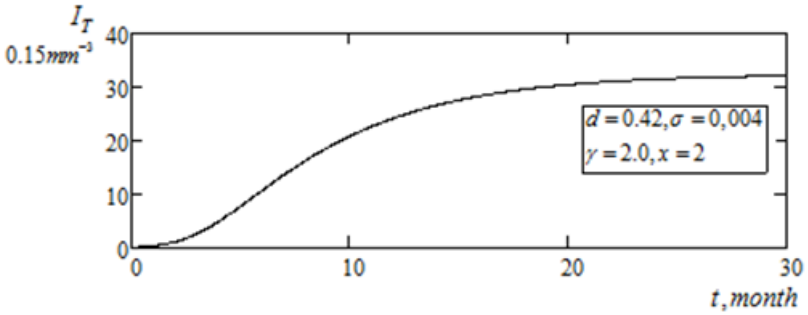
Figure 2 (e), simulated the objective functional, capturing the corresponding optimal control cost as justified by the optimal benefit exhibited by the maximization of the healthy $CD4^+$ T cells in Figure 2 (a). We observed an optimal cost, which maintained a steady insignificantly slight increase in treatment cost with $(0.6\rightarrow 0.64)mm^{-3}$, from treatment set point to treatment terminal schedule.



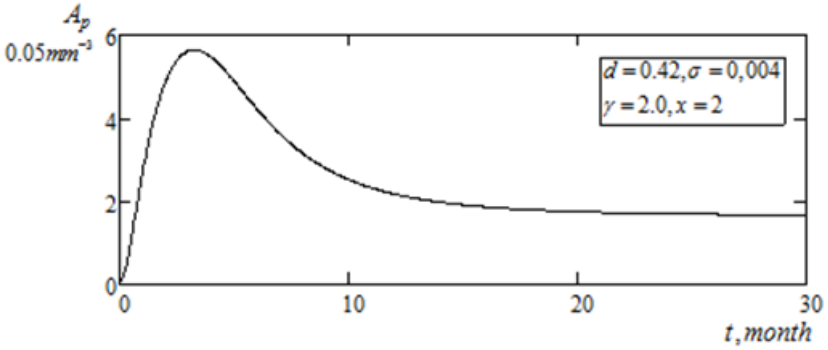
a) Simulation of uninfected CD4⁺ T cells with $q_1 = 0.02, \phi_1 = 12, q_2 = 0.5, \phi_2 = 3$



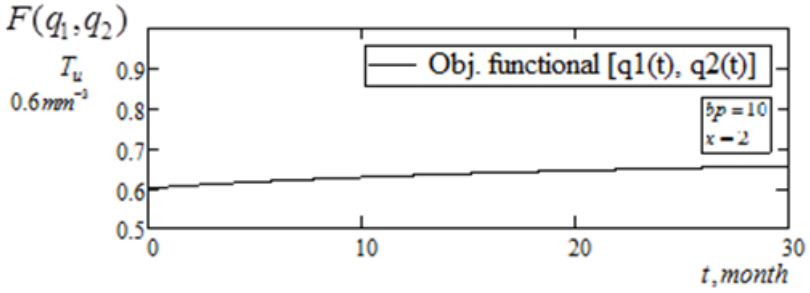
b) Simulation of latent infected T-cells with $q_1 = 0.02, \phi_1 = 12, q_2 = 0.5, \phi_2 = 3$



c) Simulation of infected T-cells with $q_1 = 0.02, \phi_1 = 12, q_2 = 0.5, \phi_2 = 3$

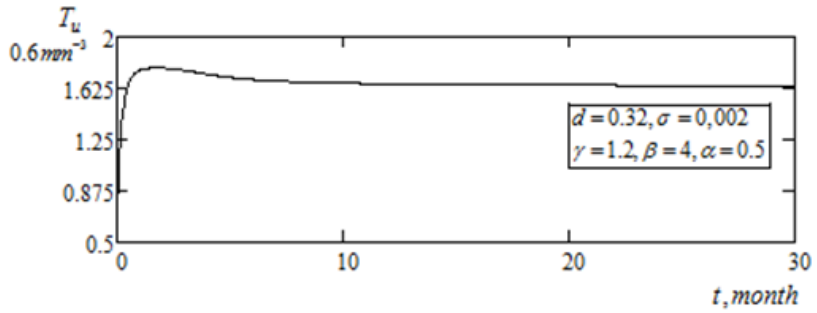


d) Simulation of full-blown AIDS T-cells with $q_1 = 0.02, \phi_1 = 12, q_2 = 0.5, \phi_2 = 3$

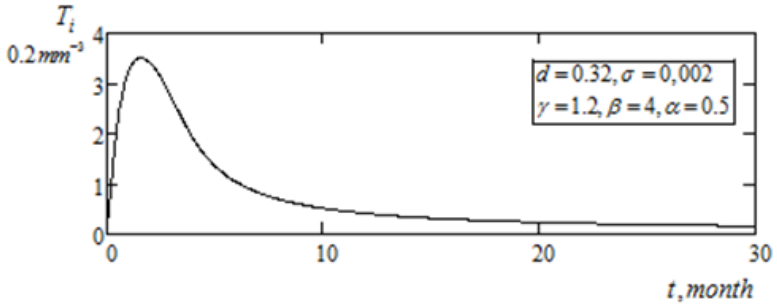


e) Simulation of objective functional with $q_1 = 0.02, \phi_1 = 12, q_2 = 0.5, \phi_2 = 3$

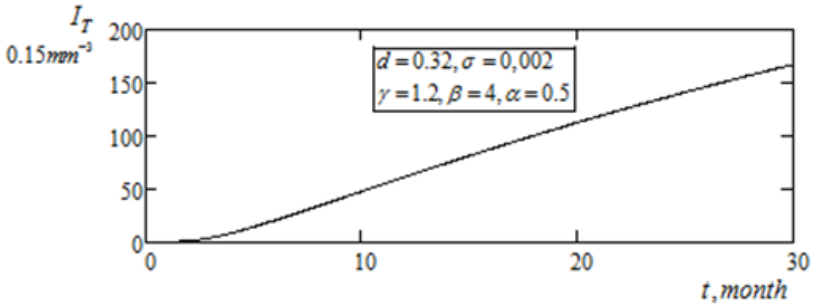
Figure 2(a-e). Simulation of dual infectious with dual treatment, under temporal delay immunity chambers, for $q_1 = 0.02$, $\phi_1 = 12$, $q_2 = 0.5$, $\phi_2 = 3$



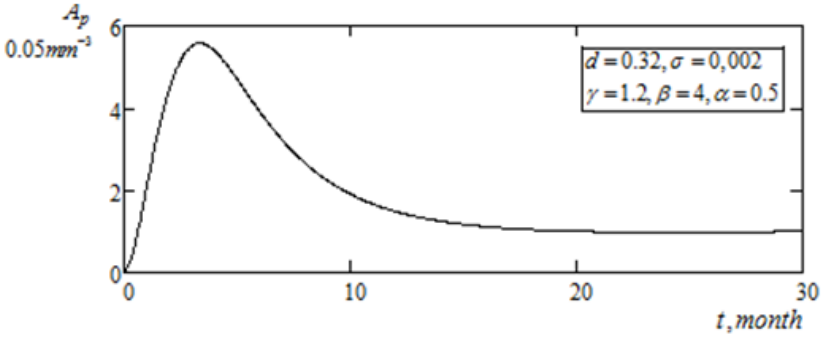
a) Simulation of uninfected CD4⁺ T cells with $q_1 = 0.21, \phi_1 = 7, q_2 = 0.02, \phi_2 = 10$



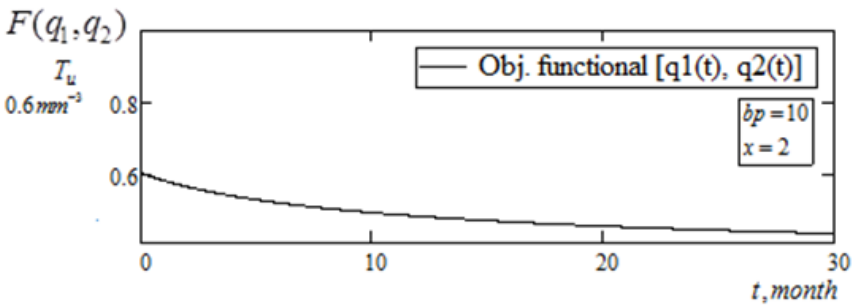
b) Simulation of latent infected T-cells with $q_1 = 0.21, \phi_1 = 7, q_2 = 0.02, \phi_2 = 10$



c) Simulation of infected T-cells with $q_1 = 0.21, \phi_1 = 7, q_2 = 0.02, \phi_2 = 10$



d) Simulation of full-blown AIDS T-cells with $q_1 = 0.21, \phi_1 = 7, q_2 = 0.02, \phi_2 = 10$



e) Simulation of objective functional with $q_1 = 0.21, \phi_1 = 7, q_2 = 0.02, \phi_2 = 10$

Figure 3(a-e). Simulation of dual infectious with dual treatment, under temporal delay immunity chambers, for $q_1 = 0.21$, $\phi_1 = 7$, $q_2 = 0.02$, $\phi_2 = 10$

We further intensify model treatment schedule in order to ascertain our initial numerical illustration. Some notable variations of model predominant parameters were further considered for $d = 0.32, \sigma = 0.02, \gamma = 1.2, \beta = 4$, $\alpha = 0.5$, and having constant transversality conditions ($\ell_1 = 0.4$, $\ell_2 = 0.2$, $\ell_3 = 0.2$, $\ell_4 = 0.1$). Of interest in this second investigation, are the enhanced variations of the system control function, regulated at $q_1 = 0.21$, $q_2 = 0.02$, and each normalized by optimal weight factor of $\phi_1 = 7$ and $\phi_2 = 10$ respectively, as represented by Figure 3(a-e) below.

From Figure 3 (a), we observed the maximization of healthy CD4+ T cells, following the enhancement of consistent treatment chemotherapy schedule as inscribed by model predominant parameters and the toxicity of suppressing chemotherapy. Optimal benefits is seen to increase with apex at $T_u(t) = 1.773mm^{-3}$, as against $T_u(t) = 1.489mm^{-3}$, of Figure 2 (a) above. Continuous administration of treatment schedule within validity of 30 months treatment period saw stabilization of uninfected T-cells at $T_u(t) = 1.625mm^{-3}$, when compared with the stable level of $T_u(t) = 1.485mm^{-3}$ as in Figure 2 (a).

Furthermore, at the asymptomatic stage, when infectivity by viruses on $CD4^+$ T cells are at latent level, Figure 3 (b), indicates high concentration of viruses (viral load and parasitoid-pathogen) invasion of the immune system with apex at $T_i = 3.507mm^{-3}$, at the third month. Active immune boosting chemotherapy and commencement of suppressing immune chemotherapy as latently infected T-cells progresses to active infectious stage, saw a drastic decline of latently infected T-cells group to as low as $T_i(t) = 0.161mm^{-3}$, within the duration of treatment schedule. Again, an improved result is achieved here, when compare with that of Figure 2 (b) above.

From Figure 3 (c) above, the transmutation of latently infected T-cells, which are basically exposed to immune boosting chemotherapy, become the source of active infectious T-cells. The population of infectious T-cells exhibit diagonal elevation at the early stage, with increasing number of viruses' infectivity. The measure of the effect of treatment schedule in this compartment is seen by the decline of full-blown AIDS patients as in Figure 3 (d) above.

From Figure 3 (d) above, we again experience initial concentration of full-blown AIDS victims to as high as $A_p(t) = 5.576mm^{-3}$, at the third month, following early proliferation of latently infected T-cells with very little or no preventive and suppressive measures. However, with intense exposure to HAART treatment schedule at the infectious compartment, acute AIDS infected compartment gradually exhibit accelerated declination with stability tendency at $A_p(t) = 0.8mm^{-3}$, after 20 months of treatment schedule. The outcome showed an improvement as against $A_p(t) = 1.8mm^{-3}$, of Figure 2 (d).

With enhanced optimal control functions $q_1 = 0.21$, $q_2 = 0.02$ balanced by optimal weight factors of $\phi_1 = 7$ and $\phi_2 = 10$ respectively, Figure 3 (e) above indicated a tremendous reduction in systemic cost as seen from Figure 2 (e) with $0.640mm^{-3}$ to as low as $0.424mm^{-3}$ in Figure 3 (e). The aim of the investigation was justified as minimization of optimal cost yields maximization of uninfected $CD4^+$ T cells concentration, evident by Figure 3 (a) above.

4.2. Discussion

Here, we have formulated an optimal pair control mathematical strategy, which accounted for the maximization of the optimal benefits based on the optimal cost analyses. The model was basically conducted as 4-Dimensional dynamic dual HIV-pathogen infectivity model, enhanced by dual temporal delay-immunity treatment chambers. Consisting the model population understudy, were four subgroups of $CD4^+$ T cell counts, which played host to viral load and parasitoid-pathogen as visitors. Dual suppressing and preventive treatment chemotherapies were allowed in the interplay of the epidemiological cycle.

The method explore was an optimal control problem with optimal solution established. The existence and uniqueness of model solution was critically viewed using well known technique from numerical methods – the Pontryagin's Maximum Principle and optimization control system defined by the state system coupled with the adjoint system with the initial and transversality conditions together with the characterization of the optimal control pair was derived. Thus, optimality control system is a two-point boundary value problem due to state initial data and adjoint system final time data. Concrete illustrative examples were simulated for which model investigated the methodological progression of chemotherapy treatment trend at set-point (considered as latent infection) and at active stage, known as infectious $CD4^+$ T cells.

Two optimal control functions $q_i, i = 1,2$, was explored and clinically balanced by optimal weight factors ϕ_i, $i = 1,2$, with each associated to upperbounds c_1 and c_2 , respectively. Analyses of the results indicated that with predominant parameters such as $d = 0.42$, $\sigma = 0.004$, $\eta = 2.0$, $x = 2$; having control functions $q_1 = 0.02$, $q_2 = 0.5$ and weight factors of $\phi_1 = 12$ and $\phi_2 = 3$ for all $c_i = 20$, infectivity (viral load and parasitoid-pathogen) were under control. Latent infected T-cells (Figure 2b) declined as low as $T_i(t) = 0.4mm^{-3}$, from initial apex of $T_i(t) = 3.507mm^{-3}$, while acute infectious T-cells, $I_T(t)$ attained controllable stability. The effects of declination of viruses infectivity are evident by the maximization of healthy $CD4^+$ T cells concentration (Figure 2a), with $T_u(t) = 1.489mm^{-3}$, in the first three months and attaining growth stability of $T_u(t) = 1.485mm^{-3}$, through rest treatment validity period. Acute full-blown AIDS infected $CD4^+$ T cells ascertained the positivity of the investigation as overall declination of AIDS victims reduced drastically from $A_p(t) = 5.842mm^{-3}$ to $A_p(t) = 1.8mm^{-3}$.

The systemic cost $F(q_i)_{i=1,2}$ showed impressive stability value with somewhat insignificant increase of $(0.6 \rightarrow 0.64)mm^{-3}$.

Further intensification of the experiment as analyzed by Figure 3 (a-e), showed further enhancement of maximization of healthy $CD4^+$ T cells concentration up to $T_u(t) = 1.773mm^{-3}$, in the first three months with attained stability of $T_u(t) = 1.625mm^{-3}$, through rest treatment period. Latent infected T-cells and active infectious $CD4^+$ T cells were under immune boosting and suppressive chemotherapy measures, as justified by the reduction in acute full-blown AIDS infected immune system with $A_p(t) \leq 0.8mm^{-3}$. The corresponding treatment schedule indicated credible minimization of optimal cost at $F(q_i)_{i=1,2} = 0.424mm^{-3}$, as in Figure 3(e) when compared with $F(q_i)_{i=1,2} = 0.64mm^{-3}$ of Figure 2(e) above.

The implications were that the administration of chemotherapies requires step-wise approach as in time-delay chambers G_1 and G_2 with drug toxicity as a function of optimal weight factors ϕ_1 and ϕ_2. The initialization of treatment with high drug intensity at set-point indicated more rewarding treatment outcome whereas, the positivity of treatment outcome are independent of treatment duration. On the other hand, optimal cost is a function of treatment duration i.e. minimization of systemic cost was better achieved with prolonged treatment schedule (see Figure 2 (e) & Figure 3 (e)) above.

5. Conclusion

The present model have been formulated as a 4-Dimensional dynamic HIV-pathogen mathematical model, presented as an optimal control problem strategy for the investigation of the methodological application of dual treatment factors, systematically sandwiched in a two time-delay immunity treatment chambers in dual infectious system. The method explored well-known numerical methods – Pontryagin's Maximum Principle in the analysis of the model. Computation of resulting outcome indicated that, for a step-wise combination of dual chemotherapy, enhanced by optimal control functions with normalizing optimal weight factors, maximization of healthy immune system concentration was best achieved with the administration of significantly high toxicity chemotherapies at infection set-point. Furthermore, sustainability of declined infectivity and significant minimization of optimal cost is primordial to sequential prolong treatment schedule and within drug validity period. The outcome of the study were therefore, not only in consonant with the investigations of [1,2,3], but an enhancement to those existing results, studied with one control function and without temporal time-delay chambers. The study thus, suggests further investigations with more lengthy interplay of multiple control functions and could be readily adopted for other infectious diseases.

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