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Quantitative Approximability of Optimal Control by Linear Programing Model for Asymptomatic Dual HIV - Pathogen Infections

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Abstract: *Propelled by the weakness of some notable scientific investigations and the continual desire to achieve a more précised result for the eradication of dual HIV-pathogen infections, the present paper formulated a 7-Dimensional nonlinear mathematical dynamic model presupposed to account for the optimal treatment of asymptomatic dual HIV-pathogen infections studied under quadrupled treatment functions. The model was presented as a linear optimal control time problem (LOCTP) analyzed using linear programing approximability approach, embedded with theoretical measured space. The study as well established the positivity and boundedness of model state variables and numerical simulations conducted. Results of simulations clearly raises positive variations in comparison of healthy $CD4^+$ T lymphocytes count, dual HIV-pathogen infections, critical role of dual CTLs and the aggressiveness of virions before and after the introduction of multiple chemotherapy treatment. Therefore, in justifying the application of linear programing approximation model, the study strongly advocates the articulation of delay intracellular into the state variables for enhancement of future investigation.*

Keywords: *quantitative-approximability, linear-programing, asymptomatic, quadrupled, functional-space, measured-space, Lebesgue-measurable*

1. INTRODUCTION

It has become obvious that the human race have been skewed to the realization of the painful fact that human immunodeficiency virus (HIV) in their negative affinity, have become an important integral component of the human immune systems with the later as primary victim. This negativity in affiliation has rather place the scientific community and beyond in a most seeming precarious dehumanization following the near insurmountable and colossal activities of the deadly disease, which have been without outright medical cure. A situation, which often transmute to full-blown acquired immunodeficiency syndrome (AIDS) with lethal outcome as final consequences.

Non-the-less, considerable height has been attained by research scientists towards the prolongation of lifespan of infected patients and in most cases, aimed at the eradication of the dreaded HIV/AIDS disease, see for example [1-7]. Of interest, these notable achievements have been fronted by the central role of mathematical modeling. However, mathematical modeling as a seeming panacea to the curative approach of HIV/AIDS infection are usually confronted with the difficulty of formulating simplified model with précised and coincides state variables and corresponding parameter functions [8-10]. A situation that has multifaceted dimensions and which are better handle by the judgmental abilities of professionals with the objectives of defining possible solutions to an epidemic.

Modeling of epidemiological outbreak are usually determined by a set of compactible state variables, which in the case of HIV/AIDS, we are commonly concern with the maximization of the host target cells in the class of $CD4^+$ T–lymphocytes, macrophages and follicular dendritic cells; suppression/elimination of the vectors – viral load and parasitoid-pathogen; maximization of natural anti-HIV (adaptive immune effectors response) known as cytotoxic lymphocytes (CTLs). Cytotoxic lymphocytes are often subdivided into precursors (CTLp) and effectors (CTLe). Other considered state components includes: critical role of time-delay immunity period (or delay intracellular) and the

functioning capacities of therapeutic chemotherapies, which are generally classified into two families of HAART – reverse transcriptase inhibitors (RTI) and protease inhibitors (PIs) [11-16]. In most recent dimensions, indepth evaluations of viral load have resulted to the inclusion of viral aggressiveness index denoted as $r-state$ variable. This component describes the intrinsic virulence and thus, has been accorded important stay in determining epidemiological state variables in HIV dynamic models [17-19].

In this present study, references are deduced from related and compactible models with which the scope of this investigation lies. In our attempt to analyze an all-inclusive model that sufficiently represent the biological interplay of acceptable key components for dual HIV-pathogen infections; we invoke a number of closely related models. For instance, model [17] had studied a set of mathematical model of HIV pathogenesis and treatment. The model not only established the usefulness of the application of mathematical model in the dynamics of HIV transmission but as well, affirmed the capability of linear programing model in understanding the correlations of long-term immunological control of HIV. The model [19] motivated by that of [17] had formulated an optimal control model, which accounted for single drug treatment factor and crucial role of immune response (recognized as effector and memory - CTLe/p) for the control of cellular infection rate. The task of model [18] was the maximization of symptomatic stage of fast progressive HIV infected patient using embedding method. The result of this investigation was in affirmation of the technique adopted.

Resourcefully, a critical review of the aforementioned literatures shows that previous investigations have been on single viral load. This situation clearly could not account for the aggressiveness of diverse new cases of HIV and its allies of pathogenic infections. Furthermore, treatment mechanisms for these studies were either single treatment factor or more but never comprehensive. Even the studies [16, 20], where dual HIV infectivity was considered, only single and pair chemotherapies were respectively programmed. Thus, the present study equipped by the identified weakness of the aforementioned literatures, formulates using ordinary differential equations a set of novel 7-Dimensional nonlinear mathematical dual HIV dynamic model, principally to account for the optimal control treatment of asymptomatic dual HIV-pathogen infections on target cells ($CD4^+$ T-lymphocytes) under clinical application of quadrupled treatment functions, which includes linear index of virions aggressiveness. The derive model is reformulated as an optimal control problem and analyzed using linear programing approximation method.

The entire investigation is floated as a version of six sections with section 1 covering the introductory aspect. Section 2 defined the material and methods of study, which constitutes the formulation of model mathematical equations and schematic representation of the model. We shall also verify in this section, the non-negativity of model state variables and ensure that existence of solutions is bounded. We devote section 3 to the transformation of derived model to a time optimal control problem with analysis conducted using linear programing approximation method (LP-PM). We present in section 4, related procedures with specified functional and measure spaces. Affirmation of the model and its analysis are explicitly illustrated in section 5. This section also contains the discussion of the resulting outcome. Finally, in section 6, we draw succinct conclusion and remarks base on investigation. It is hoped that the method adopted here will provide some straightforward approach without the imposition of artificial conditions.

2. MATERIAL AND METHODS

We pre-occupy this section with the mathematical formulation of system basic model equations aided with schematic representation. Since the model is a complete representation of living organisms, the section also considers the positivity of model state variables and validity boundedness of solution.

2.1. Formulation of Mathematical Model

Drawing from the innovative ideas of section 1, it is of essence that the derivation of the present model takes its offspring from two compactible established models of [18, 20]. From model [18], the interplay of single HIV infection with target cells – $CD4^+$ T cells and natural anti-HIV defense mechanism was investigated. The governing equations for this model were obtained as:

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

where $x(t), y(t), w(t), z(t), v(t)$ and $r(t)$ denotes the key state components of the model. We refer readers to the cited reference for detail description of used parameter.

An extension of infection dynamics to dual infectivity was considered by model [20], where dual HIV-pathogen model studied using single treatment function - reverse transcriptase inhibitors (RTI) was investigated. The epidemiological optimal control model was derived as:

$$\begin{aligned}
\frac{dU_T}{dt} &= \frac{b}{1+V+P} + gU_T\left(1-\frac{U_T+I_T}{U_{\max}}\right) - \alpha_1 U_T - r(t)[h_1 VU_T + h_2 PU_T] \\
\frac{dI_T}{dt} &= r(t)[h_1 VU_T + h_2 PU_T] - \left(z_v + z_p\right)\alpha_2 I_T \\
\frac{dV}{dt} &= z_v \alpha_2 I_T - \alpha_3 VU_T \\
\frac{dP}{dt} &= z_p \alpha_2 I_T - \alpha_4 PU_T
\end{aligned} \tag{2}$$

with equation description as contain in cited reference. Thus, for the derivation of standard equations that adequately guarantee the scope of this present study, we utilize the ideas of models (1) and (2) guided by the following assumption.

Assumption 2.1

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

ii. Precursors of CTLs exhibit dual characteristic behavior for immune memory replication and effective contamination by virions.

iii. The effective development of CTL memory by precursor of CTL depends on the efficacy and threshold of therapy at initiation point.

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

Therefore, from the above synopsis, we formulates a novel epidemiological model that accounts for an asymptomatic dual HIV-pathogen infections on host target cells – $CD4^+$ T-lymphocytes under articulated subdivided CTLs and critical role of virulence linear index R with multiple chemotherapies – reverse transcriptase inhibitors (RTI) and protease inhibitors (PIs). So, if the concentration of the present model as characterized by 7-subpopulations is measured in $cells\ per\ ul$, then U_T - uninfected $CD4^+$ T cells count, I_T - infected $CD4^+$ T cells (by both virions), V -free viral load, P - free pathogen virus, W - precursor (CTLp), Z - effectors (CTLe) and R - intrinsic virulence index represents the biological state variables. Furthermore, if we let q_1 and q_2 denote chemotherapies control functions, then the epidemiological interactions of the components yields the following derive mathematical equations:

$$\begin{aligned}
\frac{dU_T}{dt} &= \frac{b}{1+V+P} + gU_T\left(1-\frac{U_T+I_T}{U_{\max}}\right) - \alpha_1 U_T - (1+q_1(t))[h_1V+h_2P]U_T R \\
\frac{dI_T}{dt} &= (1-q_1(t))[h_1V+h_2P]U_T R - \left(z_v+z_p\right)\alpha_2 I_T - \rho I_T Z \\
\frac{dV}{dt} &= (1-q_2(t))z_v\alpha_2 I_T - \alpha_3 V \\
\frac{dP}{dt} &= (1-q_2(t))z_p\alpha_2 I_T - \alpha_4 P \\
\frac{dW}{dt} &= cU_T I_T W - \lambda I_T W - \alpha_5 W \\
\frac{dZ}{dt} &= \lambda I_T W - \alpha_6 Z \\
\frac{dR}{dt} &= R_0 - q_1(t)R
\end{aligned} \tag{3}$$

with initial conditions $U_T(0)=U_{(T)0}, I_T(0)=I_{(T)0}, V(0)=V_0, P(0)=P_0, W(0)=W_0, Z(0)=Z_0$ and $R(0)=R_0$ at $t=t_0$ and satisfying the biological state variables and parameters as describe in tables (1 & 2) . Thus, model (3) is the standard equation system that satisfies the scope of the present study with biological behavior schematically represented as in fig. 1, below:

Remark 1 It is worth to note that the quadrupled treatment function as applied here includes: reverse transcriptase inhibitors (RTI), protease inhibitors (PIs), cytotoxic T-lymphocytes (CTLs) subdivided into precursors of $CTLp$ and effectors of $CTLe$.

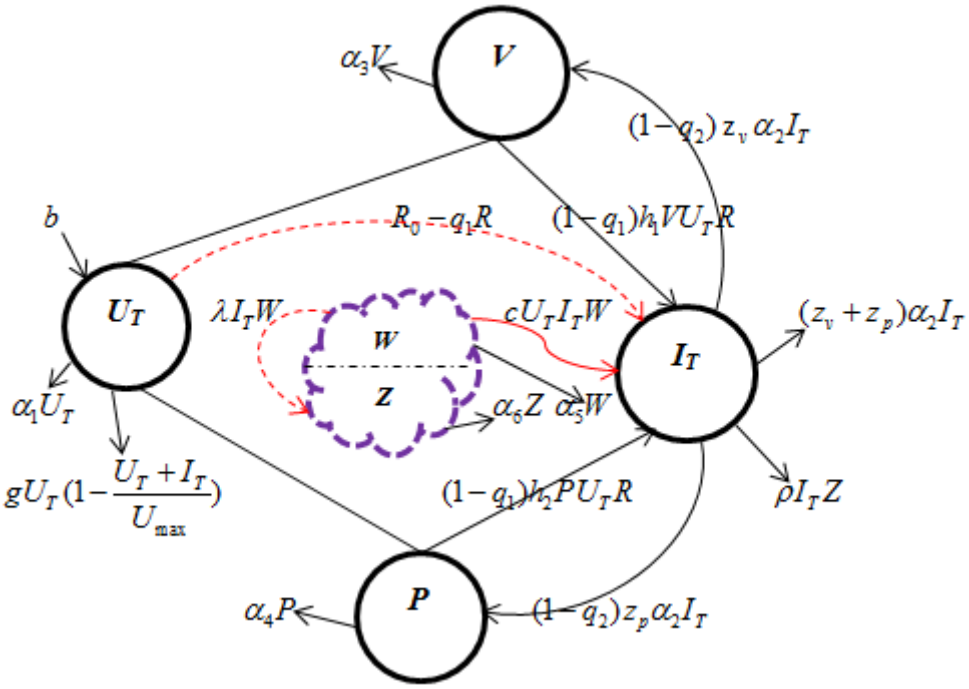

Fig. 1 *Schematic representation of dual HIV-pathogen infection with quadruple treatment functions* $(RTI, PIs, CTLp, CTLe)$

An indepth appreciation of model (3) is informed by the following explicit description of each of terms of the equations. For instance: in the first equation, the first term $\frac{b}{1+V+P}$ denotes natural

source of uninfected CD4$^+$ T cells having a logistic term $gU_T\left(1-\frac{U_T+I_T}{U_{\max}}\right)$. This term account for the fact U_T is always never larger than $U_{\max}$. Uninfected cells die natural death at a rate $\alpha_1 U_T$ and is loss due virions at the rates $h_1 V$ and $h_2 P$, while $(1-q_1(t))U_T R$ is the infection rate associated with linear index of virions aggressiveness in the presence of control chemotherapy function $q_1(t)$.

In the second equation, the first term $(1-q_1(t))[h_1 V + h_2 P]U_T R$ define the inflow of virions infection into susceptible T-cells leading to transmutation to infectious T-cells. The second term $\left(z_v + z_p\right)\alpha_2 I_T$ describes the clearance rate of infectious cells, which are sustained by virions replication rate z_v and z_p respectively. The last term $\rho I_T Z$ explain the critical role of active immune effectors response in clearing significant amount of infected T-cells.

From third and fourth terms, we define the behavioral tendencies of both virions V and P with inflow of $(1-q_2(t))z_v\alpha_2 I_T$ and $(1-q_2(t))z_p\alpha_2 I_T$ as replicated infectious cells, which are subjected to chemotherapy distortion $q_2(t)$. Both equations experience clearance rate of $\alpha_3 V$ and $\alpha_4 P$. Taking lead from [16, 20], the present model incorporates CTLs population, which is subdivided into precursor of cytotoxic T-lymphocytes – CTLp (*w*) and effector of cytotoxic T-lymphocytes – CTLe (*z*). Thus, from fifth equation, the first term $cU_T I_T W$ denotes the proliferation of CTLp population, which is proportional to both infected T-cells I_T and quantified amount of uninfected T-helper cells U_T. CTLp is differentiated into effectors at the rate $\lambda I_T W$, which becomes inflow in the sixth equation. CTLp and CTLe are loss at the rates $\alpha_5 W$ and $\alpha_6 Z$.

Finally, the seventh equation describe the dynamics of the intrinsic dual virulence (or aggressiveness of dual virions) denoted by R. This index increases linearly for an untreated dual HIV-pathogen infected patient with growth rate that depends on the constant R_0 and are cleared due to $q_1(t)$ at the rate $q_1(t)R$.

Remark 2 Precursor of CTLp are responsible for the development of immune memory, while effectors of CTLe are responsible for the active defense of foreign agents i.e. elimination (killing) of virions.

Remark 3 The functions q_1 and q_2 are control variables for RTI and PIs with q_1 acting as active inhibitors that reduces infection rate on healthy CD4$^+$ T cells and growth rate of intrinsic dual virulence. The term q_2 acts in virions reproduction by inhibiting virions replications from infectious cells.

Remark 4 The constants h_1, h_2 and the R-state variable of first, second and seventh equations of present model represents the coefficient β of model [17] and state variable of model [21].

From remarks (1and 2), validation of model (3) follows the establishment of realistic values for both state components and parameters as seen in tables 1 and 2 below:

Table 1. *Description of model state variables with values*

Variables	Dependent variables Description	Initial values	Units
U_T	Uninfected T-lymph cells population	0.4	$cells\,\mu l^{-1}$
I_T	Infected CD4$^+$ T-lymphocytes population	0.2	$cells\,\mu l^{-1}$
V	Infectious free viral load population	0.2	$copies ml^{-1}$
P	Infectious free pathogen population	0.1	$copies ml^{-1}$

W	Precursors of CTLp	0.02	$cells\mu l^{-1}$
Z	Effectors of CTLe	0.04	$cells\mu l^{-1}$
R	Intrinsic virulence index	0.025	$mlcopies^{-1}d^{-1}$
$U_{\max}$	Maximum saturation of $CD4^+$ T cells	$\in[0,1]$	

Note: *Table 1is a modification of validated models of [18, 20, 21]*

Table 2. *Summary of constants and parameter values of model (3)*

Parameter symbols	Parameters and constants Description	Initial values	Units
b	Natural source of uninfected $CD4^+$ T cells	0.6	$cells.\mu l^{-1}d^{-1}$
g	Growth rate of uninfected $CD4^+$ T cells	0.04	$cells.\mu l^{-1}d^{-1}$
α_1	Natural death rate of uninfected $CD4^+$ T cells	0.02	d^{-1}
$q_{i=1,2}$	Treatment control functions for U_T, I_T, V, P	$q_i \in [0,1]$	
h_1	Rate of viral load infection on uninfected $CD4^+$ T cells	0.0044	$cells.\mu l^{-1}d^{-1}$
h_2	Rate of pathogen infection on uninfected $CD4^+$ T cells	0.0016	$cells.\mu l^{-1}d^{-1}$
z_v	Replication rate of viral load by I_T cells	0.5	$copiesml^{-1}cells^1\mu ld^{-1}$
z_p	Replication rate of pathogen by I_T cells	0.3	$copiesml^{-1}cells^1\mu ld^{-1}$
α_2	Death rate of infected $CD4^+$ T cells	0.09	d^{-1}
ρ	Clearance rate of infected cells by immune effectors response	2.5	$\mu lcells^{-1}d^{-1}$
α_3	Natural death rate of viral load	0.04	$mlcopies^{-1}d^{-1}$
α_4	Natural death rate of pathogen	0.05	$mlcopies^{-1}d^{-1}$
c	CTLp proliferation	0.005	$\mu lcells^{-2}d^{-1}$
λ	CTLp differentiation	0.006	$\mu lcells^{-1}d^{-1}$
α_5	Natural death rate of CTLp	0.017	d^{-1}
α_6	Natural death rate of CTLe	0.006	d^{-1}
R_0	Growth rate of virulence	10^{-7}	$copies^{-1}mld^{-2}$
σ_1	Optimal weight ratio q_1	10	
σ_2	Optimal weight ratio q_2	100	

Note: Table 2 is a clinical modification of [18, 20, 21] to accommodate the present novel dual HIV-pathogen model solvable using RK4 software

Epidemiological analysis of tables (1 & 2) in comparison to model [18, 20], reveal the critical role of susceptible growth rate g; the effect of treatment function $(1-q_1(t))$, which inhibits further invasion by virions on healthy $CD4^+$ T cells. Remarkably, the presence of logistic term in the first equation clearly defines the limit of $CD4^+$ T cells under investigation. Furthermore, natural source of uninfected cells is seen been differentiated with respect to viral load and pathogen following the fact that infected T-cells once infected, is continuously infiltrated by virions. Next, been spur by the above analysis, we are bound to show that our state variables constitute set of living organisms and are therefore positive with bounded characterized solutions.

2.2. Positivity of State Variables and Boundedness of Solution

Suppose $S = D([-\tau,0],\Re^7)$ be the Banach space of continuous mapping in the interval $[-\tau,0]$ into

$\Re^7$ equipped with the sup-norm (topology of uniform convergence). Then, from [22, 23], applying the fundamental theory of functional differential equations (FDEs), there exist unique solutions: $(u_T(t), i_T(t), v(t), p(t), w(t), z(t), r(t))$ to model (3) and having initial conditions

$$(u_T(t), i_T(t), v(t), p(t), w(t), z(t), r(t)) \in S. \tag{4}$$

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

$$\begin{aligned} &u_T(\theta) \geq 0, i_T(\theta) \geq 0, v(\theta) \geq 0, p(\theta) \geq 0, \\ &w(\theta) \geq 0, z(\theta) \geq 0, r(\theta) \geq 0 \; for \; all \theta \in [-\tau, \theta] \end{aligned}. \tag{5}$$

Then, the positivity of state variables and boundedness of solution for model (3) with initial functions satisfying condition (4) and (5) is presented in the theorem hereof.

Theorem 2.1 Let $(u_T(t), i_T(t), v(t), p(t), w(t), z(t), r(t))$ be the solutions of model (3) satisfying conditions (4) and (5). Then $u_T(\theta), i_T(\theta), v(\theta), p(\theta), w(\theta), z(\theta), r(\theta)$ are all non-negative and bounded for all $t \geq 0$ of which solution exists.

Proof Invoking the result of (Thm. 2.1, p514-515, [23]), it is obvious to see from model (3) that

$$u_T(t) = u_{(T)}(0) e^{-\int_{t_0}^{t_f} \{\alpha_1 + g(1 - \frac{u_T(\xi) + i_T(\xi)}{u_{\max}}) + (1 - q_1(t))[h_1 v(\xi) - h_2 p(\xi)] r(\xi)\} d\xi}$$

$$+ \int_{t_0}^{t_f} \frac{b}{1 + V(t) + P(t)} e^{-\int_{\eta}^{t_f} \{\alpha_1 + g(1 - \frac{u_T(\xi) + i_T(\xi)}{u_{\max}}) + (1 - q_1(t))[h_1 v(\xi) - h_2 p(\xi)] r(\xi)\} d\xi} d\eta,$$

$$i_T(t) = i_t(0) e^{-\int_{t_0}^{t_f} ((z_v + z_p)\alpha_2 + \rho z(\xi)) d\xi} + \int_{t_0}^{t_f} (1 - q_1(t)) r(\eta) u_T(\eta) [h_1 v(\eta) - h_2 p(\eta)]$$

$$\bullet e^{-\int_{\eta}^{t_f} ((z_v + z_p)\alpha_2 + \rho z(\xi)) d\xi} d\eta,$$

$$v(t) = v(0) e^{-\alpha_3(t)} + \int_{t_0}^{t_f} (1 - q_2(t)) z_v \alpha_2 i_T(\eta) e^{-\alpha_3(t)} d\eta,$$

$$p(t) = p(0) e^{-\alpha_4(t)} + \int_{t_0}^{t_f} (1 - q_2(t)) z_p \alpha_2 i_T(\eta) e^{-\alpha_4(t)} d\eta,$$

$$w(t) = w(0) e^{-\alpha_5(t)} + \int_{t_0}^{t_f} (c u_T(\xi) i_T(\xi) - \lambda i_T(\xi) - \alpha_5) d\xi,$$

$$z(t) = z(0) e^{-\alpha_6(t)} + \int_{t_0}^{t_f} (\lambda i_T(\xi) w(\xi) - \alpha_6) d\xi,$$

and

$$r(t) = r(0) e^{-q_1(t)} + \int_{t_0}^{t_f} (r_0(\xi) - q_1) d\xi.$$

Positivity immediately follows from the above integral forms and conditions (4) and (5) satisfied.

For boundedness of the solution, we define

$$U(t) = c(z_v + z_p)u_T(t)r(t) + c(z_v + z_p)i_T(t) + \frac{c}{2}(v(t)\,p(t)) + (z_v + z_p)\rho z(t)$$

and $b = \min\{\alpha_1, \alpha/2, \alpha_3, \alpha_4, \alpha_5, \alpha_6\}$. By non-negativity of the solution, it follows that

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

$$+c(z_v + z_p)(h_1.h_2)v(t)\,p(t)u_T(t)r(t) - \alpha_2 c(z_v + z_p)i_T(t)$$
$$-c(z_v + z_p)\rho\lambda i_T(t)w(t)z(t) + \frac{\alpha_2 c(z_v + z_p)}{2}i_T(t)$$
$$-\frac{c(\alpha_3 + \alpha_4)}{2}v(t)\,p(t) + c(z_v + z_p)\rho\lambda i_T(t)w(t)z(t)$$
$$-(z_v + z_p)\rho\lambda(\alpha_5 + \alpha_6)w(t)z(t) - (z_v + z_p)r_o(t)r(t)$$

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

$$-\frac{c(\alpha_3 + \alpha_4)}{2}v(t)\,p(t) - (z_v + z_p)\rho\lambda(\alpha_5 + \alpha_6)w(t)z(t)$$

$$< c(z_v + z_p)\frac{b}{1+v(t)+p(t)} - bU(t).$$

This implies that $U(t)$ is bounded and so are $u_T(t), i_T(t), v(t), p(t), w(t), z(t)$ and $r(t)$. Hence, this completes the proof.

Remark 5 The consequences of Thm. 2.1 in conjunction to conditions (4) and (5) is that if $i_T(0) > 0$ or $\{v(0), p(0)\} > 0$, then $u_T(t), i_T(t), v(t), p(t), w(t), z(t)$ and $r(t)$ are actually positive. Furthermore, the boundedness as validated in Thm. 2.1 ensures the existence of solution for all $t \geq 0$.

At this point, we next validate the inclusion of two chemotherapy control measures and the crucial role of dual CTLs as immune system enhancement agent. The optimality control immediately comes to bear.

3. Optimal Control Problem for QCT

For a quadrupled chemotherapy treatment (QCT), we invoke the epidemiological investigation of model [9], where minimum count of $CD4^+$ T cells for an infected patient with which treatment is bound to commence is at $t_0(3) = 0.25mm^3$ for $t \in [3, 30]$ months. Moreso, in the absence of medication transmutation of HIV to full-blown AIDS for infected patient is bound to occur if $CD4^+$ T cells count fall below $CD4^+_{AIDS}$ count of $< 200cell/\mu l$.

Accounting for this sort of precarious situation, the present study is therefore prime with the proposition of treatment regimen that aim at maximizing asymptomatic stage of dual HIV-pathogen infections. This is to say that we seek to maximize the performance index, which is the benefits base on $CD4^+$ T cells and CTLs (= CTLp + CTLe) levels with ascertained minimization of systemic cost. In a balance situation, suppose HIV-pathogen infection transmute to AIDS after t_f, then we are confronted with the equation

$$U_T(t) = CD4^+_{AIDS}, U_T(t) \geq CD4^+_{AIDS}, \forall t \in [t_0, t_f]. \quad (6)$$

Now, suppose systemic cost of chemotherapy is proportional to $q_1^2(t)$ and $q_2^2(t)$ for all $t \in [t_0, t_f]$ then the overall cost of treatment, which defines the objective functional, is given by

$$J(q_1, q_2) = \int_{t_0}^{t_f} \{U_T(t) + Z(t) + W(t) - [\sigma_1(q_1(t))^2 + \sigma_2(q_2(t))^2]\} dt \tag{7}$$

where $\sigma_{i=1,2} \leq 1$ are the optimal weight factors necessary to balance the variation of drug toxicity. Furthermore, accounting for emergence of drug resistance, we observe that fixing a maximum cost of chemotherapy regimen amount to restricting the quantity of chemotherapeutic application. This is to say that the limit of chemotherapy should be sufficiently small positive integer. If we let this integer be τ , such that risk of drug resistivity is sufficiently ignored, then equation (7) can be rewritten as:

$$J(q_1, q_2) = \int_{t_0}^{t_f} \{U_T(t) + Z(t) + W(t) - [\sigma_1(q_1(t))^2 + \sigma_2(q_2(t))^2]\} dt \leq \tau \tag{8}$$

Setting $y_i = (u_T, i_T, v, p, w, z, r), i = 1, ..., 7$ and $q(t) = (q_1(t), q_2(t))$ the differential equations of model (3) can be represented as:

$$\dot{y}(t) = j(t, y_i(t), q(t)) = \begin{pmatrix} \frac{b}{1 + y_3 + y_4} + g(1 - \frac{y_1 + y_2}{y_{\max}})y_1 - \alpha_1 y_1 (1 - q_1)[h_1 y_4 + h_2 y_5] y_1 y_7 \\ (1 - q_1)[h_1 y_4 + h_2 y_5] y_1 y_7 - (z_v + z_p)\alpha_2 y_2 - \rho y_2 y_6 \\ (1 - q_2) z_v \alpha_2 y_2 - \alpha_3 y_3 \\ (1 - q_2) z_p \alpha_2 y_2 - \alpha_4 y_4 \\ c y_1 y_2 y_5 - \lambda y_2 y_5 - \alpha_5 y_5 \\ \lambda y_2 y_5 - \alpha_6 y_6 \\ R_0 - q_1 R \end{pmatrix} \tag{9}$$

Therefore, from equations (7), (8) and (9), the optimal chemotherapy control (regimen) problem can be derive as:

$$\max_{q, t_f} \int_{t_0}^{t_f} dt \tag{10}$$

subject to

$$\left.\begin{array}{c} \dot{y} = j(t, y, q) \\ \int_{t_0}^{t_f} \{u_T(t) + z(t) + w(t) - [\sigma_1(q_1)^2 + \sigma_2(q_2)^2]\} dt \leq \tau \\ y_1(t_0) = y_0, y_1(t_f) = CD4^+_{AIDS} \\ y_1(t) \geq CD4^+_{AIDS}, t \in [t_0, t_f] \end{array}\right\} \tag{11}$$

Equations (10) and (11) represent a linear optimal control time problem (LOCTP)*.

For most cases, control function $q(\cdot)$ and corresponding state $y(\cdot)$ for final time t_f that satisfy equation (11) may not exist. Then, overcoming such constraints, the problem of an LOCTP is conveniently solve using linear programing approach known as ***measure space***.

4. LINEAR PROGRAMMING MODEL FOR LOCTP

The appreciation of a linear programing approach for an LOCTP requires the transformation of the LOCTP to a functional space, which is further transform to a measure space of infinite dimensional linear programing problem. Finally, the solution of this problem is then approximated by the solution of a finite dimensional LP of sufficiently large dimension. This classical measure theory for the computation of optimal control problem was first adopted by [24], applied by [25, 26] and extensively improved by [27]. Of note, model [18] recently applied the method in the calculation of time optimal control problem (TOCP), which led to the approximation of linear programing model.

4.1. Transformation of LOCTP to Functional Space

Let the compact set $X = X_1 \times ..... \times X_7 \subset \Re^7$ and $Q = Q_1 \times Q_2 \subset \Re^2$ be the respective values of the model state variables $y(\cdot)$ and control input $q(\cdot)$, such that we set $N = [t_0, t_f]$.

Definition 4.1 We define a triple $k = [t_f, y, q]$ to be admissible if the following conditions hold:

i. The vector function $y(\cdot)$ be absolutely continuous and contain in X for all $t \in N$

ii. The function $q(\cdot)$ takes its values in the set Q and is Lebesgue measurable on N

iii. The function q satisfies in system (11), i.e. on T^0, the interior of N.

Then, we assume that the set of all admissible triple is non-empty and is denoted by m. Let k be an admissible triple and B be an open ball in $\Re^7$ containing $N \times X$ and $D'(B)$ be the space of all real-valued continuous differential equation on it. Let $\delta \in D'(B)$ and define δ^g as follows:

$$\delta^g(t, y(t), q(t)) = \frac{d\delta(t, y(t))}{dt}$$

$$= \sum_{n=1}^{7} \frac{\partial \delta(t, y(t))}{\partial y_n} g_n(t, y(t), q(t)) + \frac{\partial \delta(t, y(t))}{\partial t} \qquad (12)$$

for each $[t, y(t), q(t)] \in \Omega$, where $\Omega = N \times X \times Q$. The function δ^g is in the space $D(\Omega)$, the set of all continuous functions on the compact set Ω. Since $k = [t_f, y, q]$ is an admissible triple, we obtain

$$\int_{t_0}^{t_f} \delta^g(t, y(t), q(t))dt = \delta(t, y(t_f)) - \delta(t_0, y(t_0)) = \Delta\delta \qquad (13)$$

for all $\delta \in D'(B)$.

Let $H(N^0)$ be the space of infinitely differentiable all real-valued function with compact support in N^0. Define:

$$B^n(t, y(t), q(t)) = y_n(t)\delta'(t) + g_n(t, y(t), q(t)\beta(t), n = 1, ..., 7 \forall \beta \in H(N^0) \qquad (14)$$

Then, if $k = [t_f, y, q]$ be admissible triple for $n = 1, ..., 7$ and $\forall \beta \in H(N^0)$, by equation (14), we obtain

$$\int_{t_0}^{t_f} \beta^n(t, y(t), q(t))dt = \int_{t_0}^{t_f} y_n(t), \beta'(t)dt + \int_{t_0}^{t_f} g_n(t, y(t), q(t))\beta(t)dt$$

$$= y_n(t)\beta(t)\Big|_{t_0}^{t_f} + \int_{t_0}^{t_f} y_n(t), \beta'(t)dt + \int_{t_0}^{t_f} g_n(t, y(t), q(t))\beta(t)dt$$

since the function $\beta(\cdot)$ has compact support in N^0, so $\beta(t_0) = \beta(t_f) = 0$ and $\dot{y}_n = g_n$. So,

$$\int_{t_0}^{t_f} \beta^n(t, y(t), q(t))dt = 0. \tag{15}$$

Furthermore, by adopting the functions of time dependent, we have:

$$\int_{t_0}^{t_f} \eta(t, y(t), q(t))dt = a_\eta, \forall \eta \in D'(\Omega) \tag{16}$$

where $D^1(\Omega)$ is the space of all functions in $D(\Omega)$ that depend only on time linearly and a_η is the integral of η on N. Equations (13), (15) and (16) are really weak form of the first, third and fourth equations of equation (11). It's obvious that third constraint of equation (11) is considered on the right side of equation (13) with functions $\delta \in D'(B)$, which are monomials of y_1. Similarly, the fourth constraint is considered by appropriate definition of set X. Then, we can now consider the following linear functional on $D(\Omega)$. Define:

$$\Gamma_k : G \to \int_\eta G(t, y(t), q(t))dt, \forall G \in D(\Omega) \tag{17}$$

Proposition 4.1 The transformation $k \to \Gamma_k$ of admissible triple in M into the linear mappings Γ_k defined in (17) is an injection.

Proof Here, we start by showing that if $k_1 \neq k_2$, then $\Gamma_{k_1} \neq \Gamma_{k_2}$. Let $k_n = [t_f, y_n, q_n], n = 1, 2$ be different admissible triples. If $t_{f_1} = t_{f_2}$ then there is a subinterval of $[t_0, t_f]$, say n_1, where $y_1(t) \neq y_2(t)$ for each $t \in n_1$. A continuous function G can be constructed on Ω so that the right-hand side of (17) corresponding to k_1 and k_2 are not equal. In the same requirement, assume G b is independent of q such that foe all $t \in N_1$, the function is non-negative for the graph of $y_1(t)$ but zero on $y_2(t)$, then the linear functional are not equal. In other words, if $t_1 \neq t_2$, then Γ_{k_1} and Γ_{k_2} have different domains and are not equal.

Thus, the LOCTP of (10)-(11) is converted to the following optimization problem in functional space:

$$\text{Maximize } \Gamma_k(1) \qquad \text{(from (10))} \tag{18}$$

Subject to

$$\begin{aligned} &\Gamma_k(\psi^g) = \triangle\psi, \psi \in D'(B) \\ &\Gamma_k(\beta^n) = 0, n = 1, \ldots 7, \beta \in H(N^0) \\ &\Gamma_k(\eta) = a_\eta, \eta \in D'(\Omega) \\ &\Gamma_k(E) \leq \tau \end{aligned} \tag{19}$$

where $E(t, y(t), q(t)) = u_T(t) + z(t) + w(t) - [\sigma_1(q_1(t))^2 + \sigma_2(q_2(t))^2]$ and equation (19) generated from equations (13, 15, 16 and 10) respectively.

4.2. Transformation to Measure Space

Let $L^+(\Omega)$ denotes the space of all non-negative Radon measures on Ω. By the Riez representation theorem, there exists a unique positive Radon measure μ on Ω such that:

$$\Gamma_k(G) = \int_N G(t, y(t), q(t))dt = \int_\Omega G(t, y, q)d\mu \equiv \mu(G), G \in (\Omega). \tag{20}$$

Then, we can transform the space of optimization problem to measure space. Conveniently, this implies that optimization problem in functional space (18)-(19) can be transform to the following new problem in measure space:

$$\underset{\mu\in L^{+}(\Omega)}{Maximize}\ \mu(1) \tag{21}$$

Subject to

$$\begin{aligned}&\mu(\delta^{g}) =_{\Delta}\delta, \delta\in D'(B)\\ &\mu(\beta^{n}) = 0, n = 1,...7, \beta\in H(N^{0})\\ &\mu(\eta) = a_{\eta}, \eta\in D^{1}(\Omega)\\ &\mu(E)\le\tau\end{aligned}. \tag{22}$$

Thus, we see at once that we're now considering the maximization of (21) over a set of all positive Radon measure on Ω denoted by A and which satisfies equation (22).

Remark 6 We opt for the exploration of this measure theoretical approach for the problem following the existence of an optimal measure in the set A, which can be solve in a straightforward manner without having imposition of conditions of artificial convexity. The following theorem further buttresses the above assertion.

Theorem 4.1 Revoking ([18], Thm. 4.2.1, p.52)

The measure theoretical problem of maximizing (21) with equality and inequality constraints (22) has an optimal solution μ^{*}.

Proof Here, we show that second and third equations of (22) are special version of the first equation of (22). Therefore, the set A can be written as $A = A_{1}\cap A_{2}$, where

$$A_{1} = \bigcap_{\delta\in D'(B)}\{\mu\in L^{+}(\Omega): \mu(\delta^{g}) =_{\Delta}\psi\}$$

and

$$A_{2} = \{\mu\in L^{+}(\Omega): \mu(E)\le\tau\}$$

Assume that $k = [t_{f}, y, q]$ is an admissible triple. It is well-known that the set $\{\mu\in L^{+}(\Omega): \mu(1) = t_{f} - t_{0}\}$ is compact in weak* - topology. Furthermore, A_{1} as intersection of inverse image of closed singleton set $\{\Delta\delta\}$ under continuous function $\mu\to\mu(\delta^{g})$ is also closed. It can be shown in a similar way that A_{2} is closed. Thus, A is a close subset of a compact set. This proves the compactness of the set A. Since the functional as intersection $\mu\to\mu(1)$ mapping the compact set A on the real line is continuous and so has a maximum on the compact set A.

Next, following the analysis in [26], the problem (21)-(22) is approximated by a LP problem and a triple k^{*}, which approximate the action of $\mu^{*}\in A$ is achieved.

4.3. Approximation for Measure space Problem

Of interest, the problem in measure space (21)-(22) is an infinite dimensional linear programing problem of which all the functions in (22) are linear with respect to measure μ. This is obvious following the fact that $L^{+}(\Omega)$ is infinite dimensional space. Remarkably, approximation of solution of this problem is overcome by the solution of a finite dimensional LP of sufficiently large dimension. Then, from the solution of this new finite dimensional LP, we induce an approximated admissible triple in a suitable manner.

The simplification of these processes requires us to construct an intermediate problem still infinite-dimensional for (21) but not over the set A. Rather, over a subset $L^{+}(\Omega)$ and having only a finite

numbers of constraints with (22) being satisfied. We achieve this by choosing countable sets of functions whose linear combinations are dense in the sets $D'(B), D^1(\Omega)$ and $H(N^0)$ from which we then select a finite number of them.

Assume the set $\{\delta_i : i = 1,2,.....\}$ be such that the linear combinations of the functions $\delta_i \in D'(B)$ are uniformly dense in $D'(B)$. For instance, these functions can be taken to be monomials in t and the components of the vector y. Next, we show that these monomials are suitable for our problem i.e.

$$t^i y_1^n = y_1^n y_h^i, i \in \{0,1\}, n \in \{1,2,.....\}, h \in \{2,3,..,7\}. \tag{23}$$

We set $\{\beta_i : i = 1,2,.....\}$ such that the linear combinations of the functions $\beta_i \in H(N^0)$ are uniformly dense in $H(N^0)$. For $s = 1,2,.....$ with some function designated as [27]:

$$\beta_{2s-1}(t) = \begin{cases} \sin(\frac{2\pi s(t-t_0)}{\triangle T}) & t \le t_1 \\ 0 & otherwise \end{cases}$$

and

$$\beta_{2s}(t) = \begin{cases} 1-\cos(\frac{2\pi s(t-t_0)}{\triangle T}) & t \le t_1 \\ 0 & otherwise \end{cases} \tag{24}$$

where $\triangle T = t_1 - t_0$ and t_1 is a lower bound for optimal time, which can be obtain via controllability.

Finally, let the set $\{\eta_i : i = 1,2,.....\}$ be such that the linear combinations of the functions $\eta_i \in D^1(\Omega)$ are uniformly dense in $D^1(\Omega)$. These functions are monomials in t and are given as:

$$\eta_w(t) = t^w, w = 0,1,2..... \tag{25}$$

Remark 7 From the basis of (12) and (14), it is obvious that second and third equations of (11) are also derived from the first equation of (11) if we set $\delta(t, y(t)) = y_n(t)\beta(t)$ and $\delta(t, y(t)) = \int_0^t \eta(\xi)d\xi$ respectively.

Therefore, completion of approximation approach for the measure space is subject to the following 3 propositions:

Proposition 4.2 Assuming the linear program is consisting of maximizing function $\mu \to \mu(1)$ over the set U_L of measures in $L^+(\Omega)$ and satisfying: $\mu(\delta_i^g) = \triangle\delta_i, i = 1,....., L$ and $\mu(E) \le \tau$. Then $\gamma_L \equiv \max_{U_L} \mu(1)$ tends to $\gamma \equiv \max_U \mu(1)$ as $L \to \infty$.

Proof Given that $U_1 \supseteq U_2 \supseteq .....U_L \supseteq ..... \supseteq U$, then $\gamma_1 \ge \gamma_2 \ge .....\gamma_L \ge ..... \ge \gamma$. Hence, $\{\gamma_r\}$ is non-increasing and bounded sequence, which converges to the number λ, such that $\lambda \ge \gamma$.

Set $R \equiv \bigcap_{L=1}^{\infty} U_L$, then $R \supseteq U$ and $\lambda \equiv \max_R \mu(1)$. It is sufficient to show $R \subseteq U$. Assume $\mu \in R$ and $\delta \in D'(B)$. Since linear combinations of the functions $\{\delta_n, n = 1,2,.....\}$ are uniformly dense in $D'(B)$, there is the sequence $\{\tilde{\delta}_p\} \in span\{\delta_n, n = 1,2,.....\}$ such that $\tilde{\delta}_p$ tends to δ uniformly as $p \to \infty$. Hence, W_1, W_2 and W_3 tends to zero as $p \to \infty$ where $W_1 = \sup\left|\delta_y - \tilde{\delta}_{p_y}\right|, W_2 = \sup\left|\delta_t - \tilde{\delta}_{p_t}\right|$

and $W_3 = \sup\left|\delta - \tilde{\delta}_p\right|$. Then, we have $\mu \in R$ and functional $g \to \mu(g)$ is linear. Therefore, $\mu(\tilde{\delta}_p^g) = \triangle\tilde{\delta}_p$ and $\left|\mu(\delta^g) - \triangle\delta\right| = \left|\mu(\delta^g) - \triangle\delta - \mu(\tilde{\delta}_p) + \triangle\tilde{\delta}_p\right|$

$$= \left|\int_\Omega \{[\delta_y(t,y) - \tilde{\delta}_{p_y}(t,y)]g(t,y,q) + [\delta_t(t,y) - \tilde{\delta}_{p_t}(t,y)]\} d\mu - (\triangle\delta - \triangle\tilde{\delta}_p)\right|$$

$$\leq W_1 \int_\Omega \left|g(t,y,q)\right| d\mu + W_2 \int_\Omega d\mu + 2W_3.$$

Since the R.H.S. of the above inequality tends to zero as $p \to \infty$, while L.H.S. is independent of p, then $\mu(\delta^g) = \triangle\delta$. Thus, $R \subseteq U$ and $\lambda \geq \gamma$, which implies $\lambda = \gamma$.

□

Proposition 4.3 The measure optimal solution $\mu*$ in the set U_L at which the functional $\mu \to \mu(1)$ attains its maximum has the form

$$\mu* = \sum_{n=1}^{L+1} \alpha_n^*(z_n^*) \tag{26}$$

where $\alpha_n^* \geq 0, z_n^* \geq 0$ and $\varphi(z)$ is unitary atomic measure with the support being the singleton set $\{z_n^*\}$, characterized by $\varphi(z)(G) = G(z), z \in \Omega$.

Proof In restricting our attention to finding measure in the form $\mu = \sum_{n=1}^{L+1} \alpha_n \varphi(z)$, which maximizes functional $\mu \to \mu(1)$ and satisfies last equation (22) and L number of constraints in the form of first-third of equation (22), we invoke the result of appendix of [25]. Clearly, $\mu(G) = \sum_{n=1}^{L+1} \alpha_n G(z_n), \forall G \in D(\Omega)$. Therefore, by choosing L number of functions in the form of (23), W number of functions in the form of (24), which leads to $L_2 = 7L_2'$ number of functions of the kind (16) for which we have numbers sequentially as $\kappa o_h, h = 1, ..., L_2$. Then, the infinite dimensional problem (21)-(22) is approximated with the aid of finite dimensional non-linear programing (NLP) problem:

$$\underset{\alpha_n \geq 0, z_n \in L^+(\Omega)}{Maximize} \sum_{n=1}^{L+1} \alpha_n \tag{27}$$

Subject to

$$\begin{aligned} &\sum_{n=1}^{L+1} \alpha_n \delta_i^g(z_n) = \triangle\delta_i, i = 1, ..., L_1 \\ &\sum_{n=1}^{L+1} \alpha_n IO_h(z_n) = 0, h = 1, ..., L_2 \\ &\sum_{n=1}^{L+1} \alpha_n \eta_w(z_n) = a_\eta, w = 1, ..., W \\ &\sum_{n=1}^{L+1} \alpha_n E(z_n) \leq \tau \end{aligned} \tag{28}$$

where $L = L_1 + L_2 + W$. We are then confronted with NLP with more than $2(L+1)$ unknown $\alpha_n, z_n, n = 1, ..., L+1$.

Finally, using the finite dimensional linear programing problem, the following last proposition guarantees the approximation of the problem.

Proposition 4.4 Let $\Omega_j = \{x_1, x_2, ..., x_j\}$ be a countable dense subset of Ω, for any J sufficiently large number. Given $\varepsilon \geq 0$, a measure $\omega \in L^+(\Omega)$ can be found such that

$$\begin{aligned} &\left|\omega(\delta_i^g) - \mu^*(\delta_i^g)\right| \leq \varepsilon, i = 1, ...L_1 \\ &\left|\omega(ю_h) - \mu^*(\delta_h)\right| \leq \varepsilon, h = 1, ...L_2 \\ &\left|\omega(\eta_w) - \mu^*(\eta_w)\right| \leq \varepsilon, w = 1, ...W \\ &\left|\omega(E) - \mu^*(E)\right| \leq \varepsilon \end{aligned} \tag{29}$$

where ω is a measure with the form:

$$\omega = \sum_{n=1}^{L+1} \alpha_n^* \varphi(z_n) \tag{30}$$

and having the coefficient $\alpha_n^*, n = 1, ..., L+1$ been the same as optimal measure (26) and $z_n \in U_J, n = 1, ..., L+1$.

Proof Suppose functions $\delta_i^g\,'s, ю_h\,'s, \omega_s\,'s$ and E are sequentially rename as $G_n, n = 1, ..., L+1$. Then for $n = 1, ..., L+1$,

$$\left|(\mu^* - \omega)G_n\right| = \left|\sum_{n=1}^{L+1} \alpha_n^* [G_n(z_n^*) - G_n(z_n)]\right|$$

$$\leq \left(\sum_{n=1}^{L+1} \alpha_n^*\right) \max_{i,n} \left|G_n(z_n^*) - G_n(z_n)\right|$$

with $G_n\,'s$ continuous. Therefore, $\max_{i,n}$ can be made less than $\dfrac{\varepsilon}{\sum_{n=1}^{L+1} \alpha_n^*}$ by choosing $z_i, i = 1, ..., L+1$, sufficiently near z_i^*. We then construct the dense subset Ω_J, such that N is divided into W subintervals as follows:

$$N_w = \left[t_0 + \frac{(w-1)\Delta T}{W-1}, t_0 + \frac{w\Delta T}{W-1}\right), w = 1, 2, ..., W-1$$

and

$$N_w = \left[t, t_f\right). \tag{31}$$

Furthermore, the intervals $P_i\,'s$ and $Q_n\,'s$ are divided into u_i and v_j subintervals respectively. Then, the set Ω is divided into $J = Wu_1u_2u_3u_4u_5u_6v_1v_2$ cells. One point is chosen from each cell, yielding a grid of points, which are numbered sequentially as $x_n = (t_n, y_{1_n}, ..., y_{7_n}, q_{1_n}, q_{2_n}), n = 1, ..., J$.

Remark 8 The function of the kind (25) can be conveniently approximated by a linear combination of characteristic function of subintervals of N. Therefore, in reality, we observe the function $\eta_w(t) \equiv \chi_{N_w}(t), w = 1, ..., W$ instead of the function (25), where $N_w\,'s$ are represented by (31) and χ_{N_w} denotes the characteristic function of N_w. This is obvious for the choice of $\eta_w\,'s$ because of it crucial role in construction of control functions [24, 25].

Therefore, considering the equation (30), the NLP (27)-(28) is transformed to LP of the form:

$$\underset{\alpha_n \geq 0}{Maximize} \sum_{n=1}^{J} \alpha_n \tag{31}$$

Subject to

$$\begin{aligned} &\sum_{n=1}^{J} \alpha_n \delta_i^{g}(\gamma_n) = \Delta\delta_i, i = 1,....,L_1, \quad \sum_{n=1}^{u} \alpha_n = \frac{\Delta T}{W-1} \\ &\sum_{n=1}^{J} \alpha_n IO_h(\gamma_n) = 0, h = 1,....,L_2, \quad \sum_{n=(W-2)u+1}^{(W-1)u} \alpha_n = \frac{\Delta T}{W-1} \\ &\sum_{n=1}^{J} \alpha_n E(\gamma_n) \leq \tau, \quad \sum_{n=(W-1)u+1}^{Wu} \alpha_n = t_f - t_u, \quad y_i(t_f) \in P_i, i = 2,3,4,5,6,7 \end{aligned} \tag{33}$$

where $u = \frac{J}{W}$. So, more importantly we need only to construct the function $q(\cdot)$, since $y(\cdot)$ is simply the corresponding solution of differential equations of the system (3), which can be numerically estimated.

Thus, by simplex method approach, nonzero optimal solution $\alpha_{i_1}^*, \alpha_{i_2}^*, ...\alpha_{i_k}^*$ of LP (32)-(33) can be obtain with k not exceeding the number of constraints i.e. $k \leq L_1 + L_2 + W + 1$. By setting $\alpha_{i_0}^* = t_0$, piecewise control pair $r(t) = (r_1(t), r_2(t))$, which thus approximate the action of the optimal control base on the nonzero coefficients i.e.

$$q(t) = \begin{cases} (q_{1_{i_n}}, q_{2_{i_n}}) & t \in \left[\sum_{h=0}^{n-1} \alpha_{i_h}^*, \sum_{h=0}^{n} \alpha_{i_h}^* \right), n = 1,2,....,k \\ 0 & otherwise \end{cases}$$

where $q_{1_{i_n}}$ and $q_{2_{i_n}}$ are respectively 8th and 9th components of x_{i_n} .

5. Numerical Simulations and Discussion

In affirmation of our established model, we shall simulate a number of illustrative examples for a no treatment situation and then for the application of chemotherapy. This is followed by the analyses (discussion) of the achieved results.

5.1. Numerical Simulations

We set to perform a number of numerical simulations to account for our analysis in sections 2, 3 and 4 respectively. First, we illustrate the viability of the methodological application of treatment functions by considering the case when treatments were not initiated i.e. $q_1, q_2 = 0$. Then, the implication is that for a standard model of equation (3), we investigate the crucial role of natural adaptive immune effectors response and the intrinsic virulence of dual viruses.

For simplicity and compatibility with Runge-Kutter of order 4 in Mathcad surface, we convert the state variables to read $\{U_T, I_T, V, P, W, Z, R\} = \sum_{i=1}^{7} H_i, i = 1,..,7$, such that for $q_1, q_2 = 0$ and applying [9] with time interval of $[t_0, t_f] = (3,30]$ and model values as in tables (1 & 2), we investigate as depicted by fig. 2(a-d) an infected patient with only immune effectors response as the only anti-HIV antigens.

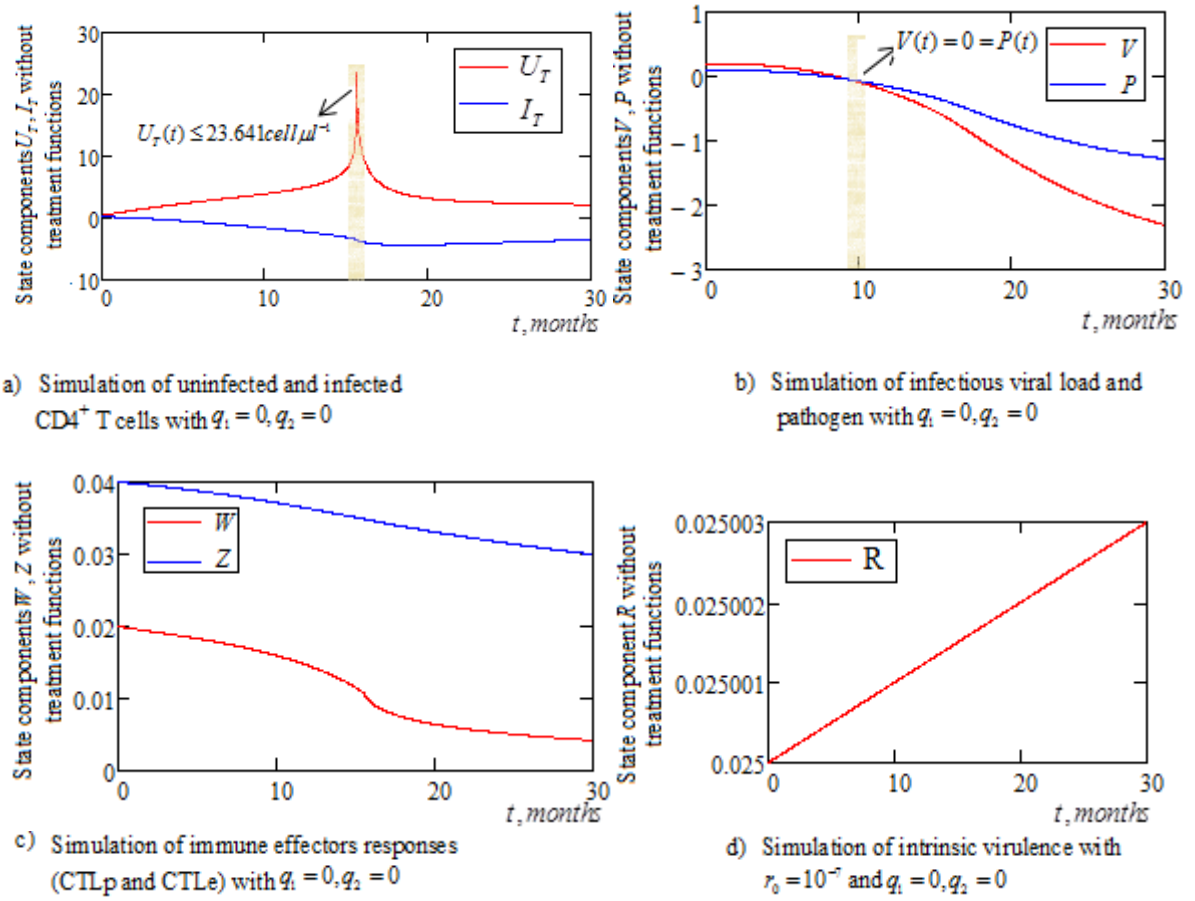

Fig. 2 (a-d) *Simulation of untreated dual HIV-pathogen with* $CTLp = 0.2 = CTLe$ *and* $q_1 = 0 = q_2$

Specifically, fig. 2(a) depicts two key state components – the epidemiological behavior of healthy CD4$^+$ T cells, $U_T(t)$ and the corresponding ravage infected CD4$^+$ T cells $I_T(t)$. Here, we observe that the first function $U_T(t)$ exhibits gradual inclination with geometric peak value $0.4 \le U_T(t) \le 23.641 cell\,\mu l^{-1}$ only at the interval $14 \le t_f \le 16$ months. Healthy CD4$^+$ T cells thereafter decline to minimal value of $U_T(t) = 2.5 cell\,\mu l^{-1}$ for $16 \le t_f \le 30$ months. The second function denoting infected T-cells are characterize by gradual decline due to active immune effectors response with minimal value $-4.364 cell\,\mu l^{-1}$ at $18 \le t_f \le 21$ months and thereafter incline slightly to $I_T(t) = -3.72 cell\,\mu l^{-1}$.

From fig. 2(b), we see infectious patient with high adaptive natural immune effectors response combating replication of virions at the early set-point of infection i.e. $t_f \le 10$, following possible self-restriction and adherent to medicated conditions. Both virions (viral load and pathogen) achieve zero elimination at the time interval $t_f \ge 10$ months due to concentration of CTLp and CTLe. Fig. 2(c) reveals an undulating trajectory decline of precursors of CTLs with $0.01 \le W(t) \le 0.02 cell\,\mu l^{-1}$ at $t_f \le 16$ months. The component further decline upon prolong observation with $W(t) \le 4.203 \times 10^{-3} cell\,\mu l^{-1}$ at $16 \le t_f \le 30$ months. The second state component $Z(t) \le 0.04 cell\,\mu l^{-1}$ representing active effectors of CTLs exhibits slight linear decline at initial period at $t_f \le 16$ months with sharper decline to $Z(t) \le 0.03 cell\,\mu l^{-1}$ at $16 \le t_f \le 30$ months. Furthermore, under the auspices of only adaptive immune effectors response, the aggressiveness of

virions (intrinsic virulence) remains slightly on the increase as depicted by fig. 2(d). Here, $R(t)$ increases from $R(t) = 0.025 \rightarrow 0.025003 mlcopies^{-1}d^{-1}$ at $3 \le t_f \le 30$ months.

Further investigation is conducted following the introduction of treatment functions, which ensure that $q_{i=1,2} \ge 0$ and with parameter values as prescribed by tables (1 & 2). Clearly, we investigate the initiation of highly toxic chemotherapy at set-point, i.e. $q_1(t) = 0.5, q_2(t) = 0.3$, such that the optimal weight factors regulating these chemotherapies is given by $\sigma_1 = 10, \sigma_2 = 100$. Then, fig. 3(a-d) below represents the linear programing for treated asymptomatic dual HIV-pathogen infected patient under multiple chemotherapy and dual cytotoxic T-lymphocytes.

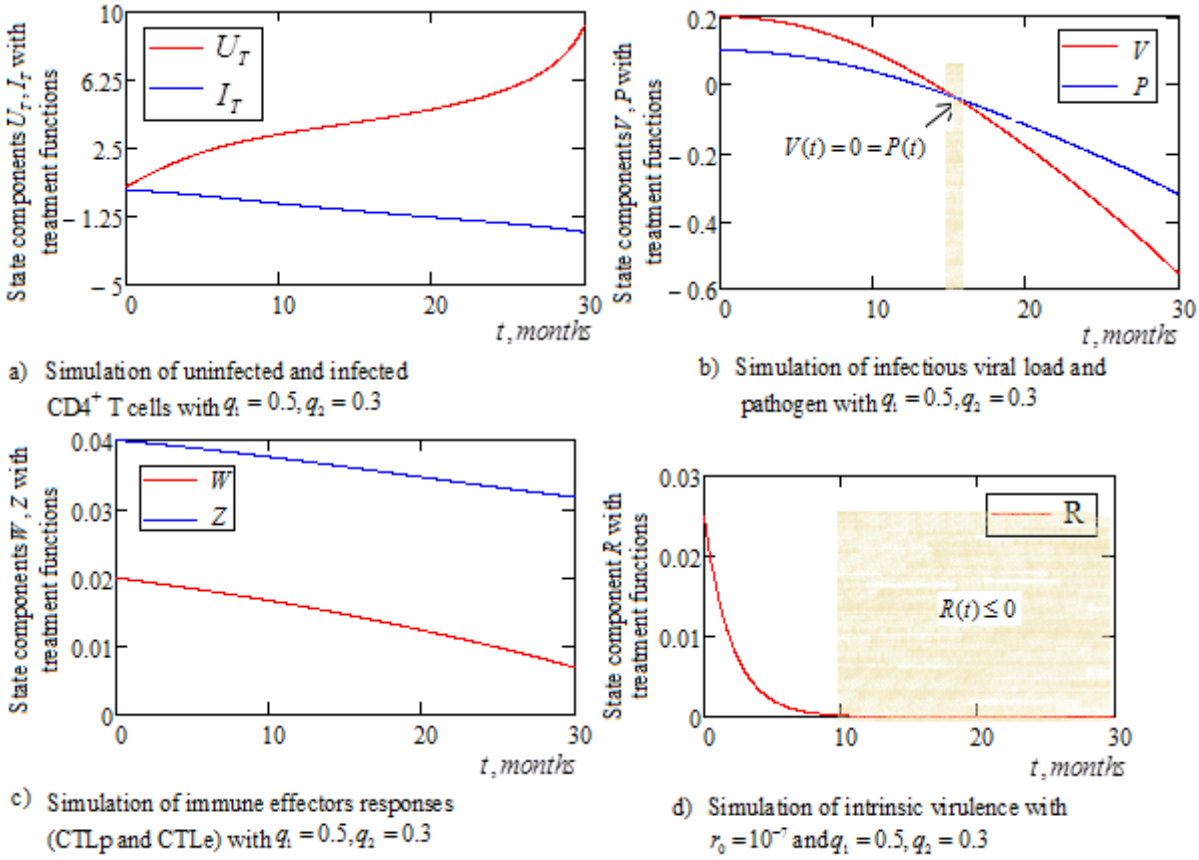

Fig.3(a-d) *Behavioral dynamics of treated state components* U_T, I_T, V, P, W, Z, R *with* $q_1 = 0.5, q_2 = 0.3$

From fig. 3(a), we investigate the healthy and infected CD4$^+$ T cells progression given the above medical conditions. In the first case for $U_T(t)$, we observe overall initial slight concave inclinatory trend in the interval $3 \le t_f \le 14$ months and then assume slant convex inclination achieving maximum value of $U_T(t) \le 9.328 cell\,\mu l^{-1}$ at $t_f \le 30$ months. The second state function – the infected CD4$^+$ T cells shows smooth linear decline of infectious particles to complete zero in the time interval $16 \le t_f \le 30$ months. In fig. 3(b), the first function representing viral load $V(t)$ is seen to exhibit initial sharp concave declination with minimal zero value at $t_f \le 16$ months. The second state function – parasitoid-pathogen $P(t)$, exhibits similar declining behavior with shallow initial decrease when compared to viral load. Of note, the elimination of both virions is achieved at $t_f \le 16$ months (i.e. $t_f \equiv 480 days$).

From fig. 3(c), we investigate the contributive roles of two sub-CTLs (CTLp and CTLe). The first state function $W(t)$ representing the passive immune precursor of CTLs exhibits slight concave declination with value $6.833 \times 10^{-3} \le W(t) \le 0.02 cell\,\mu l^{-1}$ at $3 \le t_f \le 30$ months. Similarly, the active

immune effectors of CTLs shows linear decline with value $0.032 \leq Z(t) \leq 0.04 cell\,\mu l^{-1}$ in the interval $3 \leq t_f \leq 30$ months of clinical investigation. Finally, from fig. 3(d), following the introduction of multiple chemotherapies functions and dual cytotoxic T-lymphocytes concentration, virions aggressiveness (intrinsic virulence) denoted by $R(t)$ is seen subdue to near zero value at $10 \leq t_f \leq 30$ months.

5.2. Discussion

The present study seek using ODEs the formulation of 7-Dimensional nonlinear mathematical dual HIV-pathogen dynamic model for the determination of time optimal control problem for a fast progressing asymptomatic HIV-pathogen infected patient. The treatment functions as applied in this study involve quadrupled treatment controls with model transformed to a time optimal control problem. The model analyses explored approximation approach of linear programing method followed by quantitative numerical simulations. The study is an explicit extension of related scientific investigations as was carefully highlighted in literature of this paper.

In the circumstance of our formulated model, investigation was initiated for situation where infected patients had no access to medicated treatment but were rather left to the critical role of adaptive natural immune effectors response. Results showed that for a patient with harmonized immune effectors, quantifiable healthy $CD4^+$ T cells are sustained with flash peak value of $U_T(t) \leq 23.641 cell\,\mu l^{-1}$ at the interval $14 \leq t_f \leq 16$ months. On the other hand, infected $CD4^+$ T cells reduced to near zero in the same time interval but thereafter submerges. The toxicity of both virions exhibited slight sustainability at the early time interval of $t_f \leq 10$ months and thereafter declined. The critical role of both CTLp and CTLe is evidence by the ever positive values with slight decline due to possible natural clearance rate. This situation affirmed the minimal sustainability of healthy $CD4^+$ T cells by infected patient. Moreso, increase sustenance of virions aggressiveness ascertains the absence of chemotherapy at this situation.

Further deduction following the introduction of treatment functions resulted to enhanced maximization of healthy $CD4^+$ T cells with steady increase to $U_T(t) \leq 9.328 cell\,\mu l^{-1}$ while infected $CD4^+$ T cells were eliminated after $t_f \leq 16$ months. This situation was visualized with the elimination of both virions at the 16^{th} month of active chemotherapy application. The model thus aligned the study by [18], which had set upperbounds time benefit on cost to be $480 days \cong 16$ months. This outcome suggests possible termination of chemotherapy administration and concurrently accounted for any possible drug side-effects. Furthermore, the ascertainment of the present investigation is ascertained by the complete elimination of intrinsic virulence of infectious viruses as in fig. 3(d). The implication is that with the application of chemotherapy treatments, linear growth of intrinsic virulence is reversed. Moreso, we as well observed that prolongation of chemotherapies, which boosted CTLs leads to significant maximization of healthy $CD4^+$ T cells and are in collaboration with the experimental findings of [14, 29, 30].

Thus, the overall results which indicated $t_f \leq 16$ months of cohesive treatment administration, translate to the desired minimization of cost of medication. Moreso, the decline in infected $CD4^+$ T cells following the presence of treatment functions were comprehensively vindicated by the sharp decline of dual virions to very low level with healthy $CD4^+$ T cells sustained at maximum level and linear expansion of both precursors and effectors of CTLs.

6. CONCLUSION

In overcoming the weakness identified from a number of related scientific investigations, this paper had formulated using ODEs, a novel 7-Dimensional non-linear mathematical dynamic model for the optimal control treatment of asymptomatic dual HIV-pathogen infections on host target $CD4^+$ T cells. The study adopted quadrupled treatment functions with model constructed as a time optimal control problem and analyzed using linear programing approximation method. Results of numerical simulations affirmed the maximization of healthy $CD4^+$ T-lymphocytes, suppression of dual HIV-

pathogen infectivity, increase sustainability of dual CTLs critical role, early elimination of virions aggressiveness with an overall minimization of benefit on cost. Therefore, the result which justified the application of linear programing approximability approach, strongly advocates the inclusion of delay intracellular component on state variables as an enhancement in future studies.

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