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Research Article

Mathematical Analysis of Non-Autonomous HIV/AIDS Transmission Dynamics with Efficient and Cost-Effective Intervention Strategies

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Abstract: This study focuses on the analysis of a controlled dynamical system for the time evolution of Human Immunodeficiency Virus/Acquired Immunodeficiency Syndrome (HIV/AIDS) incorporating vertical (mother-to-child) transmission route of HIV and saturated treatment as two distinguishing factors. The impact of key epidemiological parameters of the model on the basic reproduction number is assessed via sensitivity analysis based on the normalized forward sensitivity approach. As a consequence of the sensitivity analysis, three time-dependent control intervention strategies including, therapeutic measure responsible for blocking vertical transmission route of HIV, condom usage measure, and treatment efforts with highly active anti-retroviral treatment (HAART) are considered to hinder HIV/AIDS transmission in the population. The non-autonomous system is analysed using optimal control theory, the existence of optimal control is qualitatively analysed and the optimal control triple is characterized by the famous Pontryagin's maximum principle. The optimal control triple considered are categorized into three different policies combining any two of the interventions namely, Policy **A** (combination of vertical transmission preventive effort and control intervention for condom measure); Policy **B** (combination of vertical transmission preventive effort and treatment measure with HAART); and Policy **C** (combination of condom usage measure and treatment effort), and detailed analyses of the efficiency and economic methodologies are explored. It is shown among other findings that Policy **C** is the most efficient and most cost-effective intervention. Therefore, the policy that averts highest cases of HIV/AIDS is recommended. The study emphasizes the importance of cost-effective intervention policies in resource-limited settings, which is crucial for policymakers.

***Keywords*:** HIV/AIDS model, vertical transmission, saturated treatment, optimal control, efficiency index, cost-effectiveness ratio

MSC: 34A34, 34H05, 37N35, 92B05, 93C15

1. Introduction

Human Immunodeficiency Virus (HIV) remains one of the significant and overwhelming public health challenges in human population. HIV is the agent responsible for the chronic immune system disease called Acquired Immune

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Deficiency Syndrome (AIDS) [1]. HIV primarily affects the immune system of the host by targeting the white blood cells, thereby resulting in a progressive collapse of the body immune system [2–4]. Spontaneous collapse in the body immune system as a result of the viral loads opens the body to some opportunistic infections such as, hepatitis C, hepatitis B and monkeypox, since the white blood cells capable of fighting against the infections have been destroyed by the disease. The first case of HIV was reported by the US Centre for Disease Control and Prevention (CDC) in 1981 [5, 6]. At the end of 2023, World Health Organization (WHO) reported that HIV has claimed about 42.3 million lives to date and nearly 39.9 million people are living with the disease with 65 percent of them from the WHO African nations. Moreover, an estimated 630,000 people died from HIV-related causes and about 1.3 million people acquired HIV [2].

Epidemiologically, it has been established that HIV/AIDS is contracted primarily through seminal fluids such as vaginal or anal secretions, semen, blood, breast milk. Consequently, HIV can be transmitted through unprotected sexual practice, mother-to-child, injection with needles contaminated with HIV/AIDS, transfusion of contaminated blood and organ transplant [7–9]. HIV infected individuals may develop flu-like symptoms within the first 21 days of exposure to the deadly viral disease. However, HIV infected individuals receiving anti-retroviral treatment may not develop further symptoms. While symptoms such as night sweats, cough, weight loss, headaches, diarrhea, sunburn-like rash, body aches, joint pain and tonsillitis may appear as the virus replicates, thereby causing the body immune system to deteriorate [2]. Untreated HIV infection typically leads to the severe or chronic stage of HIV, acquired immune deficiency syndrome (AIDS) if effective anti-retroviral drug is not sought early enough to curtail its replication in the human system. It is worth mentioning that up till this time, no specific vaccine or cure has been discovered to fight against the menace of HIV/AIDS in human population [10]. Notwithstanding, medications such as anti-retroviral drugs have been put in place to effectively manage the spread trend of HIV/AIDS in human population [11].

Several studies have been conducted on the transmission dynamics of HIV/AIDS in the literature through the application of mathematical modelling, a prominent tool used in gaining further comprehension of the mechanisms associated with the infectious diseases dynamics in human population. Moreover, mathematical modelling enhances decision-making processes through consideration of effective intervention strategies procured to set the dynamics of HIV/AIDS to utter extinction. For instance, the following recent mathematical studies and some of the references cited therein provided some insights into the transmission dynamics of HIV/AIDS [12–24]. In most recent times, Gweryina et al. [17] developed a nonlinear mathematical model featuring three control intervention strategies representing condoms use, anti-retroviral drugs, and vaginal microbicides to study the transmission dynamics of HIV/AIDS in the population with the aim of flattening the curve of HIV/AIDS cases in the population. Habibah and Rois [19] stressed on the transmission dynamics of HIV/AIDS with special interest in educated and uneducated HIV-infectious individuals. Their model was later extended to incorporate two time-variant control interventions namely, public enlightenment campaign and anti-retroviral treatment to curb the menace of the disease. Abbas et al. [20] used a mathematical epidemic model to explore the effects of screening and treatment on the HIV-affected populations in both Pakistan and the USA. It was shown that improved screening rate could help in controlling HIV spread in the populations.

Furthermore, the authors in [21] considered an optimal control-based analysis for HIV/AIDS and pneumonia transmission co-dynamics in human population. In another related study conducted by Tollett and associates [22], a robust mathematical model for HIV/AIDS featuring the combined effects of pre-exposure prophylaxis (PrEP) and risk level on the transmission of the disease in a population of men-who-sex-men was formulated and rigorously analysed. Moreover, the influence of potent anti-retroviral drugs in curtailing the spread of HIV/AIDS in the population was examined in [23] using a mathematical model considering undetectable equals untransmittable viral load level. In another development, Olaniyi and co-workers [24] explored the influence of mother-to-child transmission of HIV/AIDS and nonlinear treatment using a novel mathematical model governed by a system of ordinary differential equations. A robust analysis was conducted to understand the disease dynamics and it was reported that the delay due to nonlinear treatment caused the HIV/AIDS model to exhibit backward bifurcation phenomenon that makes the disease elimination difficult in the population. Implying that delay in treatment plays an important role in controlling the dynamics of HIV/AIDS in human population. Nevertheless, there was no consideration for optimal control intervention strategies that could be adopted to effectively stem the risk posed by the deadly disease in their study. Hence, the need for the extension of the work to accommodate time-dependent intervention strategies.

As a consequence, and motivated by existing studies in the literature, the novelty of this study is concerned with the analysis of the controlled version of the time-independent system presented in [24] with efficiency and cost-effectiveness analyses so as to identify the most efficient intervention as well as the most cost-effective intervention to be employed in curtailing the dynamics of HIV/AIDS in the population. The remnants of the study are organized thus: Section 2.1 deals with the formulation of the HIV/AIDS model with three optimal control variables. The sensitivity of the parameters relative to the basic reproduction number and optimal control analysis of the HIV/AIDS model are presented in Section 2.2. The efficiency and cost-effectiveness analyses of the intervention strategies considered in mitigating the infection dynamics are explored in Section 3.2. While the study was wrapped up with concluding remarks in Section 4.

2. Materials and methods

2.1 *Non-autonomous HIV/AIDS model*

This section gives the description of the control dynamical system to be used in stemming the spread of HIV/AIDS in human population. The mathematical model presented in [24] explored the combined effects of nonlinear treatment and vertical (mother-to-child) transmission on the dynamics of HIV/AIDS via an autonomous system of equations. The model classified the total human population, $N(t)$, at any time t, into four mutually exclusive compartments including, the susceptible population depicted by $S(t)$, HIV infectious population duly represented by $I(t)$, HIV patients under treatment delineated by $T(t)$, and population of full blown AIDS individuals designated by $A(t)$. This study extends the autonomous system in [24] to a non-autonomous counterpart by incorporating three time-variant control intervention strategies. The optimal control triple $0 \leq u_i(t) \leq 1,\ i = 1,\ 2,\ 3$ in consideration includes control intervention $u_1(t)$ representing therapeutic agent for blocking vertical transmission of HIV/AIDS which may occur during pregnancy, childbirth or through breastfeeding (otherwise known as mother-to-child transmission (MTCT)) [25], $u_2(t)$ representing effective use of condom, and control intervention $u_3(t)$ representing treatment with highly active anti-retroviral treatment (HAART).

Let the influx of individuals by birth into the susceptible population be denoted by $\Pi(1 - qI) > 0$, where q is the proportion of infectious human by birth due to vertical transmission during pregnancy or childbirth. Following transmission of HIV infection from each of infectious human $I(t)$ and full blown AIDS individual $A(t)$, the susceptible population is downsized at mass action incidence rates, βSI and $\theta\beta SA$, where the transmission probability of HIV/AIDS from an infectious human is β, and $\theta \in (0,\ 1)$ is the modification parameter measuring the degree of infectiousness of AIDS-infectious human over HIV-infectious human. The population of HIV-infectious class is generated as a consequence of the vertically transmitted HIV infection at a rate, $q\Pi I$. The population is further populated at the mass action incidence rates, βSI and $\theta\beta SA$. The HIV-infectious class is reduced due to treatment by nonlinear term $\tau I/(1 + \gamma I)$, where τ is the treatment rate, and γ accounts for treatment delay. It is important to stress that the nonlinear treatment is an increasing function that is bounded by τ/γ, and it is interesting to see that the $\tau/\gamma \to 0$ as $\gamma \to \infty$, making the treatment impotent as γ increases. Hence, it suffices to state that γ serves as a delay to treatment. The nonlinear treatment used in this context is responsible for delay arising from mis-diagnosis or inadequate treatment facilities. Other models in the literature where nonlinear treatment has been used can be seen in [26, 27]. The nonlinear treatment function populates the treatment class while the AIDS patient compartment is populated as HIV-infectious individuals progress to full blown AIDS at a per capita rate ρ. The population is reduced by the HIV induced death at a rate δ. Moreover, the total human population is diminished by the per capita natural mortality rate μ.

As a result of incorporation of the optimal controls $u_i(t),\ i = 1,\ 2,\ 3$, the model describing the time evolution of HIV/AIDS dynamics in human population is given by

$$\begin{aligned}
\frac{dS}{dt} &= \Pi - (1-u_1(t))q\Pi I - (1-u_2(t))\beta S(I+\theta A) - \mu S \\
\frac{dI}{dt} &= (1-u_1(t))q\Pi I + (1-u_2(t))\beta S(I+\theta A) - \frac{(\tau + c_0 u_3(t))I}{1+\gamma I} - (\rho+\mu)I \\
\frac{dT}{dt} &= \frac{(\tau + c_0 u_3(t))I}{1+\gamma I} - \mu T \\
\frac{dA}{dt} &= \rho I - (\delta+\mu)A.
\end{aligned} \tag{1}$$

The description of variables and parameters of the control dynamical system governing the HIV/AIDS dynamics are given in Table 1 and Table 2, respectively.

Table 1. Variables of the non-autonomous HIV/AIDS model (1)

Variable	Description
$S(t)$	Population of susceptible individuals
$I(t)$	HIV-infectious class
$T(t)$	Population under treatment
$A(t)$	Population of AIDS patients
$u_1(t)$	Vertical transmission or MTCT control
$u_2(t)$	Control variable for correct use of condom
$u_3(t)$	Control variable for HAART treatment

Table 2. Parameters of the non-autonomous HIV/AIDS model (1)

Parameters	Description
Π	Birth rate
q	Vertical transmission fraction of birth rate
β	Probability of infection transmission
θ	Modification parameter responsible for the degree of infectiousness
τ	HAART treatment rate
μ	Natural death or mortality rate
γ	Treatment delay rate
ρ	HIV progression rate to full blown AIDS
δ	Death rate due to full blown AIDS

2.2 *Sensitivity and optimal control analysis*

In this section, it is important to explore the effect of each of the associated parameters of the HIV/AIDS model (1) on $\mathscr{R}_0$ with the aim of justifying the formulation of optimal control policies required to successfully contain the spread of HIV/AIDS in the population.

2.2.1 *Sensitivity analysis*

Herein, the effect of certain epidemiological features of the HIV/AIDS model (1) on the basic reproduction number is examined. Since basic reproduction number is an important metric for determining the behavior of infectious disease dynamics, it is imperative to state that basic reproduction number often represented by, $\mathscr{R}_0$, is the threshold parameter responsible for the average number of secondary cases of both vertical and horizontal HIV/AIDS infections produced by a typical HIV-infectious individual or AIDS-infectious individual during its period of infectivity in an environment of completely susceptible population. As earlier obtained in [24], the basic reproduction number, $\mathscr{R}_0$, of the HIV/AIDS model (1) using the next generation matrix technique [28], is given by

$$\mathscr{R}_0 = \frac{\Pi\beta(\delta+\mu+\theta\rho)}{\mu(\delta+\mu)(\tau+\rho+\mu-\Pi q)}, \tag{2}$$

where $\tau+\rho+\mu > \Pi q$ by algebraic simplifications.

In what follows, the normalized forward sensitivity indices of the basic reproduction number, $\mathscr{R}_0$, with respect to its corresponding parameters, r, are computed as conducted in [29, 30] using

$$\chi_r^{\mathscr{R}_0} = \frac{\partial \mathscr{R}_0}{\partial r}\left(\frac{r}{\mathscr{R}_0}\right). \tag{3}$$

Consequently, the sensitivity indices of the parameters of the HIV/AIDS model (1) relative to the associated reproduction number are given in Table 3 using the parameter values provided in [24]. As contained in Table 3, one sees that four parameters such as recruitment rate, Π, transmission probability, β, proportion of birth due to vertical transmission fraction of birth rate, q, and modification parameter, θ, have positively sensitivite, while another four different parameters including, natural mortality rate, μ, HAART treatment rate, τ, HIV progression rate, ρ, and HIV-induced death, δ, have negative sensitivity indices. Unhampered and spontaneous increase in the values of parameters with positive sensitivity indices will lead to a corresponding increase in $\mathscr{R}_0$, thereby causing more prevalence of HIV/AIDS in the population. For instance, if the probability of transmission of HIV/AIDS, β, is increased (decreased) by 100%, then $\mathscr{R}_0$ will also increase (decrease) by 100%. While increase (decrease) in the values of any parameters that are negatively sensitive will yield inverse relation with the value of $\mathscr{R}_0$. For example, increasing τ by 100% will reduce the value of $\mathscr{R}_0$ by 101.12%. This, from the viewpoint of epidemiology implies that the surge of HIV/AIDS in the population could be contained as long as effective treatment is accurately administered.

Table 3. Sensitivity indices of $\mathscr{R}_0$ relative to its parameter values

Parameters	Values	Sensitivity indices
Π	10	+1.0562
q	0.005	+0.0562
β	0.006	+1.0000
θ	0.02	+0.0291
τ	0.9	−1.0112
μ	0.01	−1.0258
ρ	0.03	−0.0046
δ	0.01	−0.0146

Hence, the control dynamical system (1) featuring the three time-dependent optimal control functions is justified, and its analysis is next performed.

2.2.2 *Analysis of the control dynamical system*

Here, optimal control theory will be applied to carry out the analysis of the non-autonomous system (1). It is worth noting that optimal control theory has been employed extensively to secure optimal ways of mitigating problems arising from biological processes using the celebrated Pontryagin's maximum principle [31] (see, for examples, [32–36] and some of the references cited therein). The Pontryagin's maximum principle is, therefore, employed to find optimal ways of hampering the spread potential of HIV/AIDS. The performance index or objective functional, $\mathfrak{J}$, required to minimize both infectious populations of HIV-infectious individuals ($I(t)$) and AIDS patients ($A(t)$), and minimize the associated implementation costs of the three control interventions $u_i(t),\ (i = 1,\ 2,\ 3)$, is given by

$$\mathfrak{J} = \int_0^{T_f} \left(B_1 I(t) + B_2 A(t) + \frac{1}{2} \sum_{i=1}^{3} C_i u_i^2(t) \right) dt, \tag{4}$$

where T_f is the final time expected to implement the optimal controls, the quantities B_1 and B_2, respectively, stand for the positive weight constants for balancing HIV-infectious population and AIDS-infectious population in the objective functional. $C_i,\ (i = 1,\ 2,\ 3)$, represent the balancing weight constants for blocking vertical transmission, condom usage, and treatment effort, accordingly. And the total implementation cost of the control functions $u_i(t),\ i = 1,\ 2,\ 3$ is given by $1/2C_i u_i^2$. It is important to bear in mind that $u_i(t) \in [0,\ 1],\ (i = 1,\ 2,\ 3)$, with $u_i(t) = 0$ representing non-availability of the control efforts and $u_i(t) = 1$ means the required maximum control effort to stem down the vertical and horizontal transmissions of HIV/AIDS in the population. Moreover, the quadratic nature of the cost control functions describing the nonlinearity of the control measures are in agreement with other relevant studies in the literature [30, 36, 37]. In particular, an optimal control triple denoted by $u^* = u_i^*,\ i = 1,\ 2,\ 3$ will be determined to satisfy the minimization problem of the form

$$\mathfrak{J}(u^*) = \min \{ \mathfrak{J}(u_1,\ u_2,\ u_3) :\ (u_1,\ u_2,\ u_3) \in \mathscr{U} \}, \tag{5}$$

subject to the non-autonomous state system (1), where the non-empty control set $\mathscr{U} = \{u_i(t) :\ 0 \leq u_i(t) \leq 1,\ t \in [0,\ T_f]\}$ is Lebesgue measurable.

2.2.3 *Existence of an optimal control triple*

Here, the following existence result for the minimization problem defined in (5) is carefully established.

Theorem 1 There exist an optimal control triple u^* that satisfies the minimization problem (5) subject to the non-autonomous state system (1).

The proof of Theorem 1 is based on preservation of the existence result in [38] with the following properties, as x-rayed in [39, 40]

(P1) $\mathscr{U}$ is a closed and convex control set.

(P2) Linear function in state and control variables of the non-autonomous system (1) bound the system above.

(P3) The integrand of the objective functional is a convex function of the control variables.

(P4) Constants $d_1,\ d_2 > 0$ and $d_3 > 1$ exist, such that the integrand of the objective functional is bounded below by $d_1(|u_i|^2)^{d_3/2} - d_2,\ i = 1,\ 2,\ 3$.

Thus, properties (P1) to (P4) are proved next.

Proof. (P1) It is easy to see that $\mathscr{U} = \{u_i(t) :\ 0 \leq u_i(t) \leq 1,\ t \in [0,\ T_f]\}, i = 1,\ 2,\ 3$, is closed by definition. Then, given any two points $p,\ w \in \mathscr{U}$, where $p = (p_1,\ p_2,\ p_3)$ and $w = (w_1,\ w_2,\ w_3)$. It can be seen that

$$(\phi p_i + (1-\phi)w_i) \in [0,\ 1],\ \forall\ 0 \le \phi \le 1,\ i = 1,\ 2,\ 3.$$

Therefore, $\phi p + (1-\phi)w \in \mathscr{U}$, satisfying the convex set definition [41]. This establishes (P1).

(P2) Let $v = (u_1,\ u_2,\ u_3) \in \mathscr{U}$, $x = (S,\ I,\ T,\ A)$ and $f(t,\ x,\ v)$ be the right-hand side of the non-autonomous HIV/AIDS system (1) given by

$$f(t,\ x,\ v) = \begin{pmatrix} \Pi - (1-u_1(t))q\Pi I - (1-u_2(t))\beta S(I+\theta A) - \mu S \\ (1-u_1(t))q\Pi I + (1-u_2(t))\beta S(I+\theta A) - \dfrac{(\tau + c_0 u_3(t))I}{1+\gamma I} - (\rho+\mu)I \\ \dfrac{(\tau + c_0 u_3(t))I}{1+\gamma I} - \mu T \\ \rho I - (\delta+\mu)A \end{pmatrix}.$$

Consequently, one can write $f(t,\ x,\ v) = g(t,\ x) + h(t,\ x)v$, where a column matrix $g(t,\ x)$ and a (4×3)-matrix $h(t,\ x)$ are, respectively, given by

$$g(t,\ x) = \begin{pmatrix} \Pi - q\Pi I - \beta SI - \beta\theta SA - \mu S \\ q\Pi I + \beta SI + \beta\theta SA - \dfrac{\tau I}{1+\gamma I} - (\rho+\mu)I \\ \dfrac{\tau I}{1+\gamma I} - \mu T \\ \rho I - (\delta+\mu)A \end{pmatrix}, \tag{6}$$

and

$$h(t,\ x) = \begin{pmatrix} q\Pi I & \beta S(I+\theta A) & 0 \\ -q\Pi I & -\beta S(I+\theta A) & -\dfrac{c_0 I}{1+\gamma I} \\ 0 & 0 & \dfrac{c_0 I}{1+\gamma I} \\ 0 & 0 & 0 \end{pmatrix}.$$

Next is to establish the boundedness of the state system following the algorithm made explicit in [40] and employed in a related work [30]. It follows that

$$||f(t,\ x,\ v)|| \leq y_1 + y_2||v||, \tag{7}$$

where y_1 and y_2 are positive constants obtained as given hereunder.

$$y_1 = \sqrt{\max(g_1,\ g_2)(\Pi^4 + \Pi^2)}, \tag{8}$$

and

$$y_2 = \sqrt{\max(h_1,\ h_2)(\Pi^4 + \Pi^2)}, \tag{9}$$

where

$$\begin{aligned} g_1 &= \frac{1}{\mu^4}(q^2\mu^2 + \beta^2(\theta+1)^2) + 2\beta q\mu(\theta+1), \\ g_2 &= 1 + \frac{1}{\mu^2}(\tau^2 + \rho^2), \\ h_1 &= \frac{2}{\mu^4}(q^2\mu^2 + \beta^2(\theta+1)^2), \\ h_2 &= \frac{2}{\mu^2}c_o^2. \end{aligned} \tag{10}$$

Therefore, the inequality, (7), establishes property (P2).

(P3) Lagrangian is integrand of the objective functional (4), and it is given by

$$\mathfrak{L}(t,\ x,\ v) = A(t,\ x) + \frac{1}{2}\sum_{i=1}^{3} C_i u_i^2(t), \tag{11}$$

where $A(t,\ x) = B_1 I(t) + B_2 A(t)$. Then, it is required to show that

$$\mathfrak{L}(t,\ x,\ \phi p + (1-\phi)w) \leq \phi\mathfrak{L}(t,\ x,\ p) + (1-\phi)\mathfrak{L}(t,\ x,\ w) \tag{12}$$

for all $p = (p_1,\ p_2,\ p_3) \in \mathscr{U}$ and $w = (w_1,\ w_2,\ w_3) \in \mathscr{U}$, where $0 \leq \phi \leq 1$. As a consequence of (11),

$$\mathfrak{L}(t,\, x,\, \phi p + (1-\phi)w) = A(t,\, x) + \frac{1}{2}\sum_{i=1}^{3} C_i(\phi p_i + (1-\phi)w_i)^2, \tag{13}$$

which shows the expression for the left-hand side of the inequality (12), while the right-hand side of the inequality is given by

$$\phi\mathfrak{L}(t,\, x,\, p) + (1-\phi)\mathfrak{L}(t,\, x,\, w) = A(t,\, x) + \frac{1}{2}\phi\sum_{i=1}^{3} C_i p_i^2 + \frac{1}{2}(1-\phi)\sum_{i=1}^{3} C_i w_i^2. \tag{14}$$

Subtracting (14) from (13), and after some algebraic simplifications therefore gives,

$$\begin{aligned}
&\mathfrak{L}(t,\, x,\, \phi p + (1-\phi)w) - (\phi\mathfrak{L}(t,\, x,\, p) + (1-\phi)\mathfrak{L}(t,\, x,\, w)) \\
&= \frac{1}{2}\phi\sum_{i=1}^{3} C_i[(\phi p_i + (1-\phi)w_i)^2 - (\phi p_i^2 + (1-\phi)w_i^2)] \\
&= \frac{1}{2}(\phi^2 - \phi)\sum_{i=1}^{3} C_i[p_i - w_i]^2.
\end{aligned} \tag{15}$$

Since $0 \leq \phi \leq 1$, it then follows from (15) that $\mathfrak{L}(t,\, x,\, \phi p + (1-\phi)w) \leq (\phi\mathfrak{L}(t,\, x,\, p) + (1-\phi)\mathfrak{L}(t,\, x,\, w))$. Hence, the Lagragian is a convex function by definition [41] and thus establishes property (P3).

(P4) Finally, using the Lagragian of the form

$$\begin{aligned}
\mathfrak{L}(t,\, x,\, v) &= B_1 I + B_2 A + \frac{1}{2}\sum_{i=1}^{3} C_i u_i^2(t) \\
&\geq \frac{1}{2}(B_1 u_1^2(t) + B_2 u_2^2(t) + B_3 u_3^2(t)) \\
&\geq d_1\left(B_1 u_1^2(t) + B_2 u_2^2(t) + B_3 u_3^2(t)\right)^{\frac{d_3}{2}} - d_2,
\end{aligned} \tag{16}$$

where $d_1 = \min\{B_1,\, B_2,\, B_3\}$, $d_2 \geq 0$ and $d_3 = 2$. This wraps up the proof. □

2.2.4 *Optimal control characterization*

The main interest here is to employ Pontryagin's maximum principle [31] to obtain the necessary conditions for the characterization of the three optimal controls u_1^*, u_2^* and u_3^*. The objective functional (4) and the minimization problem (5) subject to the non-autonomous state system (1) are converted into a problem of minimizing a Hamiltonian with respect to the three controls. Therefore, the Hamiltonian, $\mathscr{H}$, for the control problem is given by

$$
\begin{aligned}
\mathscr{H} =& B_1 I(t) + B_2 A(t) + 1/2 C_1 u_1^2 + 1/2 C_2 u_2^2 + 1/2 C_3 u_3^2 \\
&+ \lambda_S(\Pi - (1-u_1) q\Pi I - (1-u_2)\beta S(I+\theta A) - \mu S) \\
&+ \lambda_I((1-u_1) q\Pi I + (1-u_2)\beta S(I+\theta A) - (\tau + c_0 u_3) I/(1+\gamma I) - (\rho+\mu) I) \\
&+ \lambda_T((\tau + c_0 u_3) I/(1+\gamma I) - \mu T) \\
&+ \lambda_A(\rho I - (\delta+\mu) A),
\end{aligned} \tag{17}
$$

where λ_S, λ_I, λ_T and λ_A are the adjoint or co-state variables associated with the state variables of the HIV/AIDS model system (1). Then, the next result is established.

Theorem 2 If an optimal control triple (u_1^*, u_2^*, u_3^*) that satisfies the minimization problem (5) exists, then there exist adjoint variables λ_S, λ_I, λ_T and λ_A, satisfying the adjoint system given by

$$
\begin{aligned}
\frac{d\lambda_S}{dt} =& (1-u_2)\beta(I+\theta A)(\lambda_S - \lambda_I) + \mu\lambda_S \\
\frac{d\lambda_I}{dt} =& (1-u_1) q\Pi(\lambda_S - \lambda_I) + (1-u_2)\beta S(\lambda_S - \lambda_I) + \frac{(\tau + c_0 u_3)}{(1+\gamma I)^2}(\lambda_I - \lambda_T) \\
&+ \rho(\lambda_I - \lambda_A) + \mu\lambda_I - B_1 \\
\frac{d\lambda_T}{dt} =& \mu\lambda_T \\
\frac{d\lambda_A}{dt} =& (1-u_2)\beta S\theta(\lambda_S - \lambda_I) + (\delta+\mu)\lambda_A - B_2,
\end{aligned} \tag{18}
$$

with transversality conditions

$$
\lambda_S(T_f) = \lambda_I(T_f) = \lambda_T(T_f) = \lambda_A(T_f) = 0, \tag{19}
$$

and characterizations

$$u_1^* = \max\left\{0,\ \min\left\{\frac{q\Pi I(\lambda_I - \lambda_S)}{C_1},\ 1\right\}\right\},$$

$$u_2^* = \max\left\{0,\ \min\left\{\frac{(\beta S(I+\theta A)(\lambda_I - \lambda_S))}{C_2},\ 1\right\}\right\}, \tag{20}$$

$$u_3^* = \max\left\{0,\ \min\left\{\frac{c_0 I(\lambda_I - \lambda_T)}{C_3(1+\gamma I)},\ 1\right\}\right\}.$$

Proof. The adjoint (co-state) system are obtained by partially differentiating the Hamiltonian, $\mathscr{H}$, given in (17) with respect to the corresponding state variables $S,\ I,\ T$, and A, respectively, as follows

$$\frac{d\lambda_x}{dt} = -\left(\frac{\partial \mathscr{H}}{\partial x}\right),\ \lambda_x(T_f) = 0,\ \text{where } x = (S,\ I,\ T,\ A).$$

Additionally, the optimal control characterizations (20) are determined by using the following optimality conditions to solve for each of $u_1^*,\ u_2^*$ and u_3^*, respectively.

$$\frac{\partial \mathscr{H}}{\partial u_1} = C_1 u_1^* + q\Pi I(\lambda_S - \lambda_I) = 0,$$

$$\frac{\partial \mathscr{H}}{\partial u_2} = C_2 u_2^* + \beta SI(\lambda_S - \lambda_I) = 0, \tag{21}$$

$$\frac{\partial \mathscr{H}}{\partial u_3} = C_3 u_3^* - \frac{c_0 I(\lambda_I - \lambda_T)}{(1+\gamma I)} = 0.$$

Using standard control arguments involving the bounds on controls [33, 36], it can be concluded that

$$u_i^* = \begin{cases} 0, & \text{for } \sigma_i^* \leq 0 \\ \sigma_i^*, & \text{for } 0 < \sigma_i^* < 1 \\ 1, & \text{for } \sigma_i^* \geq 1, \end{cases}$$

for $i = 1,\ 2,\ 3$ and where

$$\sigma_1^* = \frac{q\Pi I(\lambda_I - \lambda_S)}{C_1},$$

$$\sigma_2^* = \frac{\beta S(I + \theta A)(\lambda_I - \lambda_S)}{C_2},$$

$$\sigma_3^* = \frac{c_0 I(\lambda_I - \lambda_T)}{C_3(1 + \gamma I)}.$$

This completes the proof. □

3. Results and discussion

3.1 *Optimality system simulation results*

The control dynamical system (1) and its co-state (adjoint) system (18) with the optimal control characterizations (20) are coupled to form the optimality system alongside their respect initial conditions, $S(0) = S_0,\ I(0) = I_0,\ T(0) = T_0,\ A(0) = A_0$ and transversality conditions (19). The optimality system so derived is solved using an iterative method with 4th-order forward-backward Runge-Kutta following the iterative scheme described in [42]. In order to successfully avert the highest number of HIV/AIDS cases in the population, the parameter values provided in Table 3 are used, except that the value of vertical transmission rate $q = 0.02$ with the treatment delay $\gamma = 0.04$, so that the basic reproduction number yields $\mathscr{R}_0 = 8.3514 > 1$. In addition, the values of the weight constants used in the objective functional are $A_1 = A_2 = 1, B_1 = 10, B_2 = 10, B_3 = 10$. And the simulations are done using the time interval $[0,\ 10]$ in years and the rate constant is chosen as $c_0 = 1$, while the initial conditions are chosen as $S(0) = 100, I(0) = 50, T(0) = 10$, and $A(0) = 10$ for the state variables.

As a consequence of the foregoing, three different control policies are considered to examine the effect of combining any two of the optimal control triple on the transmission dynamics of HIV/AIDS model (1) as follows

(i) Policy A: combination of vertical transmission preventive control $(u_1(t))$ and condom usage $(u_2(t))$,

(ii) Policy B: combination of vertical transmission preventive control $(u_1(t))$ and treatment control $(u_3(t))$,

(iii) Policy C: combination of condom usage $(u_2(t))$ and treatment $(u_3(t))$.

3.1.1 *Policy A: Combination of $u_1(t)$ and $u_2(t)$*

Figure 1 shows how implementation of Policy **A** affects the population dynamics of HIV/AIDS. It is observed that the populations of HIV and AIDS infectious humans reduce more significantly over time increases in the presence of control interventions compared to the case when the policy is not considered. This result is suggesting that HIV/AIDS can be controlled effectively in the population if the control interventions could be adopted by policymakers or public health workers to combat the dynamics of the infection. The control profile for Policy **A** is given in Figure 1(c), where both controls $u_1(t)$ and $u_2(t)$ are at maximum 100% within the first 2.5 years and 4.9 years of policy implementation before dropping to zero in final time.

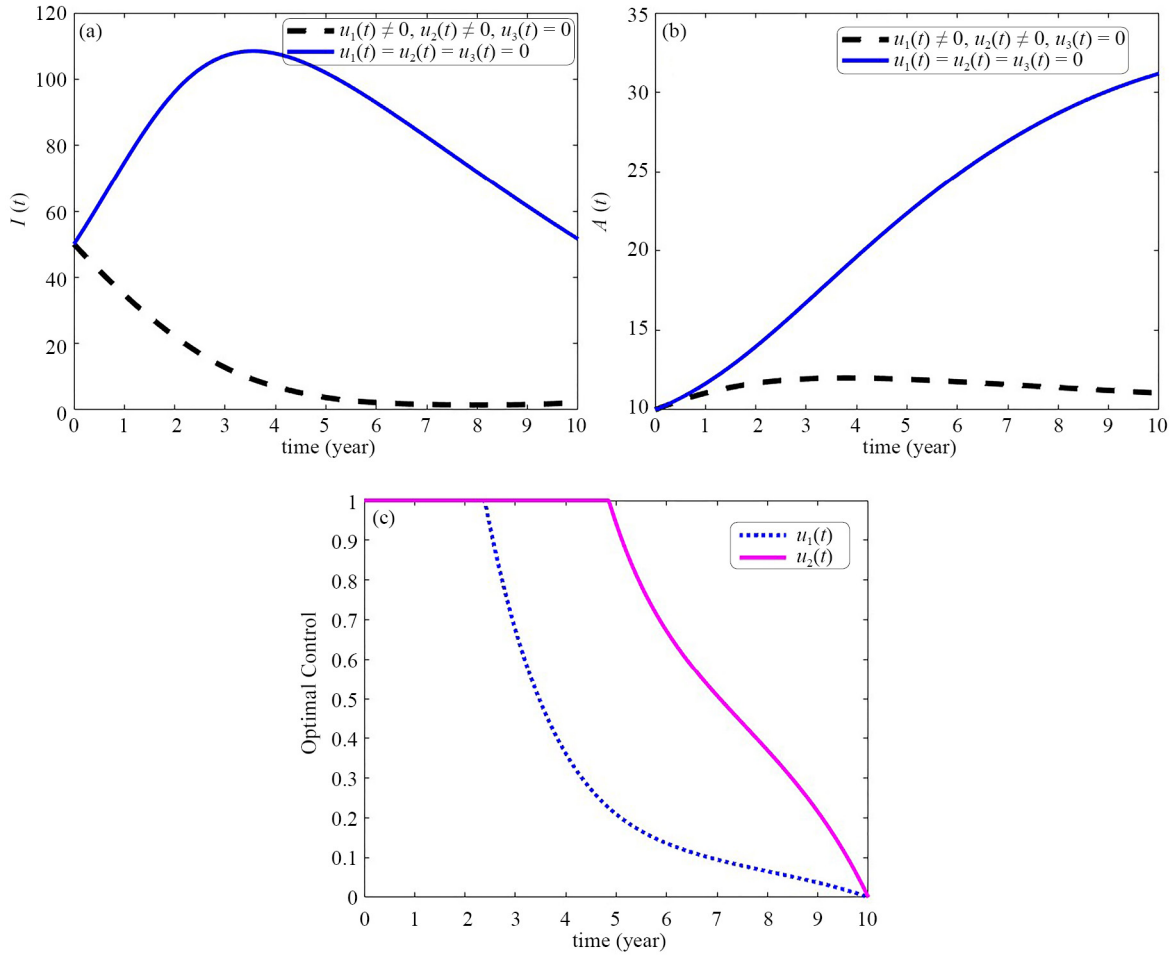

Figure 1. Combined effect of preventive control for vertical transmission and effective use of condom for protection against HIV/AIDS on the transmission dynamics of HIV/AIDS

3.1.2 *Policy B: Combination of $u_1(t)$ and $u_3(t)$*

In a similar spirit, the effects of implementing Policy **B** on the spread of HIV/AIDS are demonstrated in Figure 2. One sees that the sizes of both HIV-infectious and AIDS-infectious humans reduce tremendously when control interventions are considered in contrary to when control intervention is not put in place. This epidemiologically implies that optimal preventive control for vertical transmission of HIV and correct use of condom should be encouraged in order to optimally stem the spread dynamics of HIV/AIDS in the population. Figure 2(c) shows that Policy **B** combining $u_1(t)$ and $u_2(t)$ should be maximally implemented at 100% within the first 2.7 years and 4.2 years of the implementation period before descending to zero in final time.

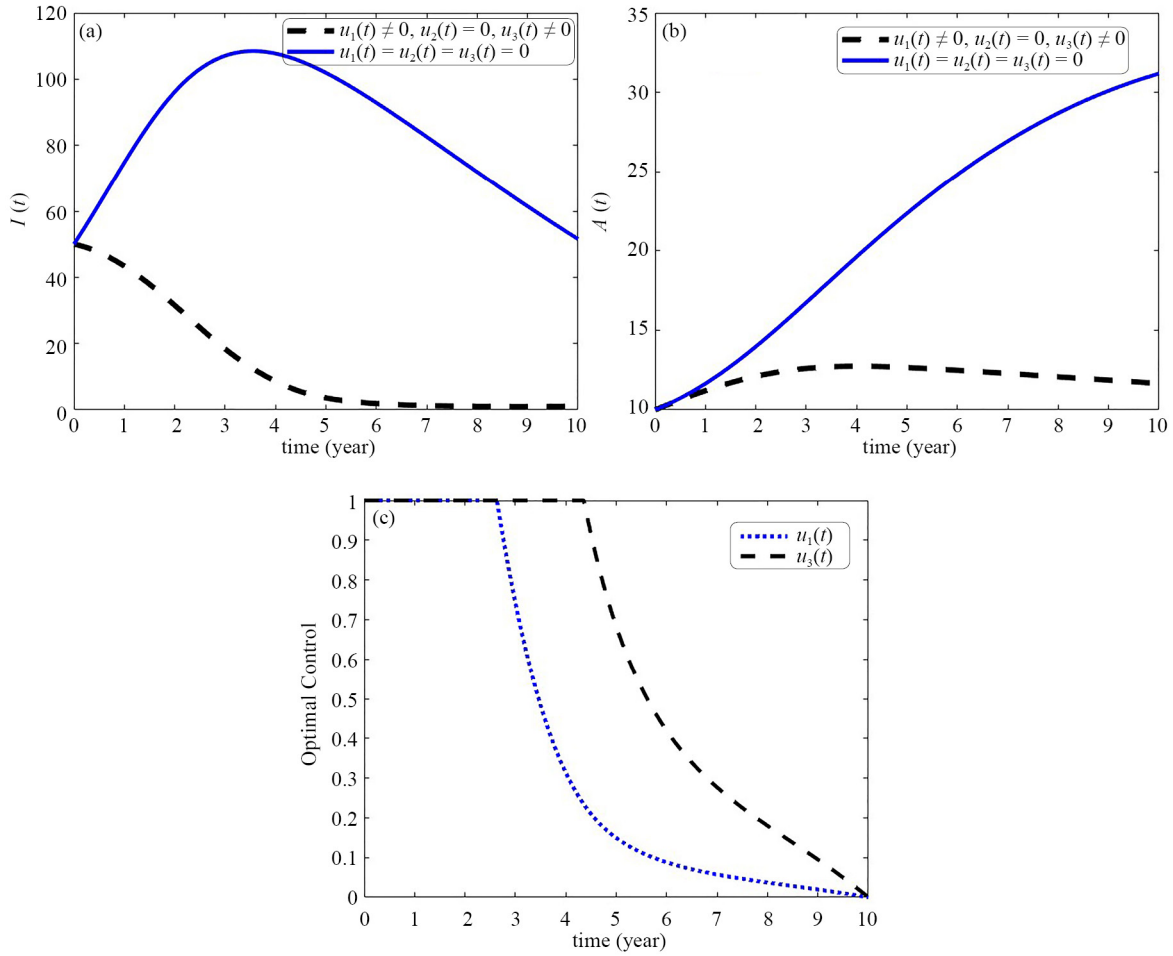

Figure 2. Combined effect of preventive control for vertical transmission and treatment control on the population dynamics of both HIV-infectious and AIDS-infectious individuals

3.1.3 *Policy C: Combination of $u_2(t)$ and $u_3(t)$*

Another significant reductions are observed in the numbers of HIV-infectious and AIDS-infectious individuals when Policy **C** is considered on the transmission of HIV/AIDS as presented in Figure 3. This is emphasizing the need for optimal implementation of condom measure, $u_2(t)$ and treatment effort, u_3, to contain the spread of HIV/AIDS in the population. The control profile given in Figure 3(b) shows that both condom measure, $u_2(t)$, and treatment control, $u_3(t)$, should be maintained at maximum 100% within the first 2 to 3 years of implementation to achieve optimal result.

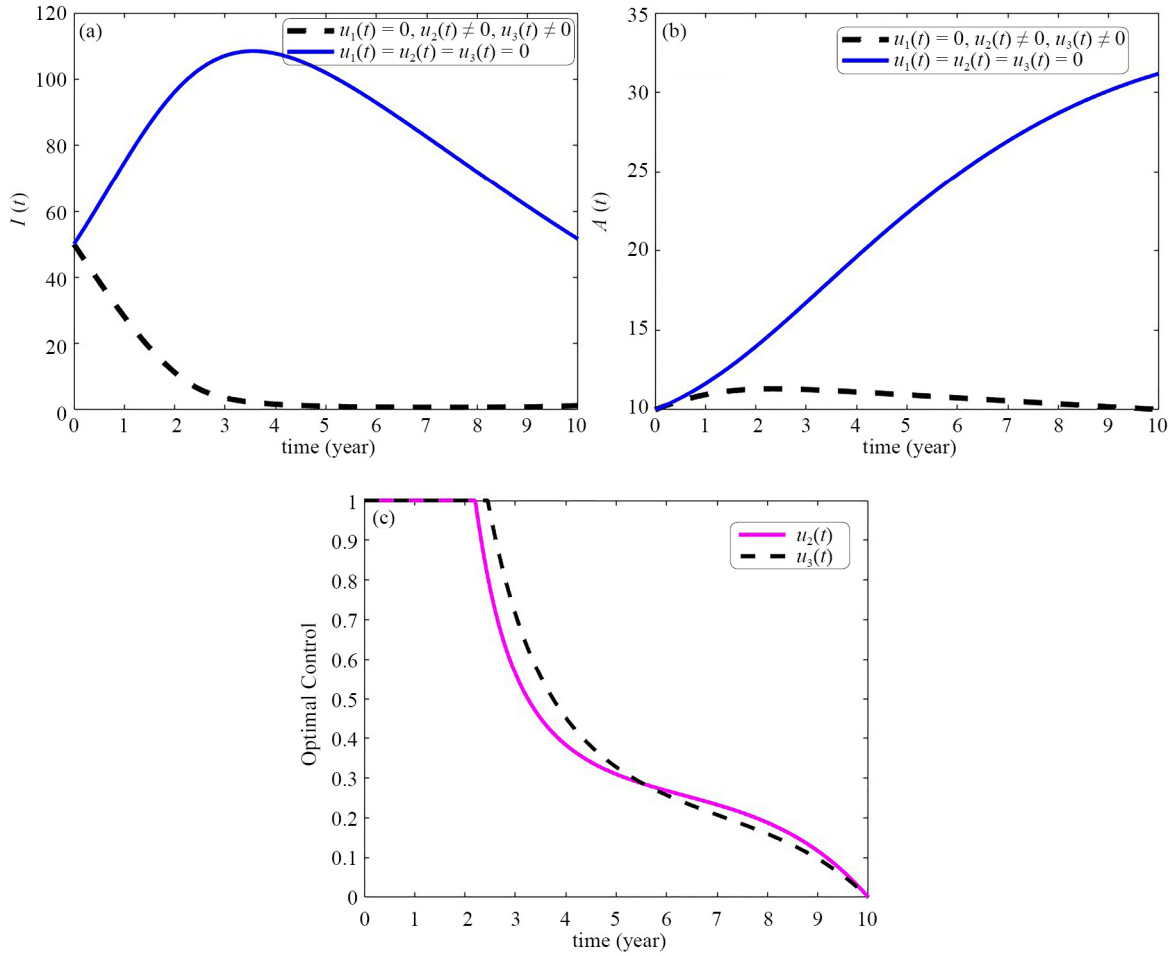

Figure 3. Combined effect of effective use of condom for protection against HIV/AIDS and treatment control on the population dynamics of both HIV-infectious and AIDS-infectious individuals

3.2 *Efficiency and cost-effectiveness analyses*

In a further attempt to effectively control the problem of HIV/AIDS in the population, this section seeks to identify the most efficient and most cost-effective policies that best averts the highest number of HIV/AIDS cases in the population, while keeping in mind that the most efficient intervention may not be the most cost-effective. Therefore, cost-effectiveness analysis of the intervention policies will also be explored to deliver the most economic intervention in the presence of limited resources.

3.2.1 *Efficiency analysis results*

In epidemiological modelling of biological processes, the magnitude of infection cases averted by implementation any interventions can be assessed through efficiency analysis [43, 44]. The efficiency analysis of the combination of the intervention strategies is investigated here without minding the associated cost of implementation. It should be mentioned that the policy with the greatest value of efficiency index is the most efficient policy. In the sense of [45], the efficiency index, denoted by $\mathbb{E}_f$, of each of the policies can be calculated by

$$\mathbb{E}_f = \frac{\text{Total number of HIV/AIDS cases averted by policy}}{\text{Total number of HIV/AIDS cases without policy}} \times 100\%. \tag{22}$$

In what follows, the efficiency indices for each of the intervention policies considered are evaluated using (22), and it can be seen that $\mathbb{E}_f(\text{Policy } \mathbf{C})$ with efficiency index 83.03%, as indicated in Table 4, is the policy with the highest efficiency index. Therefore, the policy of combining correct use of condom, $u_2(t)$, and treatment control, $u_3(t)$, is the most efficient policy to be adopted in curbing the surge of HIV/AIDS in the population.

3.2.2 *Cost-effectiveness analysis*

In a resource-limited setting, it is beneficial to seek intervention policy that is most cost-effective in controlling the spread of infectious disease. Thus, the cost-effectiveness analysis for the purpose of this study is assessed using the average cost-effectiveness ratio (ACER) and the incremental cost-effectiveness ratio (ICER).

3.2.3 *ACER*

The average cost-effectiveness ratio (ACER) of intervention policy is described as the ratio of total cost of implementation of the policy to the total number of HIV/AIDS cases averted by the policy [46–49]. Thus, ACER is mathematically expressed as

$$ACER = \frac{\text{Total cost expended on the intervention policy}}{\text{Total health benefits of the intervention policy}}. \tag{23}$$

3.2.4 *ICER*

The incremental cost-effectiveness ratio usually accounts for the difference between the total costs and health benefits of any two intervention policies [39, 50–52]. Consider any two alternative intervention strategies, s_1 and s_2, striving for the same limited resource allocation, the ICER can be evaluated by

$$ICER = \frac{\text{Change in total costs of intervention policies } s_1 \text{ and } s_2}{\text{Change in total health benefits of intervention policies } s_1 \text{ and } s_2}. \tag{24}$$

3.2.5 *ACER and ICER for the intervention policies*

The intervention policies **A**, **B** and **C** are arranged in increasing order of their total number of HIV/AIDS cases averted. And the detailed analyses of the ACER and ICER for each of the policies are summarized in Table 4 as follows.

$$\begin{aligned}
ICER(u_1u_3) &= \frac{(8.5431 \times 10^3)}{(8.0755 \times 10^4)} = 0.1058 \\
ICER(u_1u_2) &= \frac{(9.4786 \times 10^3) - (8.5431 \times 10^3)}{(8.3725 \times 10^4) - (8.0755 \times 10^4)} = 0.3149 \\
ICER(u_2u_3) &= \frac{(6.7257 \times 10^3) - (9.4786 \times 10^3)}{(8.8417 \times 10^4) - (8.3725 \times 10^4)} = -0.5867
\end{aligned} \tag{25}$$

Table 4. ACER and ICER for different HIV/AIDS intervention policies

Policy	Cases averted	Total cost	Efficiency (%)	ACER	ICER
Policy **B**: (u_1u_3)	8.0755×10^4	8.5431×10^3	75.83	0.1058	0.1058
Policy **A**: (u_1u_2)	8.3725×10^4	9.4786×10^3	78.62	0.1132	0.3149
Policy **C**: (u_2u_3)	8.8417×10^4	6.7257×10^3	83.03	0.0761	-0.5867

In the concept of ACER analysis, a policy with the least ACER value is referred to as the most economic intervention policy [48]. Table 4 reveals that Policy **C** with the smallest ACER value, ACER(Policy **C**) = 0.0761, is the most cost-effective intervention policy of the three policies competing for the same interest. The second most cost-effective intervention policy after Policy **C** is Policy **B** with ACER value 0.1058 followed by Policy **A** with ACER value 0.1132. Consequently, Policy **C** combining correct use of condom $u_2(t)$ and treatment control $u_3(t)$ is the most economic policy to hinder the storm of HIV/AIDS in the population.

As shown in Table 4, following the incremental cost-effectiveness analysis approach by comparing the first two policies in the order of HIV/AIDS cased averted, one can see that ICER value for Policy **A** is greater than the ICER value for Policy **B**. Hence, Policy **A** is said to be dominated by Policy **B**. In the spirit of ICER cost analysis, it should be mentioned that a policy with lesser ICER value dominates the alternative policy with greater ICER value. Readers may see [53] for more details on the use of dominant and dominated interventions in cost-effectiveness analysis. Therefore, Policy **A** is eliminated from the list of available intervention policies competing for the same interest. While ICER for Policy **B** remains as calculated in Table 4, the ICER for the remaining policy is re-assessed as provided in Table 5.

$$ICER(u_2u_3) = \frac{(6.7257\times10^3)-(8.5431\times10^3)}{(8.8417\times10^4)-(8.0755\times10^4)} = -0.2372. \tag{26}$$

Table 5. ACER and ICER for Policies **B** and **C**

Policy	Cases averted	Total cost	Efficiency (%)	ACER	ICER
Policy **B**: (u_1u_3)	8.0755×10^4	8.5431×10^3	75.83	0.1058	0.1058
Policy **C**: (u_2u_3)	8.8417×10^4	6.7257×10^3	83.03	0.0761	-0.2372

Clearly from Table 5, it can be observed that ICER value for Policy **B** is exceeds that of Policy **C**. This means that Policy **B** is strongly dominated, more expensive, and less effective when compared with Policy **C**. Therefore, Policy **B** is discarded from the list of alternative intervention policies contesting for the same limited resources. As a result, Policy **C** representing the combination of the intervention strategies for condom measure and optimal HAART treatment control is the most cost-effective intervention policy among all the three policies designed for combating transmission of HIV/AIDS in this study. It should be mentioned that both ICER and ACER results agree, validating the cost-effectiveness analysis result.

4. Conclusion

In this study, optimal control theory-based analysis of a time-variant deterministic model describing the evolution of human immunodeficiency virus (HIV) and acquired immune deficiency syndrome (AIDS) have been analysed in details. The deterministic non-autonomous system featured the combined effect of nonlinear treatment due to late detection or mis-diagnosis of infection and vertical transmission route of HIV. The total human population considered was classified

into four mutually exclusive compartments of sexually active humans including, susceptible human, $S(t)$, HIV-infectious human, $I(t)$, population of individuals receiving HAART treatment, $T(t)$, and AIDS-infectious human, $A(t)$, respectively. To justify the developed control dynamical system, sensitivity analysis of key epidemiological parameters that are captured by the basic reproduction number of the autonomous HIV/AIDS model was carried out using the normalized forward sensitivity index method. Parameters directly and indirectly related to the basic reproduction number were identified, and it was found that increasing parameters such as effective contact rate and vertical transmission route of HIV will propel the dynamics of HIV/AIDS from disease-free state to a disease-present state.

Consequently, three time-dependent control functions representing vertical transmission preventive control, correct use of condom, and treatment measure were considered. The existence result for the control triple was proved explicitly, and the control characterizations were obtained with the help of the optimal control theory popularized by Pontryagin's maximum principle. The control functions considered were further classified into three different policies namely, Policy **A**, combining the vertical transmission preventive control and condom measure; Policy **B**, representing optimal combination of vertical transmission preventive control and treatment measure; and Policy **C**, which combines condom use measure and treatment control. As a consequence, the optimality system was simulated to show how the trajectories of solutions of the HIV-infectious and AIDS-infectious populations reduced more significantly when each of the intervention policies was implemented at minimum cost. It is important to mention that this result is unique to this study as other existing autonomous models for HIV/AIDS lack the capacity to demonstrate the effectiveness of the time-varying intervention policies in monitoring the spread of HIV/AIDS in the population.

Further, efficiency and economic analyses of the three intervention policies were performed to ascertain the most efficient and most cost-effective policy to be adopted in mitigating the problem of HIV/AIDS transmission in the population. In particular, the economic analysis of the policies was investigated using both average cost-effectiveness ratio (ACER) and incremental cost-effectiveness ratio (ICER) methods. The efficiency and economic analyses carried out revealed that Policy **C**, combining use of condom measure and treatment control, is the most efficient and most cost-effective policy. Thus, to significantly inhibit the public health burden of HIV/AIDS, the most efficient and most cost-effective policy combining optimal control intervention representing correct use of condom measure and control with highly active anti-retroviral treatment (HAART) should be encouraged regardless of whether resources are in abundance or in limited supply.

This study has highlighted the impact of combining prevention (condom usage) and treatment (HAART) in achieving substantial reductions in HIV transmission. However, it is not without some limitations which are stated as follows. While sensitivity indices are provided, the analysis does not account for the uncertainty in parameter estimation, which can significantly affect the reliability of basic reproduction number and the optimal policies derived. The formulated model is deterministic and lacks capacity to capture randomness which may occur in the transmission of HIV/AIDS. Therefore, future directions of the study may consider accounting for uncertainty in parameter estimation and incorporate stochastic elements to account for randomness in HIV/AIDS transmission and treatment delays. Further, specific regression models that allow for the calculation and forecasting of the output parameters may equally be considered. It is also important to note that this model can potentially be solved analytically by using the Lie algebra method as proposed in [54, 55]. Incorporating feedback control variables may also be considered to examine how the adjustment of the feedback controls influence the disease outbreak following the idea in [56].

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Conflict of interest

The authors declare no competing financial interest.

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