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Optimal Control Techniques for the Role of Antiretroviral Therapy (ART) Abuse in HIV/AIDS Treatment Dynamics

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Abstract: From the studies of HIV/AIDS transmission and treatment dynamics using mathematical modeling, literature reviews have shown that attention had not been given to the behavioral attitude of screen-aware infectives not ready to receive treatment, HIV-aware infectives that initiated treatment but truncated only to resume treatment later (therapy abuse) and those on consistent treatment protocols. Moreso, following the non-outright eradication of the deadly HI-virus, recommendations have been geared towards exploring optimal control theory for the maximization of healthy uninfected CD4$^+$ T-cells. Therefore, this present investigation seeks and formulated an optimal control 6-Dimensional deterministic mathematical dynamic model, which accounted for the Role of Antiretroviral Therapy (ART) abuse in the treatment dynamics of the HIV/AIDS epidemic. The materials and methods for this model are constituted by a set of 6-Dimensional varying subpopulations interacting with concentrated HI-viral load. Interactions are investigated using bilinear control functions (condom use and ART) with empirically generated data. The model assumed a deterministic approach and was formulated using the fundamental theory of differential equations. Theoretical optimal predictions explored classical numerical methods with optimal control techniques (Pontryagin's maximum principle in conjunction with Hessian matrix) as a basis. Numerical simulations were conducted using in-built Runge-Kutta of the order of precision 4 in a Mathcad surface. Following the derived model for both off-optimal control and onset-optimal control functions and model optimal control pair as well as model optimality system, results of simulations indicated that at off-optimal control function, near zero population extinction was observed. From the application of optimal control functions under optimal control techniques, there exists tremendous rejuvenation of susceptible populations vindicated by a reduction in the rate of ART abuse under a minimal proportion of bilinear control functions. The study concluded that adopting optimal control techniques for the investigation of the role of ART abuse in HIV/AIDS treatment yield highly significant recovery of healthy CD4$^+$ T-Cells at minimal systemic cost when compared with off-optimal control outcome. Therefore, the study not only affirmed the vital concept of optimal control strategy but also, instituted the viability of the model. Thus, this model can be extensively used in Bio-system and applied mathematics.

Keywords: Hamiltonian-Argument, Pontryagin's-Maximum-Principle, Two-Point-Boundary-Value-Problem, Optimal-Control-Protocols, Dual-Bilinear-Control-Functions MSC (2010) 35F20, 93C15, 93A30, 49J15, 90C46

Introduction

Biologically, Human Immunodeficiency Virus (HIV) belongs to a well-known retroviral family known as Retroviridae. Retroviridae consists of viruses having a unique form of RNA replication. The transcription of mRNA, which leads to viral entry is more than just a known factor due to the indistinguishable nature of the

disease at the initial set point, (Ndziessi *et al.*, 2013). That is, despite enormous scientific investigations and many theories, the origin of AIDS is yet to be traced.

The problem of HIV remains an important component of mankind and the solutions are often based on the in-depth application of mathematical modeling in understanding the mechanism of the spread of the virus among the population. In reality, following the discovery of HIV in the early 80s and the assumed incurable status of the virus, understanding the dynamics of HIV/AIDS has been through theoretical and numerical explanations via mathematical modeling, (Centers for Disease Control, 1982). Mathematical modeling plays a vital role and has been used extensively for the research into the epidemiology of HIV/AIDS and proved through the overwhelming use of first-Order Differential Equations (ODEs). Moreso, the application of mathematical models often aims at formulating and investigating either the control or prevention; and contact tracing of infected individuals from identified infected persons in a period. For instance, (Anderson *et al.*, 1986) used a mathematical model to investigate the preliminary study of the transmission dynamics of HIV, the causative agent of AIDS. On the other hand, (Knox, 1986) conducted transmission dynamics with a focused discussion of the transmission model for AIDS. The effort of these researchers was further strengthened by May and Anderson (1987), who extensively studied the transmission dynamics of HIV infection. Since then, several mathematical models on HIV transmission and treatment methodologies have been developed. For example, a mathematical model has been applied in the study of nonlinear dynamics in physiology and medicine, (Glass *et al.*, 2003). The analysis of the study applied Hopf bifurcation incorporating the Hodgkin-Huxley method with results indicating the existence of fixed points in an N-dimensional system and having N eigenvalues, which can be calculated numerically using the auto option.

Of note, reviews of mathematical models indicated that existing preventive measures had not achieved complete eradication of the deadly disease HIV/AIDS. Rather, the success of these control measures is best in lowering the rate of new virions replications and prolongation of infected individuals' lifespans. This situation that had risen curiosity among scientists leading to further dimensions aimed at enhancing HIV/AIDS prevention and treatment methodology. One aspect of this mathematical theory deemed useful by scientists is the optimal control theory, which is often used for the maximization of key variables while minimizing the cost of production. To this effect, notable optimal control models as far back as the 1990s, have been formulated in the area of infectious diseases-HIV/AIDS. For instance, (Butler *et al.*, 1997), formulated an optimal control of chemotherapy affecting the infectivity of HIV. The model, which used a single reverse transcriptase inhibitor (AZT) and explored Pontryagin's maximum principle, presented a simple framework for testing and development of models, which could lead to new and improved chemotherapy strategies. The study (Culshaw *et al.*, 2004), had proposed and formulated a similar model targeted at maximization of the immune response under minimized systemic cost. This study established an optimal control model of HIV treatment, using a single drug that reduces the cellular infection rate and explicitly incorporating the specific anti-HIV immune response as represented by levels of effector and memory CTLs. Results showed that ascribed control decreases soon after initiation of treatment, only to rise again, remain close to constant, and drop rapidly near the end.

In the instance of the success of the application of optimal control strategy, multi-chemotherapy was further investigated for HIV/AIDS dynamics and as an improvement to a single drug treatment schedule. An optimal control of an HIV immunology model involving two treatment control functions was formulated and studied (Joshi, 2002). The analysis of the model explored classical Pontryagin's maximum principle. Results of numerical simulations affirmed the fact that the efficacy of treatments is a function of optimal weight factors, which defined drug toxicity. As a follow-up, (Adams *et al.*, 2004) studied optimal STIs control approaches for the dynamic multidrug therapies "drug cocktails" for HIV. With the assumption that treatment protocol changes in a continuous manner, the model explored Pontryagin's minimum principle to achieve an optimal treatment schedule, where patients move from a virus dominant to an immune-dominant state. The study proposed an optimal control scheme that accounted for the application of two treatment functions, incorporating two immune responses, which were considered dual functions: State variables as well as serving as control functions under interacting two infectious virions-HIV and parasitoid pathogen. Results of the numerical simulations not only validate the maximal systemic cost of chemotherapy but proved to be sharper and coincide in terms of the performance index of healthy $CD4^+$ T cells when compared with existing results. Recently, the application of optimal control for the treatment of tumors with a framework consisting of radio-and anti-angiogenesis control strategies that are included in a tumor growth model is investigated. The model was governed by differential constraint of a non-smooth optimal control problem that aims at reducing the volume of the tumor while keeping the radio-and anti-angiogenesis chemical dosage to a minimum. The analysis explored Pontryagin maximum principle in conjunction with Sequential Quadratic Hamiltonian (SQH) method. The results of which indicated how optimization weights could be chosen to obtain treatment functions that successfully reduce the tumor volume to zero. Other related innovative optimal control models include: Hattaf and Yousfi (2018); Adgba and Mbah (2011).

Notably, an optimal scheme in the context of mathematical models is often in use for infectious epidemics. However, from available reviews, there is currently no consensus on the treatment strategies or medical interruption schemes that produces the best optimal results. Also noted, is the fact that there are varying levels of positive results towards contracting the spread of the deadly HIV/AIDS and maximization of the uninfected healthy CD4$^+$ T cells. Yet, none of these known models and presumably beyond have considered the investigation of HIV/AIDS epidemic dynamics in a structure, which incorporates condom use and accounting for the role of treatment behavioral change for screened aware infectives not ready to receive ART treatment, the aware infectives who initiated ART treatment but suddenly stop the ART protocol and later resume ART administration (ART abuse) among other subpopulations. Accounting for the limitations of these aforementioned studies using optimal control techniques, form the pivot of this present study. In (Bassey, 2022), the application of optimal control techniques on dual-bilinear controls for COVID-19 was successfully conducted. The model explored Pontryagin's maximum principle with classical results accomplished. More importantly, the precision of results from numerical simulations for this present investigation shall explore the best approaches from numerical methods in the form of computational methods and numerical approximations as had been the case for existing models, (Al-Smadi and Arqub, 2019; Al-Smadi et al., 2021).

Materials and Methods

The materials and methods for the study are constituted by a set of 5-Dimensional varying subpopulations interacting with concentrated HI-viral load studied using bilinear control functions (condom use and Antiretroviral Therapy-ART) amidst therapy abuse. The fact behind this investigation is unveiled by the problem statement of the study, followed by the transformation of the model into an optimal control problem. Optimal criteria are deplored for the derivation of system characterization and the existence of optimal control pair. The method for optimal analysis involves classical Pontryagin's maximum principle with the incorporation of the method of Hessian matrix. In-built Runge-Kutta of the order of precision 4 in a Mathcad surface will be deplored for numerical validations for both off and onset treatment scenarios.

Problem Statement and Model Derivation

In reality, understanding infectious disease transmission and treatment dynamics have been among other methods, through the use of mathematical modeling. Existing literature on HIV/AIDS models indicated that none have accounted for the behavioral attitude to treatment consistency by those screened to be aware of

their status. Moreso, treatment inconsistency occasioned by avoidable truncation, which could lead to colossal drug abuse has not been given the desired attention. For instance, (Bassey and Atsu, 2021), recently formulated a 6-Dimensional deterministic model that accounted for the global stability analysis of the aforementioned novel treatment dynamics but was devoid of the optimal control strategy. That is by extension, the application of optimal control techniques has not been explored to investigate the role of ART abuse in the treatment dynamics of HIV/AIDS infection. Moreso, in that study, it was recommended that any approach that could maximize healthy CD4$^+$T-cells was highly encouraged. Therefore, in our quest for maximization of some designated predominant state-space, the present study extending the model by Bassey and Atsu (2021) and incorporating optimality conditions, seeks to explore optimal control techniques for the investigation of the role of ART abuse in the HIV/AIDS treatment dynamics. In that study, designated methodological treatment functions include condom use and antiretroviral therapy, which was administered on a set of 6-Dimensional deterministic compartmental HIV/AIDS dynamic model partitioned into Susceptible population $S(t)$, HIV positive (infective) individuals who are unaware of their HIV status $I_1(t)$ aware infective population not ready to receive ART treatment $I_2(t)$, HIV positive (infective) individuals receiving ART $T(t)$, HIV positive population who are under ART but truncate the use of ART and then later resume the application of the ART (abuse of ART) $T_A(t)$ and full-blown AIDS population $A(t)$. The epidemiological equations of the model, of which parameter descriptions can be found (Bassey and Atsu, 2021), were derived as:

$$\begin{cases} \dfrac{dS}{dt} = \varphi_0 - \beta_i S - \mu S, \\[2mm] \dfrac{dI_1}{dt} = \beta_i S - (\mu + \delta + \theta)I_1, \\[2mm] \dfrac{dI_2}{dt} = \theta I_1 - (\mu + \delta + a_1)I_2, \\[2mm] \dfrac{dT}{dt} = a_1 I_2 + a_3 T_A - (\mu + \pi + a_2)T, \\[2mm] \dfrac{dT_A}{dt} = a_2 T - (\mu + \delta + a_3)T_A, \\[2mm] \dfrac{dA}{dt} = \delta(I_1 + I_2 + T_A) + \pi T - (\mu + \alpha)A \end{cases} \quad (1)$$

where:

$$\beta_{i(i=1,\dots,5)} = (1 - u_1)\left(\frac{\beta_1 c_1 I_1 + \beta_2 c_2 I_2 + \beta_3 c_3 T + \beta_4 c_4 T_A + \beta_5 c_5 A}{N(t)}\right) \quad (2)$$

with:

$$N(t) = S + I_1 + I_2 + T + T_A + A$$

and having initial conditions $N_i(t) \geq 0$, $i = 1,\ldots 6$ for all $t = t_0 = 0$. Against the backdrop of the above, the present study seeks to utilize the aforementioned system, which requires the transformation of the derived basic model to an optimal control model.

Formulation of an Optimal Control Problem

Here, we attempt to optimally investigate the impact of treatment functions (condom use and ART) in the presence of abuse of the latter. In other words, to mathematically derive our optimization problem, we first assume that our control functions μ_1 and η (where $\eta = a_1 + a_3$) vary in time and have antiviral effects on virions production. M_1 represents the rate at which condom use is applied and $\eta = a_1 + a_3$ denote the rate of application of ART, where a_1 is the consistent use of ART and a_3 depicts the resumption of ART after truncation.

Then, system (1) together with Eq. (2) becomes:

$$\begin{cases} \dfrac{dS}{dt} = \varphi_0 - \beta_i S(t) - \mu S(t), \\[2mm] \dfrac{dI_1}{dt} = \beta_i S(t) - (\mu + \delta + \theta) I_1(t), \\[2mm] \dfrac{dI_2}{dt} = \theta I_1(t) - (\mu + \delta + a_1) I_2(t), \\[2mm] \dfrac{dT}{dt} = a_1 I_2(t) + a_3 T_A(t) - (\mu + \pi + a_2) T(t), \\[2mm] \dfrac{dT_A}{dt} = a_2 T(t) - (\mu + \delta + a_3) T_A(t), \\[2mm] \dfrac{dA}{dt} = \delta (I_1(t) + I_2(t) + T_A(t)) + \pi T(t) - (\mu + \alpha) A(t) \end{cases} \quad (3)$$

where:

$$\beta_{i(i=1,\ldots,5)} = \frac{(1 - u_1(t))}{N(t)} \big(\beta_1 c_1 I_1(t) + \beta_2 c_2 I_2(t) + \beta_3 c_3 T(t) + \beta_4 c_4 T_A(t) + \beta_5 c_5 A(t) \big) \quad (4)$$

and having other initial conditions of the model (1) sustained. Thus, given Eq. (4), model (3) explicitly represents the typical optimal control equation for HIV/AIDS with time-dependent onset treatment. Since our model is time-dependent, the dynamical flow-chart is depicted in Fig. 1 below:

Definition 3.1

Objective function the objective function of an optimal control problem is an integral equation, which models the trade-off between virions and pathogen concentration, organ health, and the use of therapies (Hattaf and Yousfi, 2018).

Now, by the Jacobian matrix of system (3) as established by Bassey and Atsu (2021), the control functions μ_1 and η are bounded and Lebesgue integrable. Moreso, virions production under control functions is $(1 - \mu_1)\beta_I = 1,\ldots,5$, (Hattaf and Yousfi, 2018).

Clinically, if $\eta = 1$, then inhibition of infection is 100% efficacious. Otherwise, no inhibition if $\eta = 0$ (i.e., drug abuse). On a similar note, if the control function μ_1 represents the efficacy of condom use in blocking new infection transmission, then the infection rate in the presence of condom abuse is obviously $(1-\mu_1)\beta_I = 1,\ldots,5$, (Hattaf and Yousfi, 2018; Bassey and Atsu, 2021). Therefore, the optimality problem that maximizes the goal of the study is defined by the objective functional:

$$Q(u_1, \eta) = \int_{t_0}^{t_f} \left\{ S(t) + T(t) - \left[\frac{W_1}{2}(u_1(t))^2 + \frac{W_2}{2}(\eta(t))^2 \right] \right\} dt \quad (5)$$

subject to the system (3) as a constraint and having $_{it}$ as a treatment limit.

Clearly, Eq. (5) shows that two positive constants $WI = 1,2 \geq 0$ had been introduced. These parameters denote treatment optimal weight factors, which define benefit on cost for control functions μ_1 and η respectively. Moreso, in equation (5), the first two terms represent the benefit of $CD4^+$ T cells, while the other terms are systemic cost on control functions. Indeed, the quadratic functions u_1^2, η^2 reflect the severity of the side-effect of control functions, (Joshi, 2002; Hattaf and Yousfi, 2018). Therefore, since our target is that of maximizing the objective functional defined by Eq. (5), which is justified by an increase in the number of uninfected T-cells while decreasing the viral load at minimized systemic cost, then we seek an optimal control pair (u_1^*, η^*) such that:

$$Q(u_1^*, \eta^*) = \max_{0 \leq (u_1, \eta) \leq 1} \{ Q(u_1, \eta) : (u_1, \eta) \in \mathbb{A} \}$$

where $\mathbb{A} := \{ (u_1, \eta) \setminus u_1, \eta$ is Lebesgue measurable with $x_i \leq u_1, \eta \leq y_i, \ t \in [t_0, t_f], \forall i = 1, 2 \}$ is the control set.

Remark 3.1

The benefit of the cost function is nonlinear. Thus, the introduction of linearization control function $W_{i=1,2}$ serves as simple nonlinear control. Moreso, the issues of drug side-effect are adequately accommodated.

Proposition 3.1

Assuming there exists drug hazardous side-effect, then the inequality of the control set $x_i \leq u_1, \eta \leq y_i, i = 1, 2$ holds and justifies the optimal weight factors $W_{i=1,2} \geq 0$. This is true as the application of control functions often comes with drug side-effect after a definite time interval.

Therefore, control functions are a function of boundedness with optimal weight factors serving as control indices to drug toxicity, (Joshi, 2002; Fleming *et al.*, 1975).
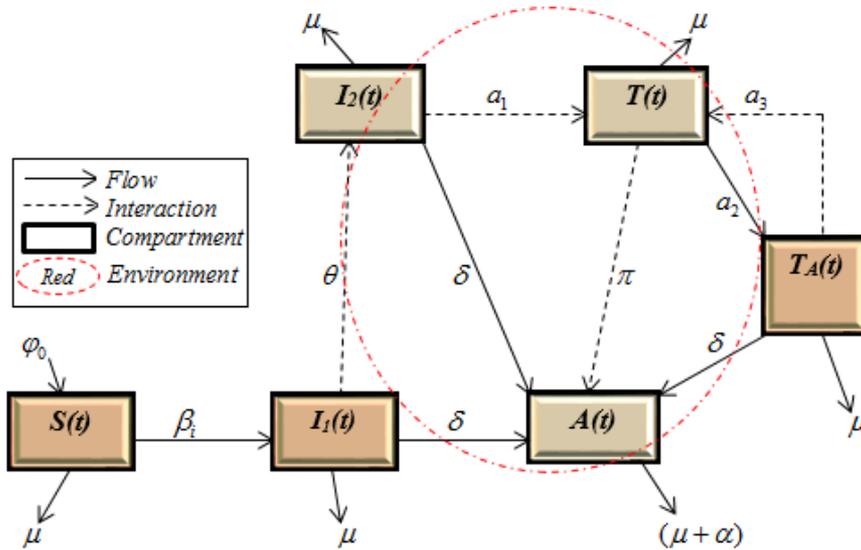
Fig. 1: Schematic diagram of HIV/AIDS transmission dynamics with ART abuse (misuse)

Mathematical Analysis and Characterization of an Optimal Control Pair

Here, we analyze the system's well-posedness properties, which include the system positivity and boundedness of solutions and the characterization of the system's optimal control pair.

Optimal Positivity and Boundedness of Solutions

Now, since the interest is that of optimal control, then for a typical optimal control problem of the model (3), we investigate the system optimal positivity and boundedness of solutions as defined by the following theorem.

Theorem 3.1 (Positivity)

The closed set $\Re_D = \left\{ \left(S, I_1, I_2, T, T_A, A\right) \in \Re_+^6 : N \leq \dfrac{\varphi_0}{\mu} \right\}$ is positively invariant and attractive concerning the system (3). Moreso, assuming the initial conditions $\left\{ S(0), I_1(0), I_2(0), T(0), T_A(0), A(0) \right\} \in \Re_+^6$, then the solution set $\left\{ S(t), I_1(t), I_2(t), T(t), T_A(t), A(t) \right\}$ of the system (3) remains positive for all $t \geq 0$.

Proof

Here, we use the classical theory of differential equations. Then system (3) can be confined to a compact subset:

$$\Omega = \left\{ \left(S, I_1, I_2, T, T_A, A\right) \in \Re_+^6 : N = S(t) + I_1(t) + I_2(t) + T(t) + T_A(t) + A(t) \leq \frac{\varphi_0}{\mu} \right\} \quad (6)$$

Let $(S(t) + 1_1(t) + 1_2(t) + T(t) + T_A + A(t))$ be any solution with positive initial conditions such that $N(t) = S(t) + 1_1 +$ $1_2(t) + T_A(t) + A(t)$. Then, the derivative of N (t) along the solution of system (3) under zero mortality rate, we have:

$$\frac{dN(t)}{dt} = \varphi_0 - \mu(S + I_1 + I_2 + T + T_A + A) \leq \varphi_0 - \mu N(t), \forall \alpha = 0$$

or:

$$\frac{dN(t)}{dt} + \mu N(t) \leq \varphi_0$$

Multiplying each term by the integrating factor $IF = e^{\int \mu dt}$, we have:

$$e^{\int \mu dt} \frac{dN(t)}{dt} + e^{\int \mu dt} \mu N(t) \leq \varphi_0 e^{\int \mu dt}$$

or:

$$\frac{d}{dt}\left[e^{\int \mu dt} \mu N(t) \right] \leq \varphi_0 e^{\int \mu dt} .$$

Integrating, we have:

$$\mu N(t) e^{\int \mu dt} \leq \varphi_0 e^{\int \mu dt} + A ,$$

where, A, is the constant of integration. Simplifying with respect to $N(t)$, we obtain:

$$N(t) \leq \frac{\varphi_0}{\mu} + A e^{-\int \mu dt} \quad (7)$$

Applying the initial condition for $t = 0 \Rightarrow N(t) = N(0)$. Then, the above differential inequality becomes:

$$N(0) \leq \frac{\varphi_0}{\mu} + A \Rightarrow N(0) - \frac{\varphi_0}{\mu} \leq A \qquad (8)$$

Substituting Eq. (8) into the inequality Eq. (7) for N(t) gives:

$$N(t) \leq \frac{\varphi_0}{\mu} + \left(N(0) - \frac{\varphi_0}{\mu} \right) e^{-\int \mu dt} \forall t \geq 0$$

Taking the limit for all $t \to \infty$, we have:

$$\underset{t \to \infty}{Lim} N(t) \leq \frac{\varphi_0}{\mu}$$

Therefore, system (3) defined i $\Re_+^6$ s confined in the region Ω, which implies the solutions are positive in the interval $[0,\infty)$.

Theorem 3.2 (Boundedness)

Let system (3) be bounded in a closed set $\Re_D$ such that $\Re_D = \left\{ (S, I_1, I_2, T, T_A, A) \in \Re_+^6 : N \leq \frac{\varphi_0}{\mu} \right\}$. Then, all the solutions of the closed set $\Re_D$ are bounded, positively invariant, and attractive concerning the system (3).

Proof

Invoking existing results on the boundedness of solutions, (Osman *et al.*, 2018; Bassey and Atsu, 2021). Then, differentiating $N(t)$ in the absence of mortality rate, we have:

$$\frac{dN(t)}{dt} = \varphi_0 - \mu(S + I_1 + I_2 + T + T_A + A) \leq \varphi_0 - \mu N(t), \forall \alpha = 0 \qquad (9)$$

Applying the integrating factor to Eq. (9) and then introducing the initial condition, $t = 0$, we have:

$$N(t) \leq \frac{\varphi_0}{\mu} + \left(N(0) - \frac{\varphi_0}{\mu} \right) e^{-\int \mu dt}$$

where, $N(0)$ is the initial population at $t = t_0 = 0$. This gives $N(t) = N(0)$ as $t \to 0$ and $N(t) \leq \varphi_0$ as $t \to \infty$. Applying Birkh and Rota's theorem on differential inequality as obtained in (Mafuta *et al.*, 2014), for all $t \to \infty$, we arrive at $0 \leq N(t) \leq \varphi_0$, $\forall t \geq 0$. But from the system (3.3),

$$\frac{dN(t)}{dt} = \frac{dS(t)}{dt} + \frac{dI_1(t)}{dt} + \frac{dI_2(t)}{dt} + \frac{dT(t)}{dt} + \frac{dT_A(t)}{dt} + \frac{dA(t)}{dt} = 0$$

which gives:

$$\frac{dN(t)}{dt} = 0$$

Integrating, we have:

$$N(t) = A \qquad (10)$$

where, A is the constant of integration. But we know that the total population understudy equals 1, i.e.:

$$N(t) = S(t) + I_1(t) + I_2(t) + T(t) + T_A(t) + A(t) = 1$$

since there exists zero mortality rate, i.e., the population understudy exhibits a disease-free state, implying the population is unity. It follows that A = 1. Implying that the population is constant, positive, and equal to 1. Hence, all the feasible solutions of system (3) enter the invariant region:

$$\Re_D = \left\{ (S, I_1, I_2, T, T_A, A) \in \Re_+^6 : N \leq \frac{\varphi_0}{\mu} : S(t) + I_1(t) + I_2(t) + T(t) + T_A(t) + A(t) = 1 \right\} \qquad (11)$$

Therefore, the region is not only bounded but also positive and attractive. That is, every local solution can be extended to any time $t \in [0,\infty)$. Hence, the solution exists optimally.

Mathematical Characterization of an Optimal Control Pair

A realistic and précised formulation of an optimal control pair $(\mu_1^*(t), \eta^*(t))$ requires the identification of the system's optimal control characterization, which defines the penalty terms on the constraints. In this case, we invoke the classical Pontryagin's maximum principle, noting that the design of this model is compatible with the principle. Moreso, the biological behavior of the system, and the growth and clearance rates of the system state variables are determined using the optimality system. essentially, the principle involves converting solving our optimality problem into maximizing the Hamiltonian argument defined by the Lagrangian as:

$$L \equiv L(t, S, I_1, I_2, T, T_A, A, u_1, \eta, \lambda_i) = S(t) + T(t) - \left[\frac{W_1}{2} (u_1(t))^2 + \frac{W_2}{2} (\eta(t))^2 \right] + \sum_{i=1}^{6} \lambda_i f_i \quad (12)$$
$$+ w_{11}(t)(y_1 - u_1) + w_{12}(t)(u_1 - x_1) + w_{21}(t)(y_2 - \eta) + w_{22}(t)(\eta - x_2)$$

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

$$w_{11}(t)(y_1 - u_1) = 0, w_{12}(t)(u_1 - x_1) = 0 \text{ at optimal } \mu_1^* \text{ and:}$$

$$w_{21}(t)(y_2 - \eta) = 0, w_{22}(t)(\eta - x_2) = 0$$

at optimal η^* with penalty multipliers ensuring that μ_1^* and η^* remain bounded in the domain in $(u_i, \eta) \in [0,1]$, noting that the optimality problem is time-definite and control functions must be defined to account for drug side effects, (Joshi, 2002; Pontryagin *et al.*, 1986; Fleming *et al.*, 1975). Moreso, the

function $\lambda_i(t), i = 1,....,6$ is the model adjoint variables, which determine the adjoint system, while $f_i, i = 1,....6$ the system dynamics are defined by:

$$
\begin{cases}
f_1 = \varphi_0 - \frac{(1-u_1(t))}{N(t)}(\beta_1 c_1 I_1(t) + \beta_2 c_2 I_2(t) + \beta_3 c_3 T(t) + \beta_4 c_4 T_A(t) + \beta_5 c_5 A(t)) S(t) - \mu S(t), \\
f_2 = \frac{(1-u_1(t))}{N(t)}(\beta_1 c_1 I_1(t) + \beta_2 c_2 I_2(t) + \beta_3 c_3 T(t) + \beta_4 c_4 T_A(t) + \beta_5 c_5 A(t)) S(t) - (\mu + \delta + \theta) I_1(t), \\
f_3 = \theta I_1(t) - (\mu + \delta + a_1) I_2(t), \\
f_4 = a_1 I_2(t) + a_3 T_A(t) - (\mu + \pi + a_2) T(t), \\
f_5 = a_2 T(t) - (\mu + \delta + a_3) T_A(t), \\
f_6 = \delta(I(t)_1 + I_2(t) + T_A(t)) + \pi T(t) - (\mu + \alpha) A(t)
\end{cases} \tag{13}
$$

Therefore, using Eq. (12), we then verify all the possible controls for μ_1^* and η including those of boundary conditions $0 \le \mu_1^*, \eta^* \le 1$.

The case for the set $\{t/0 < \mu_1^*(t), \eta < 1\}$: $w_{ij} = 0 \ \forall i, j = 1, 2$. Then, solving for the unconstrained optimality.

Conditions $\mu_1^* \in [0,1]$ and $\eta^* \in [0,1]$, we apply Pontryagin's maximum principle, which takes the partial derivative of the Hamiltonian argument concerning the control functions i.e., $\frac{\partial L}{\partial u_1^*} = 0 \ \frac{\partial L}{\partial \eta^*} = 0$ and. This implies that we find $\frac{\partial L}{\partial u_1^*} = 0$, $\frac{\partial L}{\partial \eta^*} = 0$ and solve for μ_1^* and η^* by setting the partial derivative of L equal to zero i.e.:

$$
\frac{\partial L}{\partial u_1^*} = -W_1 u_1^*(t) + \frac{\lambda_1(t)}{N(t)^2}[\beta_1 c_1 I_1(t) + \beta_2 c_2 I_2(t) + \beta_3 c_3 T(t) + \beta_4 c_4 T_A(t) + \beta_5 c_5 A(t)] S(t)
$$
$$
- \frac{\lambda_2(t)}{N(t)^2}[\beta_1 c_1 I_1(t) + \beta_2 c_2 I_2(t) + \beta_3 c_3 T(t) + \beta_4 c_4 T_A(t) + \beta_5 c_5 A(t)] S(t)
$$
$$
- w_{11}(t) + w_{21}(t) = at \mu_1^*
$$

Also:

$$
\frac{\partial L}{\partial \eta^*} = -W_2 \eta^*(t) - \lambda_3(t) I_2(t) + \lambda_4(t)(I_2(t) + T_A(t)) - \lambda_5(t) T_A(t) - w_{21}(t) + w_{22}(t) = 0 \, at \mu_1^*
$$

Solving for the optimal controls μ_1^* and η^* when $W_{ij} = 0$, we have:

$$
u_1^*(t) = \frac{1}{W_1}\{\lambda_1(t)(\beta_1 c_1 I_1(t) S(t) + \beta_2 c_2 I_2(t) S(t) + \beta_3 c_3 T(t) S(t) + \beta_4 c_4 T_A(t) S(t) + \beta_5 c_5 A(t) S(t)) \tag{14}
$$
$$
- \lambda_2(t)(\beta_1 c_1 I_1(t) S(t) + \beta_2 c_2 I_2(t) S(t) + \beta_3 c_3 T(t) S(t) + \beta_4 c_4 T_A(t) S(t) + \beta_5 c_5 A(t) S(t))\}
$$

since $N(t) = S(t) + I_1(t) + I_2(t) + T(t) + T_A(t) + A(t) = 1$

Similarly:

$$
\eta^*(t) = -\frac{1}{W_2}\{\lambda_3(t) I_2(t) + \lambda_4(t)(I_2(t) + T_A(t)) - \lambda_5(t) T_A(t)\} \tag{15}
$$

To complete the characterization of μ_1^* and η^* we consider the boundaries for $(\mu_1^*, \eta^*) = 0$ and $(\mu_1^*, \eta^*) = 1$, as well as non-boundary cases:

The case for the set $\{t/0 \ \mu_1^*(t) = 0, \eta^*(t) = 0\}$: $w_{ij} = 0$, $w_{i2} = 0 \forall i, j = 1$ then, the optimal controls are given by:

$$
0 = \frac{1}{W_1}\{\lambda_1(t)(\beta_1 c_1 I_1(t) S(t) + \beta_2 c_2 I_2(t) S(t) + \beta_3 c_3 T(t) S(t) + \beta_4 c_4 T_A(t) S(t) + \beta_5 c_5 A(t) S(t))
$$
$$
- \lambda_2(t)\begin{pmatrix}\beta_1 c_1 I_1(t) S(t) + \beta_2 c_2 I_2(t) S(t) + \beta_3 c_3 T(t) S(t) \\ + \beta_4 c_4 T_A(t) S(t) + \beta_5 c_5 A(t) S(t)\end{pmatrix}\} - w_{1j}
$$

Since, $W_{1j} \ge 0$, this implies that:

$$
\frac{1}{W_1}\{\lambda_1(t)(\beta_1 c_1 I_1(t) S(t) + \beta_2 c_2 I_2(t) S(t) + \beta_3 c_3 T(t) S(t) + \beta_4 c_4 T_A(t) S(t) + \beta_5 c_5 A(t) S(t))
$$
$$
- \lambda_2(t)\begin{pmatrix}\beta_1 c_1 I_1(t) S(t) + \beta_2 c_2 I_2(t) S(t) + \beta_3 c_3 T(t) S(t) \\ + \beta_4 c_4 T_A(t) S(t) + \beta_5 c_5 A(t) S(t)\end{pmatrix}\} \le 0
$$

Now, to ensure that μ_1^* is not negative, we use the notation:

$$
u_1^*(t) = \frac{1}{W_1}\{\lambda_1(t)(\beta_1 c_1 I_1(t) S(t) + \beta_2 c_2 I_2(t) S(t) + \beta_3 c_3 T(t) S(t) + \beta_4 c_4 T_A(t) S(t) + \beta_5 c_5 A(t) S(t)) \tag{16}
$$
$$
- \lambda_2(t)\begin{pmatrix}\beta_1 c_1 I_1(t) S(t) + \beta_2 c_2 I_2(t) S(t) + \beta_3 c_3 T(t) S(t) \\ + \beta_4 c_4 T_A(t) S(t) + \beta_5 c_5 A(t) S(t)\end{pmatrix}\}^+ = 0
$$

i.e.:

$$
u_1^*(t) = \frac{1}{W_1}[\lambda_1(t)(\beta_1 c_1 I_1(t) S(t) + \beta_2 c_2 I_2(t) S(t) + \beta_3 c_3 T(t) S(t) + \beta_4 c_4 T_A(t) S(t) + \beta_5 c_5 A(t) S(t))
$$
$$
- \lambda_2(t)(\beta_1 c_1 I_1(t) S(t) + \beta_2 c_2 I_2(t) S(t) + \beta_3 c_3 T(t) S(t) + \beta_4 c_4 T_A(t) S(t) + \beta_5 c_5 A(t) S(t))]^+ \tag{17}
$$

Similarly:

$$
\eta^*(t) = -\frac{1}{W_2}[\lambda_3(t) I_2(t) + \lambda_4(t)(I_2(t) + T_A(t)) - \lambda_5(t) T_A(t)]^+ .
$$

The case for the set $\{t \setminus u_1^*(t) = 1, \eta^*(t) = 1\}: w_{i1} = 0, w_{2j} \ge 0$ $\forall i, j = 2$. The optimal controls are as follows:

$$
1 = \frac{1}{W_1}\{\lambda_1(t)(\beta_1 c_1 I_1(t) S(t) + \beta_2 c_2 I_2(t) S(t) + \beta_3 c_3 T(t) S(t) + \beta_4 c_4 T_A(t) S(t) + \beta_5 c_5 A(t) S(t))
$$
$$
- \lambda_2(t)\begin{pmatrix}\beta_1 c_1 I_1(t) S(t) + \beta_2 c_2 I_2(t) S(t) + \beta_3 c_3 T(t) S(t) \\ + \beta_4 c_4 T_A(t) S(t) + \beta_5 c_5 A(t) S(t)\end{pmatrix}\} + w_{2j}
$$

which implies that:

$$
0 \le w_{2j} = \{\lambda_1(t)(\beta_1 c_1 I_1(t) S(t) + \beta_2 c_2 I_2(t) S(t) + \beta_3 c_3 T(t) S(t) + \beta_4 c_4 T_A(t) S(t) + \beta_5 c_5 A(t) S(t))
$$
$$
- \lambda_2(t)\begin{pmatrix}\beta_1 c_1 I_1(t) S(t) + \beta_2 c_2 I_2(t) S(t) + \beta_3 c_3 T(t) S(t) \\ + \beta_4 c_4 T_A(t) S(t) + \beta_5 c_5 A(t) S(t)\end{pmatrix}\} - W_1
$$

Therefore:

$$
\left\{\left(\frac{\lambda_1(t)(\beta_1 c_1 I_1(t) S(t) + \beta_2 c_2 I_2(t) S(t) + \beta_3 c_3 T(t) S(t) + \beta_4 c_4 T_A(t) S(t) + \beta_5 c_5 A(t) S(t))}{W_1} \quad \frac{-\lambda_2(t)(\beta_1 c_1 I_1(t) S(t) + \beta_2 c_2 I_2(t) S(t) + \beta_3 c_3 T(t) S(t) + \beta_4 c_4 T_A(t) S(t) + \beta_5 c_5 A(t) S(t))}{}\right) \ge 1\right\} = u_1^*
$$

Similarly:

$$
\left\{\left(-\frac{1}{W_2}[\lambda_3(t) I_2(t) + \lambda_4(t)(I_2(t) + T_A(t)) - \lambda_5(t) T_A(t)]\right) \ge 1\right\} = \eta^*
$$

This is to say that for this set, we must choose:

$$u_1^*(t) = \min \left\{ \left(\frac{\lambda_1(t)\left(\beta_1 c_1 I_1(t)S(t) + \beta_2 c_2 I_2(t)S(t) + \beta_3 c_3 T(t)S(t) + \beta_4 c_4 T_A(t)S(t) + \beta_5 c_5 A(t)S(t)\right)}{W_1} \atop -\lambda_2(t)\left(\beta_1 c_1 I_1(t)S(t) + \beta_2 c_2 I_2(t)S(t) + \beta_3 c_3 T(t)S(t) + \beta_4 c_4 T_A(t)S(t) + \beta_5 c_5 A(t)S(t)\right) \right), 1 \right\} \quad (18)$$

and:

$$\eta^*(t) = \min \left\{ \left(-\frac{1}{W_2}\left[\lambda_3(t)I_2(t) + \lambda_4(t)\left(I_2(t) + T_A(t)\right) - \lambda_5(t)T_A(t) \right] \right), 1 \right\} \quad (19)$$

Thus, we complete the characterization of the optimal controls by compatibly taking the three cases for $\mu_1^*(t)$ and $\eta^*(t)$ as defined by the following proposition.

Proposition 3.2

Taking on results of the three verified cases as in equations (14-19) for control functions $\mu_1^*(t)$, $\eta^*(t)$, then optimal controls for the system optimality control problem of the system (3) with limits $0 \le x_i \le u_1^* \le \eta^* \le y_i < 1$ are completely characterized by:

$$u_1^*(t) = \min \left\{ \max \left\{ x_i, \left(\frac{\lambda_1(t)\left({\beta_1 c_1 I_1(t)S(t) + \beta_2 c_2 I_2(t)S(t) + \beta_3 c_3 T(t)S(t) \atop + \beta_4 c_4 T_A(t)S(t) + \beta_5 c_5 A(t)S(t)} \right) \atop -\lambda_2(t)\left({\beta_1 c_1 I_1(t)S(t) + \beta_2 c_2 I_2(t)S(t) + \beta_3 c_3 T(t)S(t) \atop + \beta_4 c_4 T_A(t)S(t) + \beta_5 c_5 A(t)S(t)} \right)}{W_1} \right)^+ \right\}, y_i \right\} \quad (20)$$

$$\eta^*(t) = \min \left\{ \max \left\{ x_2, \left(-\frac{1}{W_2}\left[\lambda_3(t)I_2(t) + \lambda_4(t)\left(I_2(t) + T_A(t)\right) - \lambda_5(t)T_A(t) \right] \right)^+ \right\}, y_2 \right\} \quad (21)$$

Thus, the following remark can be drawn from Eq. (20) and (21).

Remark 3.2

Intuitively, the optimal controls of proposition 3.2 are concurrently a representation of system circulating terms associated with healthy and infectives and their adjoint variables.

Next, we show the existence of an optimal control pair.

Existence of an Optimal Control Pair

The boundedness of the solution of system (3) for a finite interval is used to prove the existence of an optimal control pair. To establish this result, we invoke the following three theorems of the existence of optimal control pair, (Joshi, 2002; Fleming *et al.*, 1975).

Theorem 3.2

Consider the control problem with system equation (3). Then, there exists an optimal control pair $(\mu_1^*, \eta^*) \in$ such that $Q(\mu_1^*, \eta^*) = \max Q(\mu_1, \eta)$.

Proof

To use an existence result, we should first check for the following properties.

(D$_1$) The class of all control sets (μ_1, η) are Lebesgue-integrable functions on $[t_0, t_f]$ with value in the admissible control sets and such that the corresponding state variables are satisfied and non-empty.

(D$_2$) The admissible control set $\mathbb{A}$, is convex and closed.

(D$_3$) The Right-Hand Side (RHS) of the state system is continuous and bounded by a linear function in the state and control variables.

(D$_4$) The integrand of the objective function is concave on $\mathbb{A}$.

(D$_5$) There exists a $\gamma > 1$ and two constants $\tau_1 \tau_2 > 0$ such that the integrand: Hattaf and Yousfi, 2018; Fleming *et al.*, 1975)

$$L(S, T, u_1, \eta) \le \tau_2 - \tau_1 \left(|u_1|^2 + |\eta|^2 \right)^{\frac{\gamma}{2}}$$

where:

$$L(S, T, u_1, \eta) = S(t) + T(t) - \left[\frac{W_1}{2}(u_1(t))^2 + \frac{W_2}{2}(\eta(t))^2 \right]$$

To verify these conditions, we use the result and we observe that the boundedness of the state system Eq. (3) with two controls ensures the existence of solutions of Eq. (1). We can therefore deduce that the set of controls and corresponding state variables are non-empty, which gives condition (D$_1$). By positivity of the state variables, the control set is convex and closed under controls $(\mu_1, \eta) \in [0,1]$ for all $t \in [t_0, t_f]$, which ensures condition (D$_2$). Moreso, since the system of the state-space, is bilinear in μ_1, η, the right-hand-side of (3) verifies condition (D$_3$), using the fact that the solutions are bounded. For condition (D$_4$), we apply the Hessian matrix for L, as follows:

$$H_L = \begin{pmatrix} -W_1 & 0 \\ 0 & -W_2 \end{pmatrix}$$

and having determinant $\det(H_L) = W_1 W_2 \ge 0\,\text{s}$ such as, $\forall(u_1, \eta) \in A$ Then, L is concave on A.

Finally, from condition (D$_5$), we have:

$$L(S, T, u_1, \eta) \le \tau_2 - \tau_1 \left(|u_1|^2 + |\eta|^2 \right)$$

With τ_2 depending on the upper bound on S, T and:

$$\tau_1 = \min\left(\frac{W_1}{2}, \frac{W_2}{2} \right) > 0$$

Then, we deduce that there exists an optimal control pair $(\mu_1^*, \eta^*) \in A$, such that $Q((\mu_1^*, \eta^*) = \max Q((\mu_1, \eta)$.

Derivation of Model Optimality System

In our previous subsection 3.3, we proved the existence of an optimal control pair for maximizing the objective functional (5), subject to the system (4). Of note, the advantage of this method-optimality system is the fact that as a vital component of the optimal control problem, the method allows for the observation of the system's biological behavior upon application of desired therapy. Moreso, the growth and clearance rates of the system state variables are determined using the optimality system.

Definition 3.2

The optimality system is a function of the state system coupled with the adjoint system with the initial conditions and transversality conditions together with the derived optimal control pair.

Definition 3.3

The adjoint system, which is determined by the adjoint variables, represents the backward effect of the optimal state variables, while the adjoint variables $\lambda_i(t), i = 1,...,6$ represent the backward effect of each of the state-space.

Now, by definitions 3.1 and 3.2, it is obvious that system Eq. (3) with initial conditions as well as the optimal control pair has been established. Thus, to complete the derivation of the optimality system, a well-posed adjoint system and transversality conditions are necessary. From (Culshaw *et al.*, 2004), using Eq. (12), the adjoint system is given by:

$$\frac{d\lambda_i}{dt} = -\frac{\partial L}{\partial \phi_i} \tag{22}$$

where, ϕ_i, $I = 1,......,6$ are the state variables. Furthermore, for a maximization problem of the type:

$$\max_{(u_1,\eta)\in A} Q(u_1,\eta) = G(\upsilon(T)) + \int_{t_0}^{t_f} f_0(\upsilon,u_1,\eta)dt$$

subject to the state system $\frac{dv}{dt} = f(t,\upsilon,u_1,\eta)$ and such that $\upsilon(T)$ belongs to some target set g (υT)).

Then, we have the following transversality conditions on the adjoint variables as Culshaw *et al.* (2004):

$$\lambda_i(T) = \nabla G(\upsilon(T)) + \sum_{i=1}^{k} c_i g_i(\upsilon(T)) \tag{23}$$

with the function G denoting terminal cost. Of note, the fact is that our optimal problem does not contain any terminal cost. Then, from Eq. (23), $G \upsilon (t)) = 0$. Furthermore, our problem does not have a target set for our state variables. Rather, we have desired result with a free final state. So, the summation term is also zero. Therefore, transversality conditions for the adjoint variables are:

$$\lambda_i(T) = 0, \forall i = 1,....,6 \tag{24}$$

Thus, from definition 3.1, taking the state system together with the adjoint system, the optimal control, and transversality conditions, we have the following theorem.

Theorem 3.3

For any optimal control pair μ_1^*,η^* and any solutions $(S^*, I_1^*, I_2^*, T^*, T_A^*, A^*)$ of the corresponding state system (3), there exist adjoint variables $\lambda_i\ I = 1,..., 6$ satisfying:

$$
\begin{aligned}
\lambda_1'(t) &= -1\Big\{\lambda_1(t)\Big[-(1-u_1^*(t))\big(\beta_1 c_1 I_1^*(t) + \beta_2 c_2 I_2^*(t) + \beta_3 c_3 T^*(t) + \beta_4 c_4 T_A^*(t) + \beta_5 c_5 A^*(t) - \mu\big)\Big]\\
&\quad + \lambda_2(t)\Big[(1-u_1^*(t))\big(\beta_1 c_1 I_1^*(t) + \beta_2 c_2 I_2^*(t) + \beta_3 c_3 T^*(t) + \beta_4 c_4 T_A^*(t) + \beta_5 c_5 A^*(t)\big)\Big]\Big\}\\[4pt]
\lambda_2'(t) &= -1\left\{\lambda_1(t)\Big[-(1-u_1^*(t))\beta_1 c_1 S^*(t)\Big] + \lambda_2(t)\begin{bmatrix}(1-u_1^*(t))\beta_1 c_1 S^*(t)\\-(\mu+\delta+\theta)\end{bmatrix} + \theta\lambda_3(t) + \delta\lambda_6(t)\right\}\\[4pt]
\lambda_3'(t) &= -1\left\{\begin{matrix}\lambda_1(t)\Big[-(1-u_1^*(t))\beta_2 c_2 S^*(t)\Big] + \lambda_2(t)\Big[(1-u_1^*(t))\beta_2 c_2 S^*(t)\Big]\\+\lambda_3(t)(\mu+\delta+a_1^*(t)) + \lambda_4(t)a_1^*(t) + \delta\lambda_6(t)\end{matrix}\right\}\\[4pt]
\lambda_4'(t) &= -1\left\{\begin{matrix}\lambda_1(t)\Big[-(1-u_1^*(t))\beta_3 c_3 S^*(t)\Big] + \lambda_2(t)\Big[(1-u_1^*(t))\beta_3 c_3 S^*(t)\Big]\\-\lambda_4(t)(\mu+\pi+a_2) + \lambda_5(t)a_2 + \pi\lambda_6(t)\end{matrix}\right\}\\[4pt]
\lambda_5'(t) &= -1\left\{\begin{matrix}\lambda_1(t)\Big[-(1-u_1^*(t))\beta_4 c_4 S^*(t)\Big] + \lambda_2(t)\Big[(1-u_1^*(t))\beta_4 c_4 S^*(t)\Big]\\+\lambda_4(t)a_3^*(t) - \lambda_5(t)(\mu+\delta+a_3^*(t)) + \delta\lambda_6(t)\end{matrix}\right\}\\[4pt]
\lambda_6'(t) &= -1\left\{\begin{matrix}\lambda_1(t)\Big[-(1-u_1^*(t))\beta_5 c_5 S^*(t)\Big] + \lambda_2(t)\Big[(1-u_1^*(t))\beta_5 c_5 S^*(t)\Big]\\+\lambda_4(t)a_3^*(t) - \lambda_6(t)(\mu+\alpha)\end{matrix}\right\}
\end{aligned} \tag{25}
$$

where, $\lambda_i(t)\ \forall i = 1,...,6$ are transversality conditions with the control pair given by proposition 3.2?

Proof

Invoking the optimality results of (Hattaf and Yousfi, 2018), we see that the transversality conditions and adjoint equations can be obtained as follows:

$$\frac{d\lambda_i(t)}{dt} = -\frac{\partial L}{\partial \phi_i},$$

where, $I = 1,...,6$ $\frac{\partial L}{\partial \phi_i}$ as depicted by Eq. (25). This implies that the transversality conditions are expressed by:

$$
\begin{cases}
\lambda_1'(t) = -\dfrac{\partial L}{\partial S}(t) & \lambda_1(t_f) = 0\\[6pt]
\lambda_2'(t) = -\dfrac{\partial L}{\partial I_1}(t) & \lambda_2(t_f) = 0\\[6pt]
\lambda_3'(t) = -\dfrac{\partial L}{\partial I_2}(t) & \lambda_3(t_f) = 0\\[6pt]
\lambda_4'(t) = -\dfrac{\partial L}{\partial T}(t) & \lambda_4(t_f) = 0\\[6pt]
\lambda_5'(t) = -\dfrac{\partial L}{\partial T_A}(t) & \lambda_5(t_f) = 0\\[6pt]
\lambda_6'(t) = -\dfrac{\partial L}{\partial A}(t) & \lambda_6(t_f) = 0
\end{cases} \tag{26}
$$

Then, from the definition of control set A and the optimal controls defined by proposition 3.2, if we substitute μ_1^*, η^* into the system (3), we obtain the target optimality system by compatibly combining Eq. (3) and (25) upon substituting Eq. (20) and (21) into Eq. (3); and Eq. (25) into Eq. (26). That is, the optimality system is derived as:

$$\frac{dS^*}{dt} = \varphi_0 - (1-u_1^*(t))\left(\beta_1 c_1 I_1^*(t) + \beta_2 c_2 I_2^*(t) + \beta_3 c_3 T^*(t) + \beta_4 c_4 T_A^*(t) + \beta_5 c_5 A^*(t)\right)S^*(t) - \mu S^*(t),$$

$$\frac{dI_1^*}{dt} = (1-u_1^*(t))\left(\beta_1 c_1 I_1^*(t) + \beta_2 c_2 I_2^*(t) + \beta_3 c_3 T^*(t) + \beta_4 c_4 T_A^*(t) + \beta_5 c_5 A^*(t)\right)S^*(t) - (\mu+\delta+\theta)I_1^*(t),$$

$$\frac{dI_2^*}{dt} = \theta I_1^*(t) - (\mu+\delta+a_1)I_2^*(t),$$

$$\frac{dT^*}{dt} = a_1 I_2^*(t) + a_3 T_A^*(t) - (\mu+\pi+a_2)T^*(t),$$

$$\frac{dT_A^*}{dt} = a_2 T^*(t) - (\mu+\delta+a_3)T_A^*(t),$$

$$\frac{dA^*}{dt} = \delta\left(I_1^*(t) + I_2^*(t) + T_A^*(t)\right) + \pi T^*(t) - (\mu+\alpha)A^*(t),$$

$$\lambda_1'(t) = -1\Big\{\lambda_1(t)\Big[-(1-u_1^*(t))\left(\beta_1 c_1 I_1^*(t) + \beta_2 c_2 I_2^*(t) + \beta_3 c_3 T^*(t) + \beta_4 c_4 T_A^*(t) + \beta_5 c_5 A^*(t) - \mu\right)\Big]$$
$$+\lambda_2(t)\Big[(1-u_1^*(t))\left(\beta_1 c_1 I_1^*(t) + \beta_2 c_2 I_2^*(t) + \beta_3 c_3 T^*(t) + \beta_4 c_4 T_A^*(t) + \beta_5 c_5 A^*(t)\right)\Big]\Big\}$$

$$\lambda_2'(t) = -1\left\{\lambda_1(t)\Big[-(1-u_1^*(t))\beta_1 c_1 S^*(t)\Big] + \lambda_2(t)\begin{bmatrix}(1-u_1^*(t))\beta_1 c_1 S^*(t)\\ -(\mu+\delta+\theta)\end{bmatrix} + \theta\lambda_3(t) + \delta\lambda_6(t)\right\}$$

$$\lambda_3'(t) = -1\left\{\begin{matrix}\lambda_1(t)\Big[-(1-u_1^*(t))\beta_2 c_2 S^*(t)\Big] + \lambda_2(t)\Big[(1-u_1^*(t))\beta_2 c_2 S^*(t)\Big]\\ +\lambda_3(t)(\mu+\delta+a_1^*(t)) + \lambda_4(t)a_1^*(t) + \delta\lambda_6(t)\end{matrix}\right\}$$

$$\lambda_4'(t) = -1\left\{\begin{matrix}\lambda_1(t)\Big[-(1-u_1^*(t))\beta_3 c_3 S^*(t)\Big] + \lambda_2(t)\Big[(1-u_1^*(t))\beta_3 c_3 S^*(t)\Big]\\ -\lambda_4(t)(\mu+\pi+a_2) + \lambda_5(t)a_2 + \pi\lambda_6(t)\end{matrix}\right\}$$

$$\lambda_5'(t) = -1\left\{\begin{matrix}\lambda_1(t)\Big[-(1-u_1^*(t))\beta_4 c_4 S^*(t)\Big] + \lambda_2(t)\Big[(1-u_1^*(t))\beta_4 c_4 S^*(t)\Big]\\ +\lambda_4(t)a_3^*(t) - \lambda_5(t)(\mu+\delta+a_3^*(t)) + \delta\lambda_6(t)\end{matrix}\right\}$$

$$\lambda_6'(t) = -1\left\{\begin{matrix}\lambda_1(t)\Big[-(1-u_1^*(t))\beta_5 c_5 S^*(t)\Big] + \lambda_2(t)\Big[(1-u_1^*(t))\beta_5 c_5 S^*(t)\Big]\\ +\lambda_4(t)a_3^*(t) - \lambda_6(t)(\mu+\alpha)\end{matrix}\right\}$$

$$u_1^*(t) = \min\left\{\max\left\{x_1, \left(\frac{\lambda_1(t)\begin{pmatrix}\beta_1 c_1 I_1(t)S(t) + \beta_2 c_2 I_2(t)S(t) + \beta_3 c_3 T(t)S(t)\\ +\beta_4 c_4 T_A(t)S(t) + \beta_5 c_5 A(t)S(t)\end{pmatrix}}{-\lambda_2(t)\begin{pmatrix}\beta_1 c_1 I_1(t)S(t) + \beta_2 c_2 I_2(t)S(t) + \beta_3 c_3 T(t)S(t)\\ +\beta_4 c_4 T_A(t)S(t) + \beta_5 c_5 A(t)S(t)\end{pmatrix}}{W_1}\right)^+\right\}, y_1\right\}$$

$$\eta^*(t) = \min\left\{\max\left\{x_2, \left(-\frac{1}{W_2}\Big[\lambda_3(t)I_2(t) + \lambda_4(t)\left(I_2(t)+T_A(t)\right) - \lambda_5(t)T_A(t)\Big]\right)^+\right\}, y_2\right\} \qquad (27)$$

where, $\lambda_i(t_f) = 0, \forall I = 1,\dots,6$ and $S(0) = S_0, I_1(0) = I_{(1)0}, I_2(0) = I_{(2)0}, A(0) = A_0$.

Finally, we investigate the uniqueness of the optimality system for the possibly small-time interval.

The Uniqueness of the Optimality System

So far, we have established the existence of an optimal control pair and went further to develop the model optimality system strategy. We complete the optimality process by investigating the uniqueness of the optimality system for a possible small-time interval. Thus, the following theorem strengthened by the accompanying lemma 3.1 (without proof), provides the required result.

Lemma 3.1

Let $\sigma^* = (\mu 1^*, \eta^*)$. Then, the function $\sigma^*(\varphi_0) = (\min(\max(\varphi_0, x, y)))$ is Lipchitz continuous in φ_0, where $x < y$ are some fixed positive constants.

Theorem 3.4

For *t*he sufficiently small, bounded solutions to the optimality system are unique.

Proof

We invoke results from two optimal control models (Joshi, 2002; Suppose $(S, I_1, I_2, T, T_A, A, \lambda_1, \lambda_2, \lambda_3, \lambda_4, \lambda_5, \lambda_6)$ $(\bar{S}, \bar{I}_1, \bar{I}_2, \bar{T}, \bar{T}_A, \bar{A}, \bar{\lambda}_1, \bar{\lambda}_2, \bar{\lambda}_3, \bar{\lambda}_4, \bar{\lambda}_5, \bar{\lambda}_6)$ e two different solutions of our optimality system (27). Now, let $\delta > 0$ be chosen such that the values of the solutions are obtained by setting:

$$S = g^{\delta t}e, I_1 = g^{\delta t}f, I_2 = g^{\delta t}c, T = g^{\delta t}i, T_A = g^{\delta t}j, A = g^{\delta t}k,$$
$$\lambda_1 = g^{-\delta t}m, \lambda_2 = g^{-\delta t}p, \lambda_3 = g^{-\delta t}q, \lambda_4 = g^{-\delta t}r, \lambda_5 = g^{-\delta t}s, \lambda_6 = g^{-\delta t}t$$

and:

$$\bar{S} = g^{\delta t}\bar{e}, \bar{I}_1 = g^{\delta t}\bar{f}, \bar{I}_2 = g^{\delta t}\bar{c}, \bar{T} = g^{\delta t}\bar{i}, \bar{T}_A = g^{\delta t}\bar{j}, \bar{A} = g^{\delta t}\bar{k},$$
$$\bar{\lambda}_1 = g^{-\delta t}\bar{m}, \bar{\lambda}_2 = g^{-\delta t}\bar{p}, \bar{\lambda}_3 = g^{-\delta t}\bar{q}, \bar{\lambda}_4 = g^{-\delta t}\bar{r}, \bar{\lambda}_5 = g^{-\delta t}\bar{s}, \bar{\lambda}_6 = g^{-\delta t}\bar{t}.$$

Then, from Eq. (20) and (21) of proposition 3.2, if we substitute the above variables into the two different solutions, our optimal control pair is rewritten as:

$$u_1^*(t) = \min\left\{\max\left\{x_1, \frac{1}{W_1}\left(\begin{matrix}g^{\delta t}m\begin{pmatrix}\beta_1 c_1 ef + \beta_2 c_2 ec + \beta_3 c_3 ei\\ +\beta_4 c_4 ej + \beta_5 c_5 ek\end{pmatrix}\\ -g^{\delta t}p\begin{pmatrix}\beta_1 c_1 ef + \beta_2 c_2 ec + \beta_3 c_3 ei\\ +\beta_4 c_4 ej + \beta_5 c_5 ek\end{pmatrix}\end{matrix}\right)^+\right\}, y_1\right\}$$

$$\eta^*(t) = \min\left\{\max\left\{x_2, \left(-\frac{1}{W_2}\Big[g^{\delta t}(qf) - g^{\delta t}r(f+j) + g^{\delta t}(sj)\Big]\right)^+\right\}, y_2\right\}$$

and:

$$\bar{u}_1^*(t) = \min\left\{\max\left\{x_1, \frac{1}{W_1}\left(\begin{matrix}g^{\delta t}\bar{m}\begin{pmatrix}\beta_1 c_1 \overline{ef} + \beta_2 c_2 \overline{ec} + \beta_3 c_3 \overline{ei}\\ +\beta_4 c_4 \overline{ej} + \beta_5 c_5 \overline{ek}\end{pmatrix}\\ -g^{\delta t}\bar{p}\begin{pmatrix}\beta_1 c_1 \overline{ef} + \beta_2 c_2 \overline{ec} + \beta_3 c_3 \overline{ei}\\ +\beta_4 c_4 \overline{ej} + \beta_5 c_5 \overline{ek}\end{pmatrix}\end{matrix}\right)^+\right\}, y_1\right\}$$

$$\overline{\eta}^*(t) = \min\left\{\max\left\{x_2, \left(-\frac{1}{W_2}\left[g^{\delta t}(\overline{qf}) - g^{\delta t}\overline{r}\left(\overline{f}+\overline{j}\right) + g^{\delta t}(\overline{sj})\right]\right)^+\right\}, y_2\right\}$$

Now, we substitute $S = g^{\delta t}e$ all corresponding terms into the first ODEs of (27) to get:

$$e' + \delta e = \varphi_0 - (1 - u_1^*(t))\left[\beta_1 c_1 g^{\delta t}f + \beta_2 c_2 g^{\delta t}c + \beta_3 c_3 g^{\delta t}i + \beta_4 c_4 g^{\delta t}j + \beta_5 c_5 g^{\delta t}k\right]g^{\delta t}e - \mu g^{\delta t}e,$$
$$f' + \delta f = (1 - u_1^*(t))\left[\beta_1 c_1 g^{\delta t}f + \beta_2 c_2 g^{\delta t}c + \beta_3 c_3 g^{\delta t}i + \beta_4 c_4 g^{\delta t}j + \beta_5 c_5 g^{\delta t}k\right]g^{\delta t}e - (\mu + \delta + \theta)g^{\delta t}f,$$
$$c' + \delta c = \theta g^{\delta t}f - (\mu + \delta + a_1^*(t))g^{\delta t}c,$$
$$i' + \delta i = a_1^*(t)g^{\delta t}c + a_3^*(t)g^{\delta t}j - (\mu + \pi + a_2)g^{\delta t}i,$$
$$j' + \delta j = a_2 g^{\delta t}i - (\mu + \delta + a_3^*(t))g^{\delta t}j,$$
$$k' + \delta k = \delta g^{\delta t}(f + c + j) + \pi g^{\delta t}i - (\mu + \alpha)g^{\delta t}k,$$

$$m' + \delta m = -1\left\{g^{\delta t}m\left[-(1 - u_1^*(t))\left(\beta_1 c_1 g^{\delta t}f + \beta_2 c_2 g^{\delta t}c + \beta_3 c_3 g^{\delta t}i + \beta_4 c_4 g^{\delta t}j + \beta_5 c_5 g^{\delta t}k - \mu\right)\right]\right.$$
$$\left. + g^{\delta t}p\left[(1 - u_1^*(t))\left(\beta_1 c_1 g^{\delta t}f + \beta_2 c_2 g^{\delta t}c + \beta_3 c_3 g^{\delta t}i + \beta_4 c_4 g^{\delta t}j + \beta_5 c_5 g^{\delta t}k\right)\right]\right\}$$

$$p' + \delta p = -1\left\{\lambda_1(t)\left[-(1 - u_1^*(t))\beta_1 c_1 g^{\delta t}e\right] + g^{\delta t}p\left[\begin{array}{c}(1 - u_1^*(t))\beta_1 c_1 g^{\delta t}e \\ -(\mu + \delta + \theta)\end{array}\right] + \theta g^{\delta t}q + \delta g^{\delta t}t\right\}$$

$$q' + \delta q = -1\left\{\begin{array}{c}g^{\delta t}m\left[-(1 - u_1^*(t))\beta_2 c_2 g^{\delta t}e\right] + g^{\delta t}p\left[(1 - u_1^*(t))\beta_2 c_2 g^{\delta t}e\right] \\ + g^{\delta t}q(\mu + \delta + a_1^*(t)) + g^{\delta t}ra_1^*(t) + \delta g^{\delta t}t\end{array}\right\}$$

$$r' + \delta r = -1\left\{\begin{array}{c}g^{\delta t}m\left[-(1 - u_1^*(t))\beta_3 c_3 g^{\delta t}e\right] + g^{\delta t}p\left[(1 - u_1^*(t))\beta_3 c_3 g^{\delta t}e\right] \\ -g^{\delta t}r(\mu + \pi + a_2) + a_2 g^{\delta t}s + \pi g^{\delta t}t\end{array}\right\}$$

$$s' + \delta s = -1\left\{\begin{array}{c}g^{\delta t}m\left[-(1 - u_1^*(t))\beta_4 c_4 g^{\delta t}e\right] + g^{\delta t}p\left[(1 - u_1^*(t))\beta_4 c_4 g^{\delta t}e\right] \\ + g^{\delta t}ra_3^*(t) - g^{\delta t}s(\mu + \delta + a_3^*(t)) + \delta g^{\delta t}t\end{array}\right\}$$

$$t' + \delta t = -1\left\{\begin{array}{c}g^{\delta t}m\left[-(1 - u_1^*(t))\beta_5 c_5 g^{\delta t}e\right] + g^{\delta t}p\left[(1 - u_1^*(t))\beta_5 c_5 g^{\delta t}e\right] \\ + g^{\delta t}ra_3^*(t) - (\mu + \alpha)g^{\delta t}t\end{array}\right\}$$

Furthermore, we subtract the equations $\overline{S}$ from S, $\overline{I}$ from I, ..., $\overline{A}$ from A, $\overline{\lambda_1}$ from λ,........, $\overline{\lambda_6}$ from λ_6 and then multiply the result obtained by the appropriate difference of functions and integrate from t_0 to t_f. Finally, we sum the twelve integral equations and use the estimation approach to derive the uniqueness of the optimality system. Then, by lemma 3.1, we have:

$$\left|u_1^*(t) - \overline{u}_1^*(t)\right| \le \frac{1}{W_1}\left|\left(ef - \overline{ef}\right) - \left(ec - \overline{ec}\right) + \dots + \left(ek - \overline{ek}\right)\right|$$

and:

$$\left|\eta^*(t) - \overline{\eta}^*(t)\right| \le \frac{1}{W_2}\left|\left(qf - \overline{qf}\right) - \left(rf - jr\right) - \left(\overline{rf} + \overline{jr}\right)\left(sj - \overline{sj}\right)\right|.$$

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

$$\frac{1}{2}(e - \overline{e})^2(t_f) + \lambda_1\int_{t_0}^{t_f}(e - \overline{e})^2 dt \le \int_{t_0}^{t_f}\mu|e - \overline{e}|^2 dt + \left[\int_{t_0}^{t_f}|u_1^*e - \overline{u}_1^*\overline{e}||e - \overline{e}| dt\right]$$

$$+ g^{\delta t}\int_{t_0}^{t_f}|(f + c) - (f + c)| dt$$

$$\le \psi_1\int_{t_0}^{t_f}\left[|e - \overline{e}|^2 + |m - \overline{m}|^2 + |j - \overline{j}|^2 + |r - \overline{r}|^2\right]dt$$

$$+ \psi_2 g^{\delta t}\int_{t_0}^{t_f}\left[|e - \overline{e}|^2 + |m - \overline{m}|^2 + |j - \overline{j}|^2 + |r - \overline{r}|^2\right]dt$$

where the constants $\Psi_{i=1,2}$ depends on the coefficients and the bounds on states and adjoint variables. Combining twelve of these estimates gives:

$$\frac{1}{2}(e - \overline{e})^2(t_f) + \frac{1}{2}(f - \overline{f})^2(t_f) + \dots + \frac{1}{2}(k - \overline{k})^2(t_f) + \frac{1}{2}(m - \overline{m})^2(t_0) + \frac{1}{2}(p - \overline{p})^2(t_0)$$

$$+ \dots + \frac{1}{2}(t - \overline{t})^2(t_0) + \lambda\int_{t_0}^{t_f}\left[\begin{array}{c}(e - \overline{e})^2 + (f - \overline{f})^2 + \dots + (k - \overline{k})^2 + (m - \overline{m})^2 \\ + (p - \overline{p})^2 + \dots + (t - \overline{t})^2\end{array}\right]dt$$

$$\le \left(\tilde{\psi}_1 + \tilde{\psi}_2 e^{3\lambda_f}\right)\int_{t_0}^{t_f}\left[(e - \overline{e})^2 + (f - \overline{f})^2 + \dots + (k - \overline{k})^2 + (m - \overline{m})^2 + \dots + (t - \overline{t})^2\right]dt$$

for all $t_0 = 0$. Therefore, we can conclude from the above result that

$$\left(\lambda - \tilde{\psi}_1 - \tilde{\psi}_2 e^{3\lambda_f}\right)\int_{t_0}^{t_f}\left[(e - \overline{e})^2 + (f - \overline{f})^2 + \dots + (k - \overline{k})^2 + (m - \overline{m})^2 + \dots + (t - \overline{t})^2\right]dt \le 0$$

where, $\tilde{\psi}_1, \tilde{\psi}_2$ depends on the coefficients and bounds on e, f, c, i, j, k, m,....,s, t. For simplicity, we choose λ such that $\quad \lambda > \tilde{\psi}_1 + \tilde{\psi}_2 \; t_f < \frac{1}{3\lambda}\ln\left(\frac{\lambda - \tilde{\psi}_1}{\tilde{\psi}_2}\right)$ and, $\quad$ then $e = \overline{e}, f = \overline{f}, c = \overline{c}, \dots, s = \overline{s}, t = \overline{t}$. Hence, for a sufficiently small time, the solution is unique.

Therefore, it is optically clear from the above result that the uniqueness of the optimality system for the small-time interval is a two-point boundary problem due to opposite time orientations, state equations, and adjoint equations, which are defined by initial and final time conditions. Moreso, the optimal controls μ_1^*, η^* are characterized in terms of the unique solution of the optimality system. Again, from the epidemiological point of view, we deduce that if $\lambda > (W_1 + W_2)$ for all $(W_1 + W_2) \triangleleft 0$ and $t_f < \frac{1}{3\lambda}\ln\left(\frac{\lambda - \tilde{\psi}_1}{\tilde{\psi}_2}\right)$, then infection is asymptotically stable, and if $t_f > \frac{1}{3\lambda}\ln\left(\frac{\lambda - \tilde{\psi}_1}{\tilde{\psi}_2}\right)$ for all $\lambda > (W_1 + W_2)$, then global endemicity is eminent. Thus, the above optimal controls give the impact of an optimal treatment strategy for HIV/AIDS control dynamics under the scenario of therapy abuse. At this point, it is crucial to numerically investigate our theoretical predictions by simulating

several numerical examples. Thus, our next section is devoted to the system's numerical simulations and results.

Numerical Simulations and Results

In this section, we will attempt to verify per the study's set goal, the viability of our derived system theoretical predictions. That is, we resort to numerical simulations to illustrate the viability of our derived optimal control model and the optimality system equations, noting that the analytic approach becomes imperative due to the complexity of the derived optimality system. Moreso, our choice of 30 months as treatment time interval arises from the fact that chemotherapies have a certain designated allowable treatment time interval, noting that HIV can build resistance after a time frame ($t_{start} - t_{final} > 2$ years) due to its mutation ability resulting to potential hazardous side-effects, (Butler *et al.*, 1997; Kirschner *et al.*, 1997; Fister *et al.*, 1998). Remarkably, our entire simulations explore in-built rkfixed from Runge-Kutta of the order of precision 4 in a Mathcad surface, noting that initial adjoint variable $\lambda_i(t) > 0$, I = 1,….6. Also, it is important to note that for précised and coincide results, we shall dwell on the accuracy of our software for the design and calibrations of the system *xy*-coordinates, (Butler *et al.*, 1997; Fister *et al.*, 1998; Naresh *et al.*, 2006).

For simplicity, the simulations shall entail an off-treatment scenario (off-optimal technique) i.e., $\mu_1 > 0$, $\eta = (a_1 + a_3) = 0$, using model (3), and when optimal treatment is administered i.e., $\mu_1 > 0$, $\eta = (a_1 + a_3) > 0$ for equation (27). Further insight into the application of the optimal technique is achieved with the simulation of the optimal control pair i.e., $\mu_1^*(t) > 0$, $\eta^*(t) > 0$.

Notably, we conduct these tasks using generated data about data from our motivating model (Bassey and Atsu, 2021), in addition to data on optimal control parameters. Thus, compatible data for the present study are depicted in Table 1.

The entire simulations explore in-built rkfixed from Runge-Kutta of the order of precision 4 in a Mathcad surface, noting that initial adjoint variables $\lambda_i(t) > 0$, $i = 1,...,6$.

Simulation of System Basic Model (Without Control Functions)

We recall that our goal is to investigate the impact of multi-treatment functions (condom use and ART) under therapy abuse. However, we simulate as leverage to the system-set goal, the system-derived optimal model Eq. (3) in a completely off-treatment scenario i.e., $\mu_1 = 0$, $\eta = (a_1 + a_3) = 0$. In reality, the essence of this simulation (as depicted by appendix **A**) is to allow us to ascertain the magnitude of HIV/AIDS infection transmission dynamics at off-treatment when compared to the accessibility of optimal control functions.

Thus, invoking optimal model (3), for all $\mu_1 = 0$, $\eta = (a_1 + a_3) = 0$, and (Table 1), we simulate the six subpopulation components as depicted by Fig. 2(a-f) below.

Fig. 2(a-f) represents the dynamical flow of HIV/AIDS transmission with ART abuse and in particular under the off-treatment scenario. Notably, Fig. 2(a), which presents the susceptible population indicates an initial inclination with $0.5 \le S(t) \le 0.72$ cell/mm^{3}at $t_f \le 3$ months. This shows that despite the onset (asymptomatic stage) of virions transmission, the population experienced initial growth due to a steady inflow of population recruitment rate $\varphi_0(t) > 0$ and the initial response of the body's natural adaptive immune system, (Adams *et al.*, 2004). However, following the concentration of virions, its transmission proves to suppress the body's natural adaptive immune response resulting in sharp unstable decline, saddling at $t_f \le 10$ months with $S(t) \le 0.305$ cell/mm^3, (Glass *et al.*, 2003). At $10 \le t_f \le 30$ months, the susceptible population exhibits symptomatic stability, following the introduction of screening mechanism and sustained recruitment rate, (Tripathi *et al.*, 2007). The abysmal unstable decline in Fig. 2(a) is vindicated by the sharp undulating inclination rate of the unaware infected population (Fig. 2(b)) with $0.1 \le I_1(t) \le 0.948$ cell/mm^{3}at $t_f \le 3$months and then exhibiting saddle point at $3 \le t_f \le 10$ months. The introduction of a screening mechanism, which has a positive effect on the behavioral attitude of the population is seen to yield stability of the transmission of the virions with value $I_1(t) \approx 0.89$ cell/mm^{3}for all $10 \le t_f \le 30$ months. Figure 2(c) represents the screened infective population that exhibited an initial sharp decline at $0 \le t_f \le 3$ months before becoming aware of their HIV status. This awareness yielded a significant behavioral attitude that resulted in early stability with value at $I_2(t) \le 0.007$ for all $3 \le t_f \le 30$ months.

From Fig. 2(d and e), we see the aware infectives that are on treatment compartments but have no access to treatment (i.e., off-treatment) exhibiting sequential near population extinctions leaving their varying population at $0.1 \le T(t) \le 0.581 \times 10^{-7}$for all $12 \le t_f \le 30$ and $0.1 \le T_A(t) \le 1.255 \times 10^{-6}$ for all $16 \le t_f \le 30$ months respectively. Finally, the depletion in the susceptible population and the increasing population of the unaware infectives is seen to transmute rapidly to full-blown AIDS as vindicated by Fig. 2(f) with a value at $0.1 \le A(t) \le 1.483$for all $t_f \le 30$ months.

Simulations of Model Optimality System (with Bilinear Control Functions)

Having simulated the system basic model (3.3) for the off-treatment scenario with known results, it becomes paramount and in line with the study set goal, to simulate the modified model with control functions (condom use and ART) amidst drug abuse. Moreso, since the study is aimed at maximizing the concentration of the susceptible and those receiving treatment, then the system control

functions denoted by $\mu_1{}^*(t)$ and $\eta^*(t)$, where $\eta^*(t) = (a_1{}^*(t)+a_3{}^*(t))$ must be such that $\mu_1{}^*(t)>0$ and $\eta^*(t)>0$. Then, Eq. (3.17) is the required equation for simulation. Of note, we solve our optimality system using an iterative method with Runge-Kutta of the order of precision 4 in a Mathcad surface. That is, since the optimality system is a complicated problem, we solve the state system with initial conditions forward in time and then, the adjoint variables backward in time with the terminal conditions (i.e., two-point boundary value problem). Moreso, we note that by propositions 3.1 and 3.2, the toxicity of control functions are clinically observed under optimal weight factors: $W_1 = 25000$, $W_2 = 250$ with drug efficacy bounded by $x_1 = 0$, $x_2 = 0.2$, $y_1 = 0.4$ and $y_2 = 0.9$. Also, it is important to note that due to the variation in the control functions, the upper bound y_1 for μ_1 is much smaller than the upper bound y_2 for η, which is then balanced by the corresponding $W_{i=1,2}$ in the objective function. Hence, the results of the computations for the state variables and the adjoint system are represented in Fig. 3(a-f) and 4(a-f) below.

The graphic images of the co-states are seen below.

From the above simulations, Fig. 3(a-f) represents the general dynamical flow for HIV/AIDS with ART abuse in a situation where control functions ($\mu_1{}^*(t),\eta^*(t)$) are clinically accessible. Specifically, Fig. 3(a) depicts the initial rapid maximal concentration of the susceptible population following coherent onset administration of control functions. Here, the susceptibility increases in the range of $0.5 \le S(t) \le 6.056$ cell/mm^3 at $t_f \le 16$ months. The concentration of the susceptible population exhibits some level of declination in the interval $16 \le t_f \le 21$ months and then inclines towards $S(t) \le 3.01$ cell/mm^3 $S(t) \le 3.01$ cell/mm^3 for all $21 \le t_f \le 30$ months. The unaware infectives affirm the trend of the outcome of Fig. 4(a). That is, from Fig. 3(b), the unaware infectives subpopulation declined rapidly to $I_1(t) \le 0.047$ cell/mm^3 from $I_1(t) \le 0.1$ cell/mm^3 for all $t_f \le 10$ months but thereafter exhibited undulating re-emergence with the declining trend of $I_1(t) \le 0.55$ cell/mm^3 at $22 \le t_f \le 30$ months.

In Fig. 3(c), we investigate the dynamical behavior of the aware infectives but not ready to receive treatment. We observe an initial decline with a value at $0.1 \le I_2(t) \le 3.195 \times 10^{-3}$, which could be attributed to the asymptomatic stage of infection and further align with the initial immune response. Since this compartment is not ready for accessing of treatment, the resurgence of infection concentration to $0.05 \le I2(t) \le 0.08$ at $10 \le t_f \le 30$ months is observed. On the other hand, under coherent control functions, the compartment designated to the accessibility of treatment as in Fig. 3(d), clearly exhibited rapid steady decline following onset medication with a value range of $0.1 \le T(t) \le 6.714 \times 10^{-3}$ cell/mm^{-3} for all $t_f \le 16$ months. This same compartment however indicates a later increase to $T(t) \le 0.04$ at $t_f \le 27$ months and thereafter declined sharply for all $t_f \le 27$ months. Illustrating the dynamical

flow of ART abuse in a scenario where control functions are accessible, the compartment represented by Fig. 3(e) exhibits initial tremendous recovery with an initial declining population range of $0.1 \le T_A(t) \le 3.718 \times 10^{-3}$ for $t_f \le 16$ months. This shows the presence and adherence to initial control protocols. The sudden surge in the number of infective to the value of $3.718 \times \le T_A(t) \le 0.024$ for $20 \le t_f \le 27$ months suggest truncation of ART and consequently, the abuse of ART. The $T_A(t)$ compartment declines thereafter, showing treatment resumption towards a later interval of $27 \le t_f \le 30$ months.

On full-blown AIDS compartment, the simulation as depicted by Fig. 3(f) indicates steady efficacy of the control measures sustaining its initial value of $A(t) \le 0.1$ through a time interval of $t_f \le 12$ months, only to resurge to a value of 2154 cell/mm^{-3} at $t_f \le 25$ months. This sudden resurgence is attributed to the possible overflow arising from ART abuse. Finally, Fig. 4(a-f) depicts the co-state variables used for the determination of the model adjoint system. This adjoint system represents the backward effect of the optimal state variables. Most notable, are the variations of the adjoint variables $\lambda'_2(t) \le 4.8$, $\lambda'_3(t) \le 3.5$, which in the controlled case are very large, indicating a high degree of sensitivity of the performance index Q (u_1,η) to the dynamic flow in $I_1(t)$ and $I_2(t)$. Thus Fig. 4(a-f) depicts the overall contributions (or impact) of the adjoint system on the optimality system.

Simulations of System Control Functions

To quantifiably illustrate the impact of varying treatment functions at varying stages of model investigations, we simulate in this section, the onset-treatment functions when the basic model was not transformed into an optimal control problem and when the control functions were derived as an optimal control pair. This procedure avails us with both biological and mathematical importance in terms of the applied optimal control theory. Thus, from the model (3.3), we simulate the applied control functions, using (Table 1) and letting $\mu_1 = 0.5,\eta = (a_1+a_2) = (0.45+0.14) = 0.59$ against time for all $t \in [t_0, t_f] = [0,30]$. For the optimal control pair $\mu_1{}^*(t),\eta^*(t)$, we use the results given by Eq. (20) and (21). The computations are depicted in Fig. 5 (a-d) below.

From Fig. 5(a-d), we observe somewhat intriguing linear curves representing pair dual characteristics of the dynamics and impact of designated control functions for our system basic model under onset-treatment (without optimal implication) and when the model was transformed to an optimal control problem. Specifically, with the weight factor and its lower and upper bounds set to zeros ($W_1 = 0$, $X_1 = 0$, $Y_1 = 0$), Fig. 5(a) depicts the dynamical increase in the proportion of condom use with a value ranging at $0.5 \le \mu1(t) \le 15.5$ for all $t_f \le 30$ months. Under similar conditions and $W_2 = 0$, $X_2 = 0$, $Y_2 = 0$, the application of therapy with a penchant for abuse of drugs

indicates that the proportion of ART used is in the range of $0.59 \leq \eta(t) \leq 18.29$ through $t_f \leq 30$ months-see Fig. 5(b).

Furthermore, the application of optimal treatment under the optimality system is depicted in Fig. 5(c and d), where for both figures, the optimal weight factors and their lower and upper bounds are not zeros (i.e., $W > 0$, $x_i > 0$, $y_i > 0$ for all $i = 1,2$). Here, Fig. 5(c) shows a relatively low proportion of condom use with a range value at $0.5 \leq \mu_1^*(t) \leq 3.5$, when compared with that of Fig. 5(a). On the other hand, the amount of ART required under the optimal control approach as described by Fig. 5(d) is in the range of $0.59 \leq \eta^*(t) \leq 6.95$. The implication is that, with the application of optimality control theory guided by clinical conditions, less amount of control functions is required when compared to a treatment schedule without optimal conditions. Moreso, the criteria for minimal systemic cost is satisfied for all $t \in [t_0, t_f]$ defined. Thus, we devote the next section to the in-depth analysis of our established results.
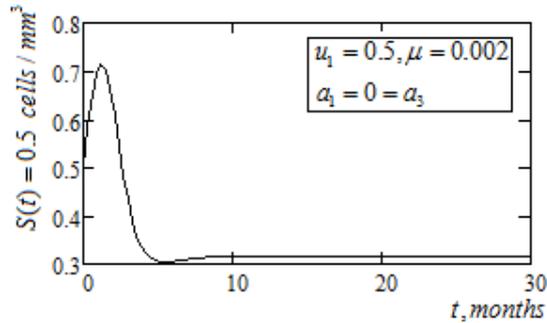
(a)
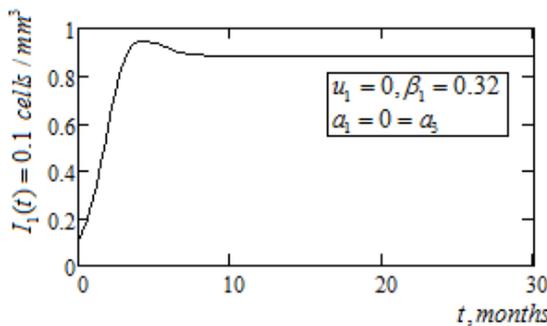
(b)
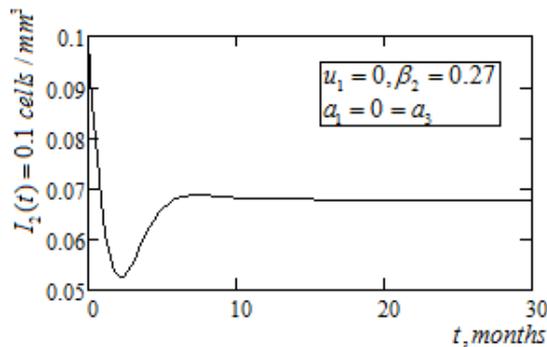
(c)
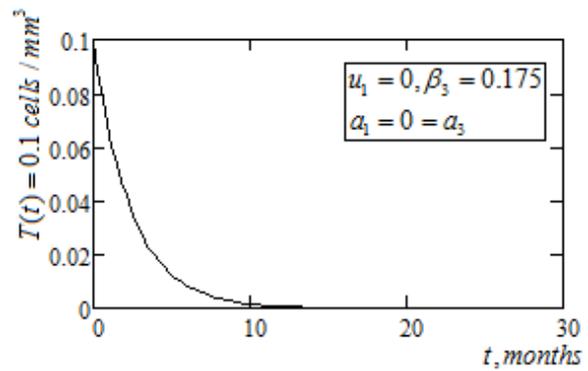
(d)
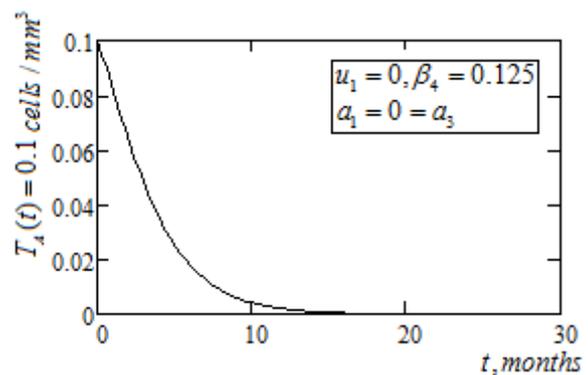
(e)
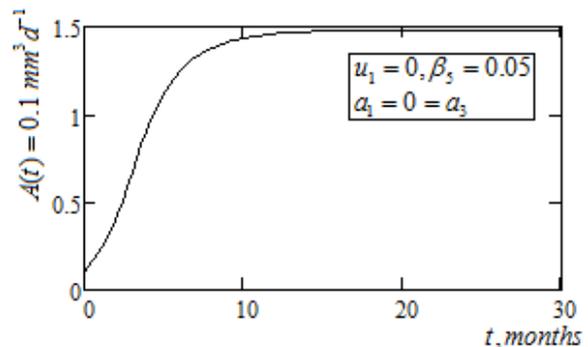
(f)

Fig. 2: (a-f) Schematic representation of off-treatment of HIV/AIDS dynamics under ART abuse scenario; (a) Dynamics of the susceptible population under off-treatment; (b) Dynamics of unaware infective under off-treatment; (c) Dynamics of aware infective not ready for treatment under off-treatment; (d) Dynamics of aware infective on treatment under off-treatment $\mu = 0.02d^{-1}$; (e) Dynamics of aware infective with ART abuse under off-treatment $\mu = 0.02d^{-1}$; (f) Dynamics of full-blown AIDS infection under off-treatment $\alpha = 0.3mm^3d^{-1}$

(a)

(b)

(c)

(d)

(e)

(f)
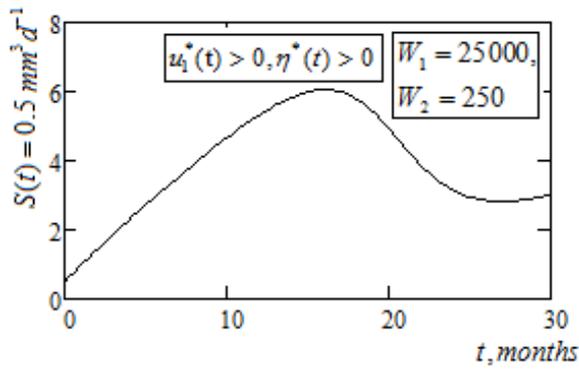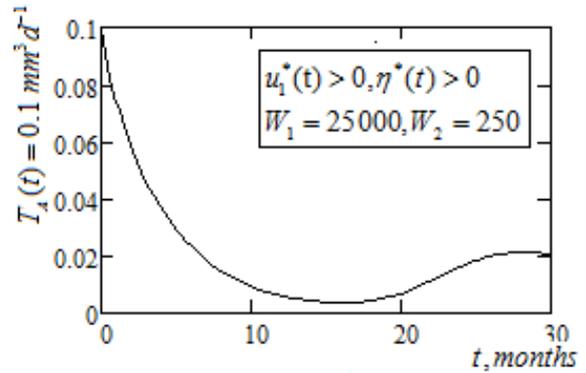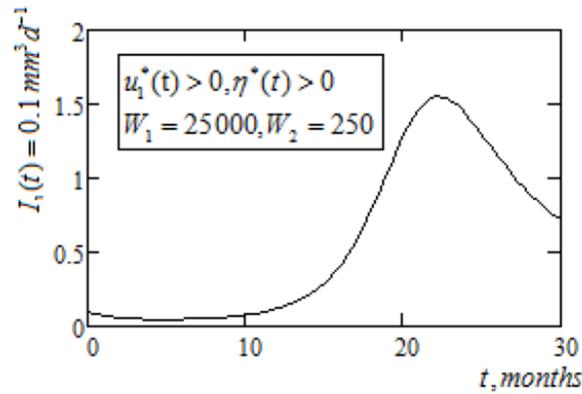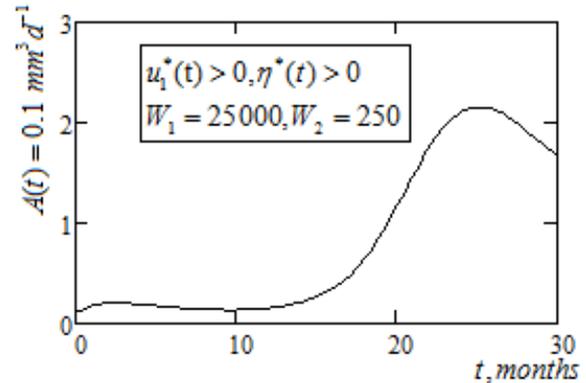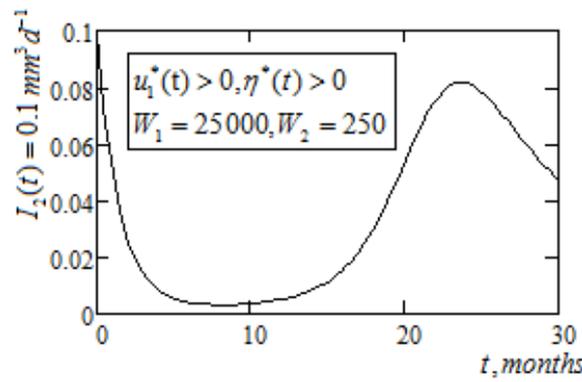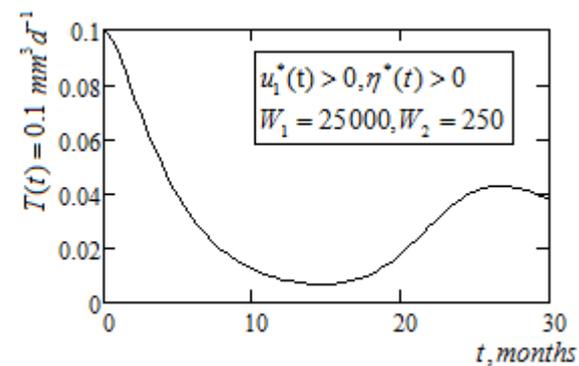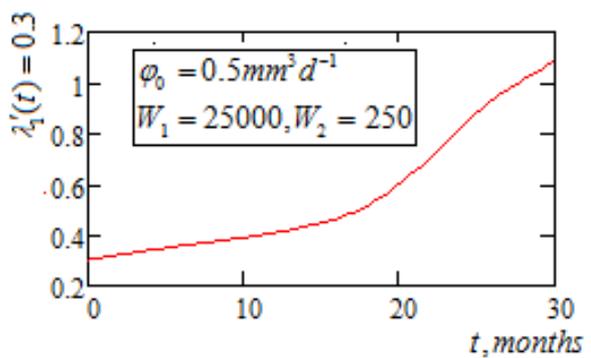
Fig. 3: (a-f) epidemiological representation of an optimality system of HIV/AIDS infection dynamics under ART abuse; (a) Dynamics of the susceptible population under control function with $\varphi_0 = 0.5mm^3d^{-1}$; (b) Dynamics of unaware infective under control function with $\beta_1 = 0.32mm^3vir^{-1}d^{-1}$; (c) Dynamics of aware infective not ready for treatment under control functions scenario,;(d) Dynamics of aware infective on treatment under control functions scenario, $\beta_3 = 0.175mm^3vir^{-1}d^{-1}$; (e) Dynamics of aware infective with ART abuse under control functions, $\beta_4 = 0.125mm^3vir^{-1}d^{-1}$; (f) Dynamics of full-blown AIDS infection under control functions, $\beta_5 = 0.05mm^3vir^{-1}d^{-1}$

(a)

(b)

(c)

(d)

(e)

(f)
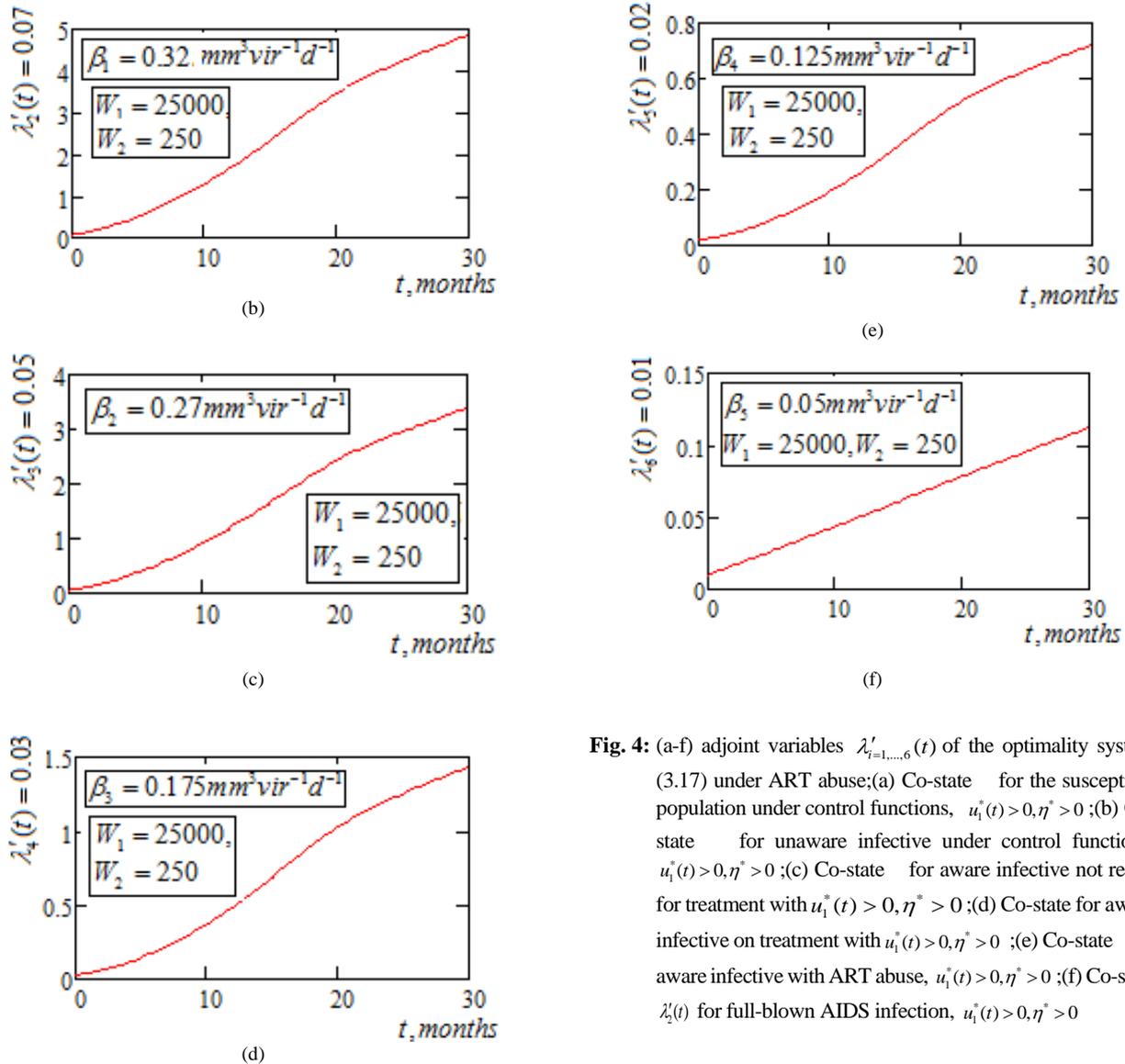
Fig. 4: (a-f) adjoint variables $\lambda'_{i=1,\dots,6}(t)$ of the optimality system (3.17) under ART abuse;(a) Co-state for the susceptible population under control functions, $u_1^*(t) > 0, \eta^* > 0$;(b) Co-state for unaware infective under control functions, $u_1^*(t) > 0, \eta^* > 0$;(c) Co-state for aware infective not ready for treatment with $u_1^*(t) > 0, \eta^* > 0$;(d) Co-state for aware infective on treatment with $u_1^*(t) > 0, \eta^* > 0$;(e) Co-state for aware infective with ART abuse, $u_1^*(t) > 0, \eta^* > 0$;(f) Co-state $\lambda'_2(t)$ for full-blown AIDS infection, $u_1^*(t) > 0, \eta^* > 0$

Table 1: Variables, parameters, and their values for model (3)

Variables	Dependent state variables description	Initial values	Units
$S(t)$	Susceptible population	0.5	
$I_1(t)$	Unaware infectives	0.1	
$I_2(t)$	Aware infectives but not receiving treatment	0.1	
$T(t)$	Aware infectives receiving treatment	0.1	cell/mm^3
$T_A(t)$	Aware infectives under ART abuse	0.1	
$A(t)$	Full-blown AIDS population	0.1	mm^{3}d^{-1}
	Parameters and Constants Description		
φ_0	Recruitment rate (population source)	0.5	mm^{3}d^{-1}
$\beta_{i=1,\dots,5}$	Probability of interaction by susceptible with various infectives	0.32; 0.27; 0.175:	mm^3 vir^{-1} d^{-1}
$c_{i=1,\dots,5}$		0.125; 0.05 0.2; 0.1	
$\lambda = (1-\mu_1)$	Sexual contact by susceptible with various infectives	0.5; 0.4; 0.3;	
θ	Successful condom use	$u_1 \in [0,1]$	day^{-1}
π	Rate at which the unaware becomes aware	0.04	

Table 1: Continue

δ			
	Progression rate of aware infective to AIDS	0.028	
μ	$mm^3 d^{-1}$		
α	Rate at which infectives develop AIDS	0.500	day^{-1}
	Natural death rate	0.002	day^{-1}
	AIDS induces a death rate	of 0.300	$mm^3 d^{-1}$
a_1	Rate of ART received by $T(t)$	0.450	
a_2	Rate of abuse of ART by $T_A(t)$	0.370	day^{-1}
a_3	Resumption rate of ART by $T_A(t)$	0.140	

(a)

(d)

(b)
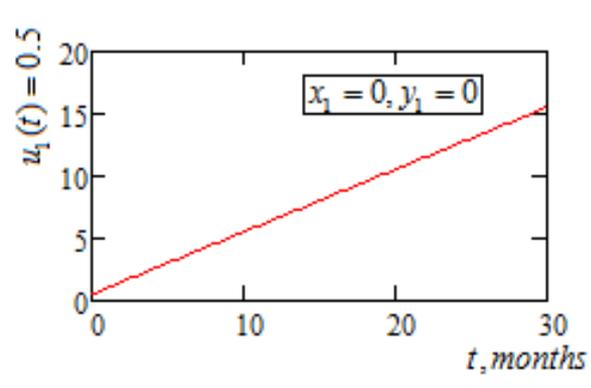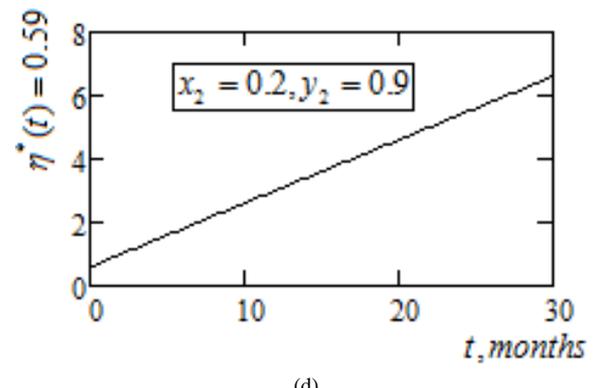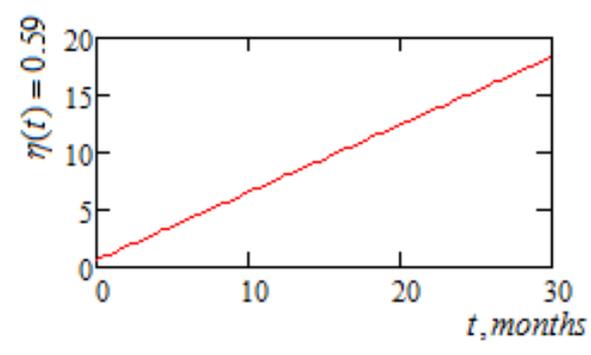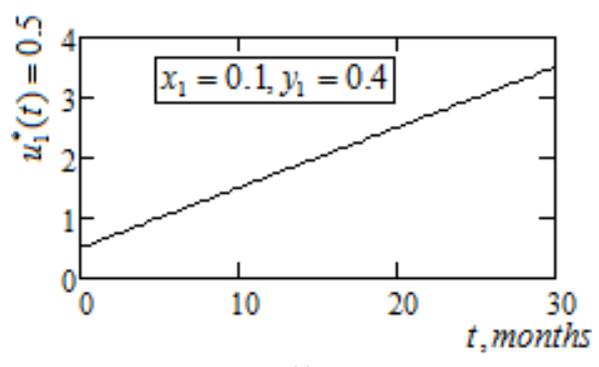
Fig. 5: (a-d) simulations of system control functions for onset-treatment $u_1(t), \eta(t)$ and optimal control pair $u_1^*(t), \eta^*(t)$;(a) Onset-treatment control functions, $u_1(t) > 0$ with $W_1 = 0, W_2 = 0$;(b) Onset-treatment control function $\eta(t) > 0$ with $W_1 = 0, W_2 = 0$;(c) Optimal control pair $u_1^*(t) > 0$ with $W_1 = 25000$;(d) Optimal control pair $\eta^*(t)$ with $W_2 = 250$

Results and Discussion

Here, we bring to bear both the mathematical and epidemiological implications of our formulated model concerning the material and methods adopted in section three, as well as the results of numerical illustrations of section four. Moreso, in an attempt to significantly rate the present study, we shall draw some comparison of the present investigation with the scientific findings of most notable and compatible studies as well as with results from our motivating model.

Discussion

This present study has considered the extended version of the model by Bassey and Atsu (2021), following the redefinition and transformation of the derived basic model to an optimal control problem. The investigation was formulated as 6-Dimensional deterministic differential dynamic equations to investigate the application of optimal control techniques as a powerful tool for studying

(c)

the role of ART abuse on the control and treatment dynamics of HIV/AIDS infection. The present research adopted as control measures, a bilinear control functions in the range of condom use and ART amidst ART abuse. That is, the present study sought to determine the optimal control treatment strategies that aimed at maximizing not only the susceptible population but also, to maximize the concentration index of the aware infective under the coherent application of designated control functions, while reducing the rate of drug abuse. Of note, the main objective of the study was to access the capability of optimal control techniques in analyzing the role of ART abuse in the treatment dynamics of the HIV/AIDS epidemic. Moreso, in addition to the assumptions of the system motivating model, the main assumptions of the present study are defined by the control functions $\mu_1{}^*(t) > 0$ and $\eta^*(t) > 0$ as functions of time variation and having an antiviral effect on disease viral load production.

The material and methods adopted in this study involved bilinear control functions (condom use and ART) in limiting the spread of the HIV/AIDS viral load epidemic. Study analysis is based on compartmental state variables constituted by the susceptible -unaware infectives-aware infectives, not on treatment-aware infectives on treatment schedules-aware infectives with ART abuse-full-blown AIDS population. Essentially, the basic model was first transformed into an optimal control problem, and optimal characterization was investigated by the use of the fundamental theory of differential functions. Incorporating the method of the Hessian matrix into classical Pontryagin's maximum principle, the study investigated the existence of an optimal control pair, derived the model optimality system, and established the uniqueness of the optimality system of solutions.

Daunted by the task of accessing the prowess of optimal control technique in the maximization of predominant variables, several numerical simulations were performed. First, the simulation was considered for an off-treatment (off-optimal) scenario, where infectives and full-blown AIDS populations inclined to an alarming proportion as evidenced by the near population extinction of the susceptible. An investigation that conformed to those of (Landi *et al.*, 2008) for an untreated HIV infection transmission dynamic. Notably, the severity of virions spread as indicated by the aware infectives with ART abuse under off-treatment was rapid and high, reducing the population to near zero with $0.1 \leq T_A(t) \leq 1.255 \times 10^{-6}$ cell/mm^3 when compared to the similar compartment under optimal control functions, where infected population under ART abuse was sustained at $0.1 \leq T_A(t) \leq 3.718 \times 10^{-3}$ cell/mm^3. That is, under off-treatment (off-optimal), we observed near population extinction for $T_A(t)$, which indicates the decline in the susceptible population with the value of $0.5 \leq S(t) \leq$ cell/mm^3.

Clearly, following the transformation and derivation of the study optimality system, far-reaching significant results were established as depicted by Fig. 4(a-e) with corresponding adverse impact (adjoint variables) represented by Fig. 5(a-e) respectively. Of note, unlike the simulation of off-treatment (without optimal approach), which indicated a maximal decline of the uninfected proportion of $0.5 \leq S(t) \leq 0.35$ cell/mm^3, the maximization of the susceptible population under optimal control technique exhibited somewhat tremendous inclination with a maximal range of $0.5 \leq S(t) \leq 6.056$ cell/mm^3 for all $t_f \leq 30$ months see Fig. 4(a). The increase in susceptible population under optimal control technique is by far an improvement to the outcome of onset treatment under global stability conditions, (Bassey and Atsu, 2021).

In Fig. 4(b), the number of unaware infectives at final time $t_f \leq 3$ months declined to $I_1(t) \leq 0.0047$ cell/mm^3 as against unaware infectives incline rate of $I_1(t) \leq 0.948$ cell/mm^3 under off-treatment. Notably, under optimal control technique, the low rate of unaware infectives was by far an improved outcome when compared to the infection rate of $I_1(t) \leq 0.1096$ for $t_f \leq 3$ months from the study. Moreso, the dynamical flow for aware infectives with ART abuse from the optimal control technique significantly presented an improved rate of survival with $T_A(t) \leq 3.718 \times 10^{-3}$ cell/mm^3 when compared to similar compartment simulated under off-treatment (without optimal protocol) with ART abuse, which exhibited near extinction rate with $T_A(t) \leq 0.255 \times 10^{-6}$ cell/mm^3 for all $t_f \leq 30$ months. Thus, the implication from the present investigation was that optimal drug treatment protocol has a very desirable effect by increasing the index value of healthy CD4$^+$ T cells of the susceptible population. Furthermore, it is observed that the undulating rebounds of infection as exhibited by aware infectives on ART treatment can be attributed to the interruption in the ART schedule. On the other hand, the compartment under coherent control functions, with a maximal value range of $T(t) \leq 6.714 \times 10^{-3}$ affirmed the later resumption of coherent treatment by the aware infectives with initial ART abuse. Moreso, the terminal gradual surge in the proportion of full-blown AIDS to $A(t) \leq 2.154$ cell/mm^3 suggested possible re-emergence in truncation of ART. In this case, this outcome intuitively affirmed the varying slight infection inclination at both $T_A(t)$ and $T(t)$ compartments.

Thus, the present results about the motivating model by Bassey and Atsu (2021), have shown that its control does behave somewhat differently from drug control systems not explicitly modeling ART abuse in the presence of optimal control strategy. Moreso, accounting for control function severities as was the case by (Culshaw *et al.*, 2004), where the control functions exhibited an initial decrease soon after initiation of

treatment, then rose to applicable stable value and finally drop rapidly near terminal time interval. A dynamic that was attributed to actions of immune response and off-treatment schedule. Importantly, from the present study, it is observed that control functions, which are a function of continuous treatment schedules, exhibited somewhat smooth linear inclined curves, typical of optimal dynamics. That is, our optimal treatment is a continuous time definite scheme, which justified the attained maximization of the susceptible index value.

Conclusion

This present investigation has been triggered by the limiting results and incisive recommendation (application of optimal control strategy) from the study motivating model, following the unaccounted consequential role of ART abuse in the transmission and treatment of the HIV/AIDS epidemic. That is, the present research sought and formulated an optimal control problem to access dynamics of the mathematical modeling of the role of ART abuse for the treatment of the HIV/AIDS epidemic using optimal control techniques. Giving an insight into the investigation, a 6-dimensional deterministic non-linear mathematical model was derived and transformed into an optimal control problem. Fundamentally, the investigation first determined the system state space and its optimal characterization. Classical numerical methods based on optimal control strategy were explored for the derivation and analysis of the system's theoretical and analytical predictions. Furthermore, the system's optimal control pair was determined and the existence of optimal control pair was established using optimal criteria in conjunction with the Hessian matrix method. Analytical predictions for the model optimality system and the uniqueness of the solution using classical Pontryagin's maximum principle were conducted. Numerical validity for system analytical predictions for both off-optimal and onset-optimal controls was conducted and results were obtained.

Results of numerical simulations indicated that for the off-treatment scenario, there exists a rapid spread of infection leading to the near extinction of the susceptible population. Moreso, following the introduction of optimal control techniques sequel to optimal control treatment protocols under ART abuse, the study revealed highly tremendous maximization of the susceptible population with a value range of $0.5 \leq S(t) \leq 6.056$ cell/mm^3 through $t_f \leq 16$ months and later exhibited an undulating optimal value of $S(t) \leq 3.01$ cell/mm^3 through $16 \leq t_f \leq 30$ months. This later decline is a function of Therapy (ART) abuse. Conspicuously, these results do not only demonstrate the role of ART abuse but by far, depicted an improved outcome when compared to the global stability analysis of the system

motivating model, where the outcome of the onset-treatment schedule (without optimal control technique) yields a less maximal value of $0.5 \leq S(t) \leq 1.203$ cell/mm^3 at $t_f \leq 3$ months. Remarkably, the present investigation does behave somewhat differently from drugs used to control systems not explicitly modeling ART abuse and not analyzing using optimal control techniques as was the case in (Culshaw *et al.*, 2004). Therefore, this research overwhelmingly portrays the significance of optimal control techniques for the control dynamics of HIV/AIDS infection under a therapy abuse scenario. Nonetheless, the incorporation of the contributive role of the adaptive immune response, time delay immunity lag, and the immeasurable effect of counseling under the presence of drug abuse in future advances is highly anticipated.

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Author's Contributions

Bassey Echeng Bassey: Conceptualization, methodology, data collections, writing – original draft, writing – reviews and editing, algorithm and software programing, analysis and writing of final version.

Adagba Odey Henry: Supervision, methodology, formal analysis, editing and validations.

Ethics

On behalf of the authors, the corresponding author declared a no conflict of interest and no funding received for this submitted manuscript. Moreso, the work described was original research that has not been published previously and not under any consideration for publication elsewhere.

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