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Optimal strategy for controlling the spread of HIV/AIDS disease: a case study of South Africa

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HIV/AIDS disease continues to spread alarmingly despite the huge amounts of resources invested in fighting it. There is a need to integrate the series of control measures available to ensure a consistent reduction in the incidence of the disease pending the discovery of its cure. We present a deterministic model for controlling the spread of the disease using change in sexual habits and antiretroviral (ARV) therapy as control measures. We formulate a fixed time optimal control problem subject to the model dynamics with the goal of finding the optimal combination of the two control measures that will minimize the cost of the control efforts as well as the incidence of the disease. We estimate the model state initial conditions and parameter values from the demographic and HIV/AIDS data of South Africa. We use Pontryagin's maximum principle to derive the optimality system and solve the system numerically. Compared with the practice in most resource-limited settings where ARV treatment is given only to patients with full-blown AIDS, our simulation results suggest that starting the treatment as soon as the patients progress to the pre-AIDS stage of the disease coupled with appreciable change in the susceptible individuals' sexual habits reduces both the incidence and prevalence of the disease faster. In fact, the results predict that the implementation of the proposed strategy would drive new cases of the disease towards eradication in 10 years.

Keywords: antiretroviral treatment; basic reproduction number; disease incidence; disease prevalence; optimal control; Pontryagin's maximum principle; optimality system

1. Introduction

Mathematical representation and analysis of infectious diseases have been central to infectious disease epidemiology. Now, mathematical models are being integrated with rigorous statistical methods to estimate the key model parameters and test hypotheses using available data [11,13]. In the absence of reliable data, Mathematics is used to formulate hypotheses, inform data-collection strategies, and determine sample sizes. Optimal control theory is one area of Mathematics that is

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used extensively in the control of the spread of infectious diseases [9,16,22,31,32]. It is a powerful mathematical tool that can be used to make decisions involving complex situations. Particularly, optimal control theory can be used in the control of the spread of most diseases for which there is either vaccination or treatment.

For example, Sethi and Staats [26] formulated some simple deterministic epidemic models for optimal control problems with the level of medicare programme effort and the level of inoculation programme effort as the control variables. They obtained the needed characterization of the optimal policies for the control of the epidemic over time using Pontryagin's maximum principle (PMP). Similarly, Gaff and Schaefer [7] applied optimal control theory to a series of epidemiological models in their attempt to find the most effective control strategy to minimize the number of individuals who become infected in the course of an epidemic using both treatment and vaccination as control measures.

Joshi *et al.* [16] used two examples to illustrate the concept of optimal control in two different disease models. In the first example, they showed how optimal control theory can be applied to find an optimal vaccination strategy that will minimize the size of the infectious population as well as the cost of vaccination. In the second example, they considered a model describing the interaction between the virus and the immune cell population in an individual under drug treatment, and they illustrated how optimal control theory can be used to determine a drug treatment strategy that minimizes the side effects of the drug together with the viral population at any point in time.

The work of Kirschner *et al.* [18] used the optimal control approach to determine the optimal strategy for the administration of reverse transcriptase inhibitors for HIV-positive individuals that minimizes the drug toxicity and their viral load while maximizing helper T-cell counts. In a related study, Fister and Donnelly [5] used optimal control theory to determine the condition for the elimination of tumour cells in individuals under treatment. Recently, Blayneh *et al.* [1] studied a deterministic model for the transmission dynamics of West Nile virus in the mosquito–bird–human zoonotic cycle using mosquito reduction strategies and human protection strategies as control measures. The numerical simulations of their resulting optimal control problem suggest that mosquito reduction strategies should be emphasized ahead of human protection measures in order to reduce the disease burden.

In this paper, we consider a deterministic for the spread of HIV/AIDS with a removed class that is made up of individuals who have sufficiently modified their sexual habits, thus making them literarily 'immune' to HIV infection by sexual contact. This differentiates the model from most of the existing models (see [14,17,23,25]). We found the inclusion of this compartment justifiable because it is true that an appreciable number of people are now changing their sexual habits sufficiently due to the awareness of the widespread nature of the disease in society, the monumental deaths resulting from the disease, increasing knowledge of the agony and psychological trauma experienced by the infected individuals, and better enlightenment due to intense HIV/AIDS educational campaigns. Note that our proposed change in sexual habits does not imply that the removed individuals would no longer engage in sexual activities, rather this class of individuals would remain faithful to their sexual partners, reduce the number of the sexual partners to the barest minimum and avoid extra-marital affairs for the rest of their lives. We formulate our model as a fixed time optimal control problem with a view to finding the optimal combination of the control measures that will reduce the spread of the disease within a specified time period, since most governments usually set time frames for the accomplishment of the stated policy or objective.

This paper is organized as follows: In Section 2, we describe our proposed model. In Section 3, we establish the local and global stability of the model disease-free equilibrium. In Section 4, we estimate the model state initial conditions and parameter values. In Section 5, we formulate an optimal control problem subject to the model dynamics, characterize the optimal controls, and constitute its optimality system using PMP. In Section 6, we solve the resulting optimality system numerically and discuss our results.

2. Model equations

We consider a sexually active population $N(t)$, divided into six compartments: $S(t)$, $H(t)$, $P(t)$, $A(t)$, $T(t)$, and $R(t)$. $S(t)$ represents the number of susceptible individuals; $H(t)$ represents the number of HIV-positive individuals in the asymptomatic stage of HIV infection; $P(t)$ represents the number of HIV-positive individuals in the pre-AIDS stage but not receiving antiretroviral (ARV) treatment; $A(t)$ represents the number of individuals with full-blown AIDS but not receiving ARV treatment; $T(t)$ represents the number of individuals who are receiving ARV treatment; and $R(t)$, the removed class, represents the number of individuals who have changed their sexual habits sufficiently such that they are, literarily, 'immune' to HIV infection by sexual contact. Note that the individuals in the R class are people who take up safe sexual habits and maintain the habits for the rest of their lives. The significance of the removed the R class is that it emphasizes the importance of prevention for a disease, such as HIV, that has no cure. Increasing the members in this class is one of the keys to controlling the spread of the disease.

A schematic diagram for the spread of the disease is shown in Figure 1.

From Figure 1, the population dynamics is given by the following equations:

$$\begin{aligned}
\dot{S} &= \Lambda - \frac{\beta_1 SH}{N} - \frac{\beta_2 PS}{N} - \mathrm{d}S - u_1 S,\\
\dot{H} &= \frac{\beta_1 HS}{N} + \frac{\beta_2 PS}{N} - k_1 H - \mathrm{d}H,\\
\dot{P} &= k_1 H - k_2 P - u_2 P - \mathrm{d}P,\\
\dot{A} &= k_2 P - u_3 A - \mathrm{d}A - \delta_1 A,\\
\dot{T} &= u_2 P + u_3 A - \mathrm{d}T - \delta_2 T,\\
\dot{R} &= u_1 S - \mathrm{d}R,
\end{aligned} \tag{1}$$

where $N(t)$ denotes total population,

$$N(t) = S(t) + H(t) + P(t) + A(t) + T(t) + R(t), \tag{2}$$

and $N(t)$ satisfies the following equation:

$$\dot{N} = \Lambda - Nd - \delta_1 A - \delta_2 T.$$

The parameters for the model are defined in Table 1.

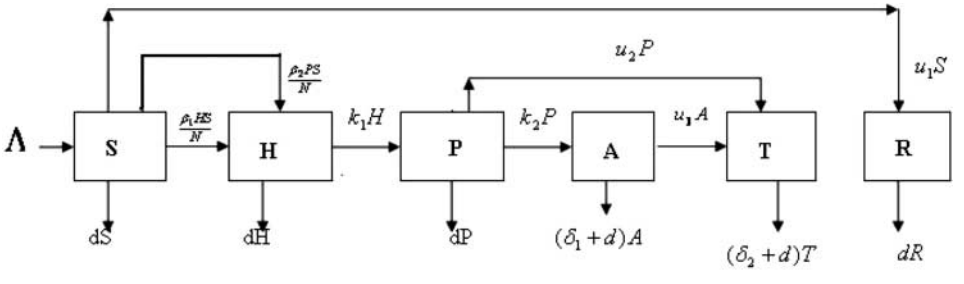

Figure 1. A schematic diagram for the spread of HIV.

Table 1. Parameters used in the model.

Parameter	Description
Λ	Recruitment rate into the S class
d	Natural death rate
β_1	Transmission rate for contact with the H class
β_2	Transmission rate for contact with the P class ($\beta_1 < \beta_2$)
k_1	Progression rate from the H class into the P class
k_2	Progression rate from the P class into the A class ($k_1 < k_2$)
u_1	Proportion of susceptible individuals who changed their sexual habits per unit time
u_2	Proportion of the P class receiving ARV treatment per unit time
u_3	Proportion of the A class receiving ARV treatment per unit time
δ_1	Disease-induced death rate for AIDS individuals
δ_2	Disease-induced death rate for the T class ($\delta_2 < \delta_1$)

Note that $\lim_{t\to\infty} N(t) \leq \Lambda/d$. However, under the dynamics described by Equation (1), the region Ω defined by

$$\Omega = \left\{(S,H,P,A,T,R) \in \mathbb{R}^6_+ | S+H+P+A+T+R \leq \frac{\Lambda}{d}\right\}$$

is positively invariant.

LEMMA 1 *The cone $\mathbb{R}^6_+$ is positively invariant for the model* (1) (*i.e. the model does not predict negative values for the state variables at any future time*).

Proof Let $t_1 = \sup\{t > 0 | S \geq 0, H \geq 0, P \geq 0, A \geq 0, T \geq 0, R \geq 0, \in [0,t]\}$. From Equation (1), we have

$$\frac{\mathrm{d}S}{\mathrm{d}t} = \Lambda - (\lambda(t) + d + u_1(t))S, \quad \text{where } \lambda(t) = \frac{\beta_1 H + \beta_2 P}{N}.$$

This is same as

$$\frac{\mathrm{d}S}{\mathrm{d}t} + (\lambda(t) + d + u_1(t))S = \Lambda,$$

and this implies that

$$\frac{\mathrm{d}}{\mathrm{d}t}\left(S(t)\exp\left\{\mathrm{d}t + \int_0^t (\lambda(\tau) + u_1(\tau))\,\mathrm{d}\tau\right\}\right) = \Lambda \exp\left\{\mathrm{d}t + \int_0^t (\lambda(\tau) + u_1(\tau))\,\mathrm{d}\tau\right\}.$$

Thus,

$$S(t_1)\exp\left\{\mathrm{d}t_1 + \int_0^{t_1} (\lambda(\tau) + u_1(\tau))\,\mathrm{d}\tau\right\} - S(0)$$
$$= \int_0^{t_1} \Lambda \exp\left\{\mathrm{d}\psi + \int_0^{\psi} (\lambda(\epsilon) + u_1(\epsilon))\,\mathrm{d}(\epsilon)\right\}\mathrm{d}\psi.$$

Hence,

$$\begin{aligned} S(t_1) &= S(0)\exp\left\{-\left(\mathrm{d}t_1 + \int_0^{t_1}(\lambda(\tau)+u_1(\tau))\,\mathrm{d}\tau\right)\right\} \\ &\quad + \exp\left\{-\left(\mathrm{d}t_1 + \int_0^{t_1}(\lambda(\tau)+u_1(\tau))\,\mathrm{d}\tau\right)\right\} \\ &\quad \times \int_0^{t_1}\Lambda\exp\left\{\mathrm{d}\psi + \int_0^{\psi}(\lambda(\epsilon)+u_1(\epsilon))\mathrm{d}(\epsilon)\right\}\mathrm{d}\psi \\ &\geq 0. \end{aligned} \tag{3}$$

Similarly, we can show that $H(t) \geq 0, P(t) \geq 0, A(t) \geq 0, T(t) \geq 0$, and $R(t) \geq 0$. This completes the proof. ■

The above lemma is important because it guarantees that the model variables are continuously biologically meaningful, since population size cannot be negative.

LEMMA 2 *Ω is a compact attracting set (i.e. the Ω limit set of any orbit starting in $\mathbb{R}^6_+$ lies in Ω).*

Proof Using the non-negativity of the model state variables as established in the preceding lemma and

$$\dot{N} = \Lambda - \mathrm{d}N - \delta_1 A - \delta_2 T$$

for initial conditions in $\mathbb{R}^6_+$ and $t \geq 0$, we have $\dot{N} \leq \Lambda - \mathrm{d}N$. This implies that

$$\frac{\mathrm{d}}{\mathrm{d}t}(Ne^{\mathrm{d}t}) \leq \Lambda e^{\mathrm{d}t} \Longrightarrow N(t)e^{\mathrm{d}t} - N(0) \leq \frac{\Lambda}{d}(e^{\mathrm{d}t}-1) \leq \frac{\Lambda}{d}e^{\mathrm{d}t}.$$

So, for all $t \geq 0$,

$$N(t) \leq N(0)e^{-\mathrm{d}t} + \frac{\Lambda}{d}. \tag{4}$$

If $(S^*, H^*, P^*, A^*, T^*, R^*)$ is an Ω limit point of an orbit in $\mathbb{R}^6_+$, then there is a subsequence $t_i \to \infty$ such that

$$\lim_{i\to\infty}(S(t_i), H(t_i), P(t_i), A(t_i), T(t_i), R(t_i)) = (S^*, H^*, P^*, A^*, T^*, R^*).$$

Hence,

$$\lim_{i\to\infty} N(t_i) = N^* = S^* + H^* + P^* + A^* + T^* + R^*.$$

From Equation (4) (by evaluation at $t = t_i$ and passing to the limit $i \to \infty$), it follows that $N^* \leq \Lambda/d$ and hence that $(S^*, H^*, P^*, A^*, T^*, R^*) \in \Omega$. ■

Thus, for any initial starting point $(S_0, H_0, P_0, A_0, T_0, R_0) \in \mathbb{R}^6_+$, the trajectory lies in Ω. Therefore, the system is both mathematically and epidemiologically well posed.

3. Stability analysis

The system (1) has a *disease-free equilibrium* solution

$$\mathcal{E}_0 = \left(\frac{\Lambda}{(d+u_1)}, 0, 0, 0, 0, \frac{\Lambda u_1}{d(d+u_1)} \right),$$

and the model basic reproduction number, $\mathcal{R}_0$, is as given below:

$$\mathcal{R}_0 = \frac{\beta_1 \mathrm{d}}{(d+u_1)(d+k_1)} + \frac{\beta_2 k_1 \mathrm{d}}{(d+u_1)(d+k_1)(d+u_2+k_2)}.$$

Note that the basic reproduction number, $\mathcal{R}_0$, is the expected number of secondary infections arising from a single individual during his or her entire infectious period in a population of susceptible individuals [12]. $\mathcal{R}_0$ is obtained using the next- generation matrix approach described in [4].

THEOREM 1 *The disease-free equilibrium is locally asymptotically stable if* $\mathcal{R}_0 < 1$.

Proof The Jacobian matrix of the system (1) is

$$\mathbf{J} = \begin{pmatrix} a_{11} - (d+u_1) & -a_{22} & -a_{33} & a_2 & a_2 & a_2 \\ -a_{11} & a_{22} - (k_1 + d) & a_{33} & -a_2 & -a_2 & -a_2 \\ 0 & k_1 & -(k_2 + u_2 + d) & 0 & 0 & 0 \\ 0 & 0 & k_2 & -(d + u_3 + \delta_1) & 0 & 0 \\ 0 & 0 & u_2 & u_3 & -(d+\delta_2) & 0 \\ u_1 & 0 & 0 & 0 & 0 & -d \end{pmatrix},$$

where

$$a_1 = \left(\frac{\beta_1 H}{N} + \frac{\beta_2 P}{N} \right), \quad a_2 = a_1 \frac{S}{N}, \quad a_{11} = a_1 \left(\frac{S}{N} - 1 \right),$$
$$a_{22} = \frac{\beta_1 S}{N} \left(1 - \frac{H}{N} \right), \quad a_{33} = \frac{\beta_2 S}{N} \left(1 - \frac{P}{N} \right).$$

■

Evaluating the Jacobian matrix $\mathbf{J}$ at the disease-free equilibrium gives

$$\mathbf{J_0} = \begin{pmatrix} -(d+u_1) & -\dfrac{\beta_1 d}{d+u_1} & -\dfrac{\beta_2 d}{d+u_1} & 0 & 0 & 0 \\ 0 & \dfrac{\beta_1 d}{d+u_1} - (k_1 + d) & \dfrac{\beta_2 d}{d+u_1} & 0 & 0 & 0 \\ 0 & k_1 & -(k_2 + u_2 + d) & 0 & 0 & 0 \\ 0 & 0 & k_2 & -(d + u_3 + \delta_1) & 0 & 0 \\ 0 & 0 & u_2 & u_3 & -(d+\delta_2) & 0 \\ 0 & 0 & 0 & 0 & 0 & -d \end{pmatrix}.$$

The eigenvalues of $\mathbf{J}_0$ are

$$\lambda_1 = -d, \quad \lambda_2 = -(d+u_1), \quad \lambda_3 = -(d+\delta_2), \quad \lambda_4 = -(d+u_3+\delta_1),$$

and we obtained λ_5 and λ_6 from the characteristic polynomial given below:

$$f(\lambda) = \lambda^2 - \left(\frac{\beta_1 d}{d+u_1} - (k_1+d) - (k_2+u_2+d)\right)\lambda + \left((k_1+d)(k_2+u_2+d) - \frac{\beta_1 d(k_1+u_2+d)}{d+u_1} - \frac{\beta_2 d k_1}{d+u_1}\right) = 0. \tag{5}$$

Taking $a = 1$, $b = (k_1+d) + (k_2+u_2+d) - \beta_1 d/d + u_1$, and

$$c = (k_1+d)(k_2+u_2+d) - \frac{\beta_1 d(k_1+u_2+d)}{d+u_1} - \frac{\beta_2 d k_1}{d+u_1},$$

we have

$$\lambda_{5,6} = \frac{-b}{2} \pm \sqrt{\frac{b^2}{4} - c}.$$

Thus, we only need to show that b and c are positive in order for both λ_5 and λ_6 to be negative. However, $\mathcal{R}_0 < 1$ implies that

$$\begin{aligned} 1 &> \frac{\beta_1 d}{(d+u_1)(d+k_1)} + \frac{\beta_2 k_1 d}{(d+u_1)(d+k_1)(d+u_2+k_2)} \\ &> \frac{\beta_1 d}{(d+u_1)(d+k_1)} \\ &> \frac{\beta_1 d}{(d+u_1)(2d+k_1+k_2+u_2)}. \end{aligned} \tag{6}$$

Note that

$$\begin{aligned} b &= (k_1+d) + (k_2+u_2+d) - \frac{\beta_1 d}{d+u_1} \\ &= (2d+k_1+k_2+u_2) - \frac{\beta_1 d}{d+u_1} \\ &= (2d+k_1+k_2+u_2)\left(1 - \frac{\beta_1 d}{(d+u_1)(2d+k_1+k_2+u_2)}\right) \\ &> 0 \quad \text{if } \mathcal{R}_0 < 1 \end{aligned} \tag{7}$$

and

$$\begin{aligned} c &= (k_1+d)(k_2+u_2+d) - \frac{\beta_1 d(k_1+u_2+d)}{d+u_1} - \frac{\beta_2 d k_1}{d+u_1} \\ &= (k_1+d)(k_2+u_2+d)\left(1 - \frac{\beta_1 d}{(d+u_1)(k_1+d)} - \frac{\beta_2 d k_1}{(d+u_1)(k_1+d)(k_2+u_2+d)}\right) \\ &= (k_1+d)(k_2+u_2+d)(1-\mathcal{R}_0) \\ &> 0 \quad \text{if } \mathcal{R}_0 < 1. \end{aligned} \tag{8}$$

Since $c > 0$ and $b > 0$, $\lambda_5 < 0$ and $\lambda_6 < 0$ if $\mathcal{R}_0 < 1$. Therefore, the disease-free equilibrium is locally asymptotically stable if $\mathcal{R}_0 < 1$.

THEOREM 2 *The disease-free equilibrium is globally asymptotically stable if* $\mathcal{R}_0 < 1$.

Proof We introduce the Lyapunov candidate function

$$V(t) = H + \theta P \quad \theta > 0.$$

Differentiating $V(t)$ with respect to time yields

$$\dot{V} = \dot{H} + \theta \dot{P}. \tag{9}$$

Substituting the model equations into Equation (9), we get

$$\dot{V} = \frac{\beta_1 HS}{N} + \frac{\beta_2 PS}{N} - (k_1 + d)H + \theta(k_1 H - (k_2 + u_2 + d)P). \tag{10}$$

With $S = \bar{S} = \Lambda/(d + u_1)$ and $R = \bar{R} = \Lambda u_1/(d(d + u_1))$, we have

$$\dot{V} \leq \frac{\beta_1 dH}{d + u_1} + \frac{\beta_1 dP}{d + u_1} - (k_1 + d)H + \theta k_1 H - \theta(k_2 + u_2 + d)P. \tag{11}$$

Hence,

$$\dot{V} \leq \left(\frac{\beta_1 d}{d + u_1} + \theta k_1 - (k_1 + d)\right) H + \left(\frac{\beta_2 d}{d + u_1} - \theta(k_2 + u_2 + d)\right) P.$$

Choosing $\theta = \beta_2 d/((d + u_1)(k_2 + u_2 + d))$, we then find that

$$\begin{aligned} \dot{V} &\leq \left(\frac{\beta_1 d}{(d + u_1)(k_1 + d)} + \frac{\beta_2 d k_1}{(d + u_1)(k_2 + d)(k_2 + u_2 + d)} - 1\right) H. \\ &= (\mathcal{R}_0 - 1)H \leq 0. \end{aligned} \tag{12}$$

It is important to note that $\dot{V} = 0$ only when $H = P = 0$. However, substituting $H = P = 0$ into Equation (1) shows that $S \to \Lambda/(d + u_1), A \to 0, T \to 0$, and $R \to \Lambda u_1/(d(d + u_1))$ as $t \to \infty$. Applying LaSalle's invariance principle, every solution of the model (1), with initial conditions in Ω, converges to $\mathcal{E}_0$ [19,27]. Hence, the disease-free equilibrium is globally asymptotically stable in Ω if $\mathcal{R}_0 < 1$. ■

4. Estimation of the model parameters and initial conditions

Each country has its own HIV/AIDS data. Here, we focus on South Africa, but the same analysis can be applied to other countries.

4.1. *Initial conditions*

The base year used in our simulations was 2006. The number of sexually active individuals (age 15–49 years) in South Africa was approximately 25.92 million in 2006. The number of HIV/AIDS-positive individuals in 2006 was 4.756 million. The number of individuals receiving ARV treatment was 0.511 million, and the number of AIDS-sick individuals not receiving ARV treatment was 0.2 million [3]. Thus, we took $A(0) = 0.2$ million, $T(0) = 0.511$ million, and $H(0) + P(0) + A(0) + T(0) = 4.756$ million. We assumed that $H(0) = 2P(0)$, so that $H(0) = 2.697$ million and $P(0) = 1.348$ million. Since $N(0) = 25.92$ million, we also had $S(0) = 25.92 - 4.756 = 21.163$ million.

4.2. *Parameter values*

Constant recruitment rate (Λ). This was estimated as the net births that occurred 15–20 years ago plus the present net migration. The net births were calculated using the average of births in South Africa between 1990 and 2000 since this gives a good rough estimate of the group of individuals who will become sexually active after the year 2005. The birth value obtained was adjusted with the infant mortality rate over the same period (Table 2). According to United Nations [30], the crude births in South Africa for 1990–1995 and 1995–2000 were 27.5 and 25.2 per thousand population, respectively, while the infant mortalities were 50.4 and 56.8 per thousand live births, respectively. Thus, we got an average of 26.3 per thousand population for the crude births and 53.6 for the infant mortality per thousand live births. We used the number of people in South Africa in 1990, which was 36.747 million, to estimate the births during 1990–2000. Also, the net annual migration into South Africa between 2000 and 2010 was 140, 000. Therefore, we computed the constant recruitment rate (Λ) as follows:

$$\begin{aligned}\Lambda &= \text{Pop.} \times \text{crude birth rate} \times \text{infant survival rate} + \text{migration}\\ &= 36.474 \times 0.026 \times (1 - 0.054) + 0.14 \text{ million}\\ &= 1.0 \text{ million}.\end{aligned} \tag{13}$$

Natural death rate (d). This was estimated using the life expectancy for a South African at birth who was 51 years old in 2006 [28]. Based on the assumption that if the population were to be normally distributed, 1 in every 51 persons will die every year. Thus, we estimated $d = 1/51 = 0.0196$.

Progression rates (k_1, k_2). Following [10], we assumed that it takes 7 years for a newly infected person to progress to the pre-AIDS stage and 3 more years to develop full-blown AIDS. Therefore, we obtained $k_1 = \text{In}2/7/2 = 0.198$ and $k_2 = \text{In}2/3/2 = 0.4621$.

Disease-induced death rates (δ_1, δ_2). Based on their analyses of findings from several studies conducted mostly in Africa to examine the survival period of HIV patients from seroconversion to death before ARV treatment becomes available, Ghys *et al.* [8] recommended that an average survival period of 11 years be used in modelling national epidemics. Thus, we computed $\delta_1 = 1/11 = 0.0909$. There is overwhelming evidence that ARV therapy substantially extends the life of HIV/AIDS patients [8,9]. Thus, we assumed that ARV treatment will extend the life of patients for an additional 4 years. Thus, the survival period for HIV-infected individuals under ARV treatment was estimated as 15 years. We computed $\delta_2 = 1/15 = 0.0667$.

Transmission rates (β_1, β_2). It is known that the infection rate (β_1) of individuals from the H class is smaller than the infection rate (β_2) of individuals from the P class [10]. We assumed

Table 2. Parameter values obtained using data from South Africa.

Parameter	Units	Value	Reference
Λ	Population/year	1.04	[3] and estimate
d	yr^{-1}	0.0196	[28]
β_1	yr^{-1}	0.11	Estimate
β_2	yr^{-1}	$\beta_2 = 5, \beta_1 = 0.55$	[10] and estimate
k_1	yr^{-1}	0.198	[10] and estimate
k_2	yr^{-1}	0.4621	[10] and estimate
u_1	yr^{-1}	$0 \le u_1 \le u_{1\max} \le 1$	Variable
u_2	yr^{-1}	$0 \le u_2 \le u_{2\max} \le 1$	Variable
u_3	yr^{-1}	$0 \le u_3 \le u_{3\max} \le 1$	Variable
δ_1	yr^{-1}	0.0909	Estimate
δ_2	yr^{-1}	0.0667	Estimate

that $\beta_1 = (1/5)\beta_2$. According to Dorrington *et al.* [3], the prevalence of HIV/AIDS among adults in South Africa for the year 2006 was 18.3%. In order to determine β_2, we used the Berkeley Madonna software for parameter fitting. We solved the system (1) with the initial conditions and the parameters (except β_2) as determined above and determined β_2, which yields $\pi = 18.3\%$, namely $\beta_2 = 0.55$.

5. Optimal control problem formulation

Our objective functional is defined by

$$J = \min_{u_1,u_2,u_3} \int_0^{t_f} \left(\frac{w_1}{2}u_1^2 + \frac{w_2}{2}u_2^2 + \frac{w_3}{2}u_3^2 + w_4 S + w_5 H + w_6 P + w_7 A \right) \mathrm{d}t \tag{14}$$

subject to the system of Equations (1) with appropriate state initial conditions, and t_f is the final time, while the control set $\mathbb{U}$ is defined as

$$\mathbb{U} = \{(u_1, u_2, u_3) | u_1 \text{Lebesgue measurable}, 0 \leq u_i \leq u_{i\max} < 1, i = 1, 2, 3\}, \tag{15}$$

and the weight constants $w_1, w_2, w_3, w_4, w_5, w_6$, and w_7 are the relative weights and help to balance each term in the integrand so that any of the terms do not dominate. Here, it is important to note that w_1, w_2, and w_3 are the relative measures of the cost or effort required to implement each of the associated controls, while w_4, w_5, w_6, and w_7 are the relative measures of the importance of reducing the associated classes on the spread of the disease and its burden.

The lower bounds for u_1, u_2, and u_3 correspond to no change in sexual habits, no ARV treatment for the P class, and no ARV treatment for the A class, respectively, while the upper bound for each of the controls ($u_{1\max}$, $u_{2\max}$, and $u_{3\max}$) will depend on the budget allocated for the execution of each of the control measures. For instance, we shall hypothetically set $u_{1\max} = 0.2$, $u_{2\max} = 0.5$, and $u_{3\max} = 0.5$ in our subsequent simulations. We wish to determine the optimal combination of controls u_1, u_2, and u_3 that will be adequate to minimize the cost of the education/enlightenment campaign together with the cost of ARV treatment as well as to reduce the incidence of the disease over a fixed time period. Note that S was included in the integrand to emphasize the need for reducing the susceptible individuals in addition to the infective individuals, particularly for a disease without cure. Moreover, S contributes to the incidence of the disease together with H and P. We also included A in the integrand to indirectly reduce AIDS-induced deaths.

5.1. *Existence of an optimal control pair*

Here, we examine the sufficient conditions for the existence of a solution to the optimal control problem.

THEOREM 3 *There exists an optimal control set* (u_1^*, u_2^*, u_3^*) *with a corresponding solution* $(S^*, H^*, P^*, A^*, T^*, R^*)$ *to the model system* (1) *that minimizes* $J(u_1, u_2, u_3)$ *over* $\mathbb{U}$.

Proof The existence of the optimal control is guaranteed by the compactness of the control and the state space and the convexity in the problem based on Theorem 4.1 of Chapter III and its corresponding corollary in [6]. The following non-trivial requirements from Fleming and Rishel's theorem are stated and verified:

(1) The set of all solutions to Equation (1) and its associated initial conditions together with the corresponding control functions in $\mathbb{U}$ is non-empty.

(2) The state system can be written as a linear function of the control variables with coefficients dependent on time and state variables.
(3) The integrand L in Equation (14) is convex on $\mathbb{U}$ and additionally satisfies $L(t, S, H, P, A, T, R, u_1, u_2, u_3) \geq c_1|(u_1, u_2, u_3)|^\alpha - c_2$, where $c_1, c_2 > 0$ and $\alpha > 1$.

We refer to Theorem 3.1 proposed by Picard–Lindelof in [2]. Based on this theorem, if the solutions to the state equations are *a priori* bounded and if the state equations are continuous and Lipschitz in the state variables, then there exists a unique solution corresponding to every admissible control set in $\mathbb{U}$. Using the fact that for all $(S, H, P, A, T, R) \in \Omega$, all the model states are bounded below and above, the solutions to the state equations are bounded. In addition, the boundedness of the partial derivatives with respect to the state variables in the system can be directly shown, and this shows that the system is Lipschitz with respect to the state variables. Thus, condition 1 holds. As we can observe from the state equations (1), the state equations are linearly dependent on the controls u_1, u_2, and u_3. Thus, condition 2 also holds. To establish condition 3, we observe that the integrand L in our objective functional is convex since it is quadratic in the controls. Then, we only need to prove the bound on L. This is shown as follows:

$$\begin{aligned}
L &= \frac{1}{2}(w_1u_1^2 + w_2u_2^2 + w_3u_3^2) + w_4S + w_5H + w_6P + w_7A \\
&\geq \frac{1}{2}(w_1u_1^2 + w_2u_2^2 + w_3u_3^2) \quad \text{since } w_i > 0 \;\; i = 1, \ldots, 7 \\
&\geq \frac{1}{2}(w_1u_1^2 + w_2u_2^2 + w_3u_3^2) - w_1 \quad \text{since } w_1u_1^2 - w_1 \leq 0 \\
&\geq \min\left(\frac{1}{2}w_1, \frac{1}{2}w_2, \frac{1}{2}w_3\right)(u_1^2 + u_2^2 + u_3^2) - w_1 \\
&\geq W\|(u_1, u_2, u_3)\|^2 - w_1, \quad \text{where } W = \min\left(\frac{1}{2}w_1, \frac{1}{2}w_2, \frac{1}{2}w_3\right).
\end{aligned} \tag{16}$$

The above then establishes a bound on L. Thus, we have a unique solution of the optimality system for small time intervals due to the opposite time orientations of the state equations and the adjoint equations. Moreover, the uniqueness of the solution of the optimality system guarantees the uniqueness of the optimal control if it exists. ■

5.2. *Characterization of the optimal controls*

We characterize the optimal controls u_1^*, u_2^*, and u_3^*, which gives the optimal levels for the various control measures and the corresponding states $(S^*, H^*, P^*, A^*, T^*, R^*)$. The necessary conditions for the optimal controls are obtained using PMP [24].

THEOREM 4 (Necessary conditions) *Let $(u_1^*, u_2^*, u_3^*) \in \mathbb{U}$ be an optimal control with the corresponding states S^*, H^*, P^*, A^*, T^*, and R^*. Then, there exist the adjoint variables λ_i for $i = 1, \ldots, 6$, which satisfy*

$$\lambda_1' = -w_4 + \lambda_1(u1 + d) + (\lambda_1 - \lambda_2)\left(\frac{\beta_1 H + \beta_2 P}{N}\right) - (\lambda_1 - \lambda_2)\left(\frac{(\beta_1 H + \beta_2 P)S}{N^2}\right) - \lambda_6 u_1,$$

$$\lambda_2' = -w_5 + (\lambda_1 - \lambda_2)\left(\frac{\beta_1 S}{N}\right) - (\lambda_1 - \lambda_2)\left(\frac{\beta_1 SH}{N^2}\right) - \lambda_3 k_1,$$

$$\lambda_3' = -w_6 + (\lambda_1 - \lambda_2)\left(\frac{\beta_1 S}{N}\right) - (\lambda_1 - \lambda_2)\left(\frac{\beta_1 SP}{N^2}\right) - \lambda_4 k_2 - \lambda_5 u_2,$$
$$\lambda_4' = -w_7 + \lambda_4(u_3 + d + \delta_1) - \lambda_5 u_3,$$
$$\lambda_5' = \lambda_5(d + \delta_2),$$
$$\lambda_6' = \lambda_6 d, \tag{17}$$

and the transversality conditions

$$\lambda_i(t_f) = 0, \quad \textit{for } i = 1, \ldots, 6, \tag{18}$$

with the optimal controls defined as follows:

$$u_1^* = \min\left\{\max\left(0, \frac{S(\lambda_1 - \lambda_6)}{w_1}\right), u_{1\max}\right\},$$
$$u_2^* = \min\left\{\max\left(0, \frac{P(\lambda_3 - \lambda_5)}{w_2}\right), u_{1\max}\right\}, \tag{19}$$
$$u_3^* = \min\left\{\max\left(0, \frac{A(\lambda_4 - \lambda_5)}{w_3}\right), u_{1\max}\right\}.$$

Proof Using PMP, we obtain Equation (17) from

$$\lambda_1' = -\frac{\partial \mathbb{H}}{\partial S}, \quad \lambda_2' = -\frac{\partial \mathbb{H}}{\partial H}, \quad \lambda_3' = -\frac{\partial \mathbb{H}}{\partial P}, \tag{20}$$
$$\lambda_4' = -\frac{\partial \mathbb{H}}{\partial A}, \quad \lambda_5' = -\frac{\partial \mathbb{H}}{\partial T}, \quad \lambda_6' = -\frac{\partial \mathbb{H}}{\partial N}, \tag{21}$$

where the Hamiltonian $\mathbb{H}$ is given by

$$\begin{aligned}\mathbb{H} = {} & \frac{w_1}{2}u_1^2 + \frac{w_2}{2}u_2^2 + \frac{w_3}{2}u_3^2 + w_4 S + w_5 H + w_6 P + w_7 A \\ & + \lambda_1\left(\Lambda - \frac{\beta_1 SH}{N} - \frac{\beta_2 PS}{N} - dS - u_1 S\right) \\ & + \lambda_2\left(\frac{\beta_1 HS}{N} + \frac{\beta_2 PS}{N} - k_1 H - dH - u_2 P\right) \\ & + \lambda_3(k_1 H - k_2 P - u_2 P - dP) \\ & + \lambda_4(k_2 P - u_3 A - dA - \delta_1 A) \\ & + \lambda_5(u_2 P + u_3 A - dT - \delta_2 T) \\ & + \lambda_6(u_1 S - dR).\end{aligned} \tag{22}$$

The transversality conditions have the form (18), since all the states are free at the terminal time.

The Hamiltonian is maximized with respect to the controls at the optimal control $u^* = (u_1^*, u_2^*, u_3^*)$, thus we differentiate $\mathbb{H}$ with respect to u_1, u_2, and u_3 on $\mathbb{U}$, respectively, to obtain

$$\begin{aligned}
\frac{\partial \mathbb{H}}{\partial u_1} &= w_1 u_1 - \lambda_1 S + \lambda_6 S = 0 \text{ at } u_1 = u_1^*, \\
\frac{\partial \mathbb{H}}{\partial u_2} &= w_2 u_2 - \lambda_3 P + \lambda_5 P = 0 \text{ at } u_2 = u_2^*, \\
\frac{\partial \mathbb{H}}{\partial u_3} &= w_3 u_3 - \lambda_4 A + \lambda_5 A = 0 \text{ at } u_3 = u_3^*.
\end{aligned} \tag{23}$$

Hence, solving for u_1^*, u_2^*, and u_3^* on the interior sets gives

$$\begin{aligned}
u_1^* &= \frac{S(\lambda_1 - \lambda_6)}{w_1}, \\
u_2^* &= \frac{P(\lambda_3 - \lambda_5)}{w_2}, \\
u_3^* &= \frac{A(\lambda_4 - \lambda_5)}{w_3}.
\end{aligned} \tag{24}$$

We can now impose the bounds $0 \le u_1 \le u_{1\max}$, $0 \le u_2 \le u_{1\max}$, and $0 \le u_3 \le u_{1\max}$ on the controls to get

$$\begin{aligned}
u_1^* &= \min\left\{\max\left(0, \frac{(\lambda_1 - \lambda_6)S}{w_1}\right), u_{1\max}\right\}, \\
u_2^* &= \min\left\{\max\left(0, \frac{P(\lambda_3 - \lambda_5)}{w_2}\right), u_{2\max}\right\}, \\
u_3^* &= \min\left\{\max\left(0, \frac{A(\lambda_4 - \lambda_5)}{w_3}\right), u_{3\max}\right\}.
\end{aligned} \tag{25}$$

■

It is important to note that the characterization of the above controls can be written in a simpler piecewise form given below:

$$u_1^* = \begin{cases} 0 & \text{when } \lambda_1 - \lambda_6 < 0, \\ \min\left\{\frac{(\lambda_1 - \lambda_6)S}{w_1}, u_{1\max}\right\} & \text{when } \lambda_1 - \lambda_6 > 0, \end{cases} \tag{26}$$

$$u_2^* = \begin{cases} 0 & \text{when } \lambda_3 - \lambda_5 < 0, \\ \min\left\{\frac{P(\lambda_3 - \lambda_5)}{w_2}, u_{2\max}\right\} & \text{when } \lambda_3 - \lambda_5 > 0, \end{cases} \tag{27}$$

$$u_3^* = \begin{cases} 0 & \text{when } \lambda_4 - \lambda_5 < 0, \\ \min\left\{\frac{A(\lambda_4 - \lambda_5)}{w_3}, u_{3\max}\right\} & \text{when } \lambda_4 - \lambda_5 > 0. \end{cases} \tag{28}$$

We can now solve the optimality system that consists of the state system (1) with its associated initial conditions and the adjoint system (17) with its transversality conditions coupled with the control characterizations (26)–(28).

6. Numerical results and discussion

We numerically solved the resulting optimality system – a two-point boundary value problem – using a fourth-order iterative Runge–Kutta scheme. This method solves the state equations with an initial guess for u_1, u_2, and u_3 forward in time, after which it solves the adjoint equations backward in time, and then the controls are updated using Equations (26)–(28). This computational procedure is done iteratively until a convergence is attained. Details on the forward- and backward-sweep procedure are given in [20]. We simulated our model with the data described below.

	Population initial conditions					
Variable	$S(0)$	$H(0)$	$P(0)$	$A(0)$	$T(0)$	$R(0)$
Value	21.16	2.7	1.35	0.51	0.2	0.0

	Parameter values							
Parameter	Λ	β_1	β_2	d	k_1	k_2	δ_1	δ_2
Value	1.04	0.11	0.55	0.0196	0.198	0.4621	0.0909	0.0667

We investigated the dynamics of the disease compartments for varying combinations of the weight constants w_1, w_2, w_3, w_4, w_5, w_6, and w_7, with the assumption that the resources available can only accommodate the following maximum levels of the controls: $u_{1\max} = 0.2$, $u_{2\max} = 0.5$, and $u_{3\max} = 0.5$. In the first scenario, we set $w_1 = 1.0$, $w_2 = 1000$, $w_3 = 10$, $w_4 = 1$, $w_5 = 10$, $w_6 = 10$, and $w_7 = 50$. This scenario corresponds to the present situation in most developing countries where ARV treatment is only given to the AIDS-sick individuals, while the pre-AIDS individuals have to wait until they develop full-blown AIDS before they can be given the treatment. This is often the case in situations where branded ARV drugs (usually very expensive) are mostly used for the treatment and the medical personnel and facilities required for the administration

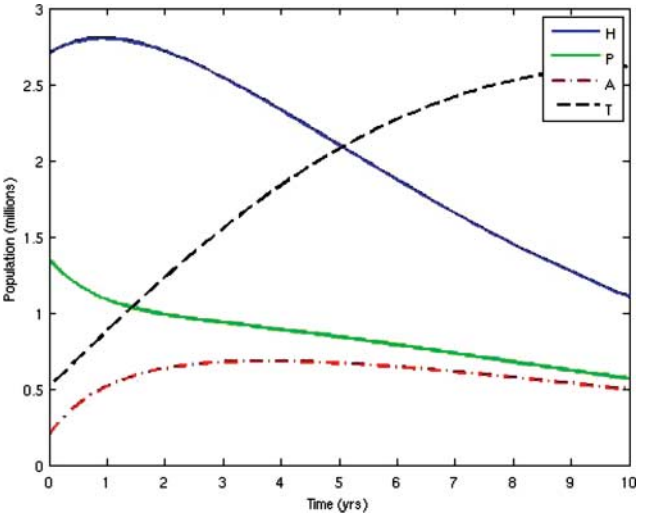

Figure 2. Population of the different disease classes with $u_2 \approx 0$ and $u_3 = 0.5$.

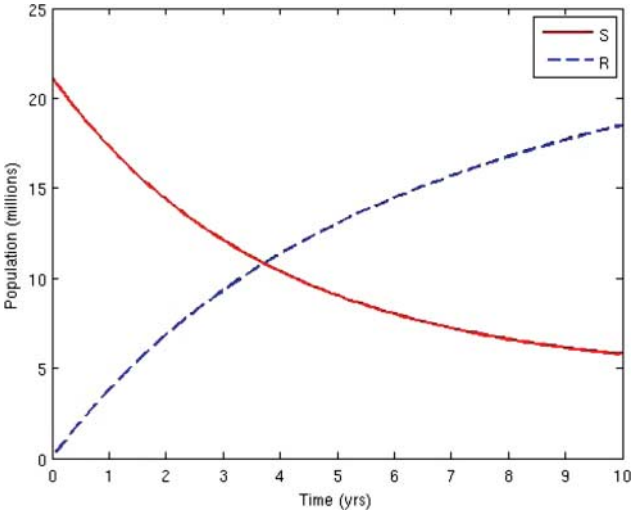

Figure 3. Population of the disease-free classes (S, R) with $u_2 \approx 0$ and $u_3 = 0.5$.

of the treatment are grossly inadequate, thus prompting the government to make the treatment available to only the patients who need it the most. The population profiles of the different disease compartments and the disease-free compartments for this case are shown in Figures 2 and 3, respectively.

In the second scenario, we alternated the values of the weights w_2 and W_3 and fixed the other weights. Thus, we set $w_2 = 10$ and $w_3 = 1000$. This scenario corresponds to the situation where HIV-infected individuals are given ARV treatment as soon as they progress to the pre-AIDS stage without waiting for the onset of AIDS. This is presently not the case in many resource-limited countries. This would be the situation in societies where generic versions (considerably cheaper) of ARV drugs are used as substitutes for the branded ones, while there are adequate medical personnel and facilities to enable a wide coverage of ARV treatment. In this instance, the cost of

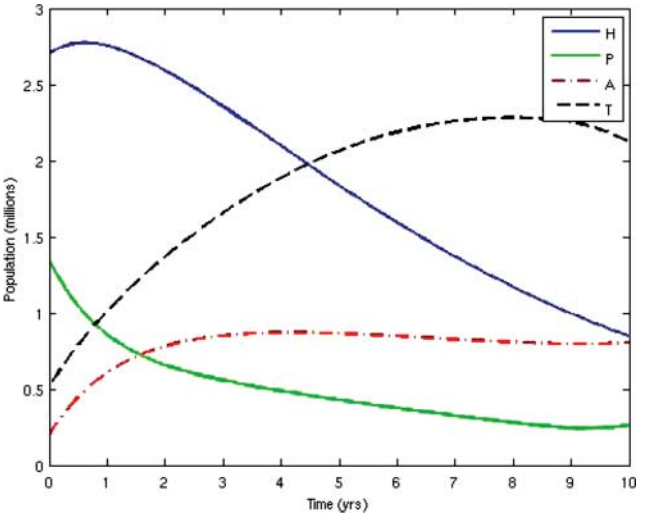

Figure 4. Population of the different disease classes with $u_2 = 0.5$ and $u_3 \approx 0$.

initiating ARV treatment at the pre-AIDS stage is significantly reduced. This strategy obviously prolongs the lifespan of HIV/AIDS patients and delays the onset of AIDS. However, the AIDS cases in this scenario are usually very serious and a lot more expensive to manage due to the patients' development of resistance to most of the first-line and second-line ARV drugs, thus leaving the doctors no options other than patients' hospitalization and use of very expensive ARV drugs.

The population profiles of the different disease compartments and the disease-free compartments for this case are shown in Figures 4 and 5, respectively.

Now, we consider the prevalence and incidence of the disease for the two scenarios. Figures 6 and 7 show the prevalence and incidence for each of the two cases, respectively.

From the above results, we can observe that the administration of ARV treatment to HIV-infected individuals before they become AIDS sick reduces both the prevalence and the incidence

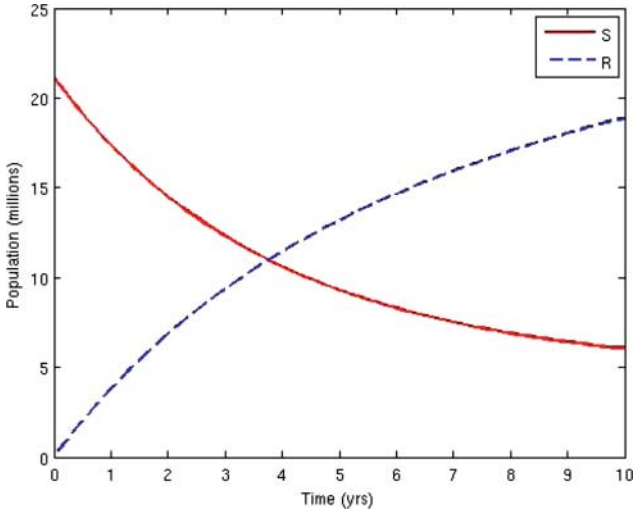

Figure 5. Population of the disease-free classes (S, R) with $u_2 = 0.5$ and $u_3 \approx 0$.

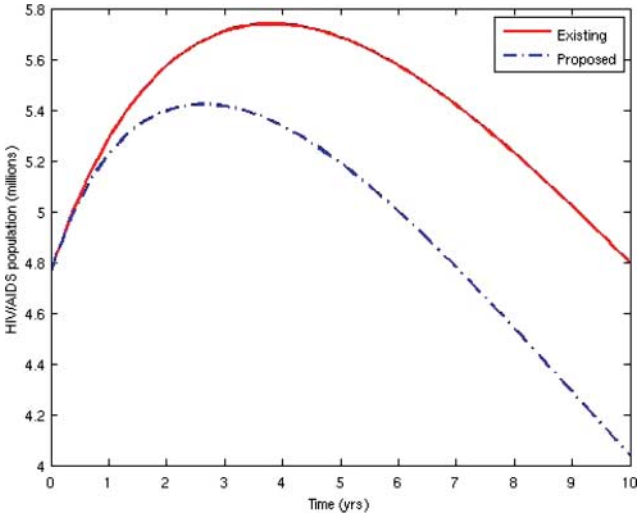

Figure 6. The disease prevalence for each of the two scenarios.

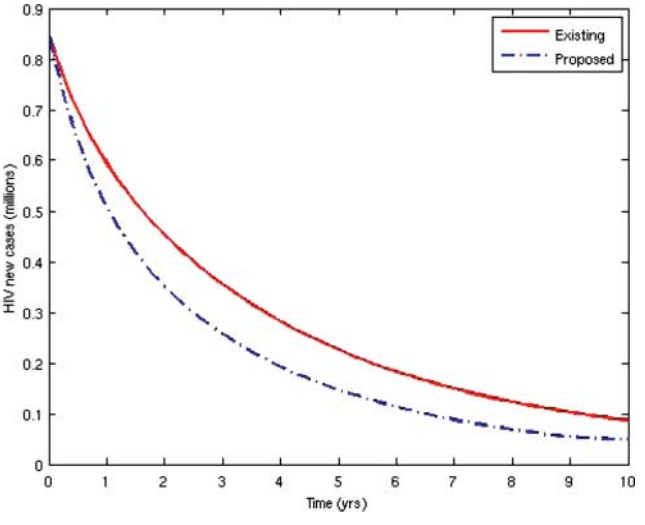

Figure 7. The disease incidence for each of the two scenarios.

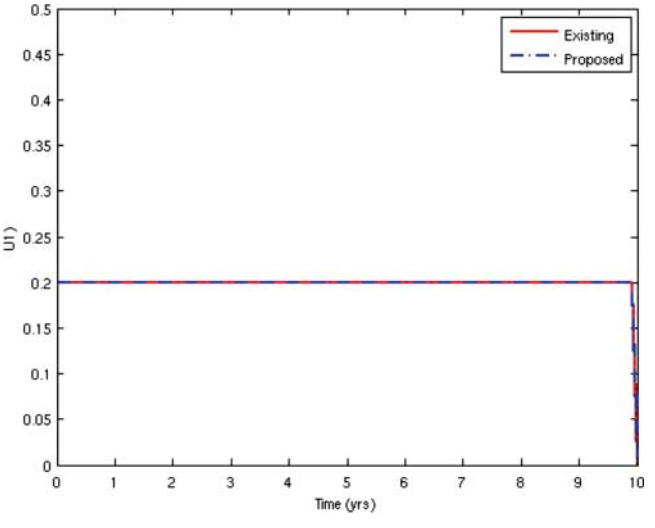

Figure 8. Control u_1 for the two scenarios.

of the disease faster than in the case where we wait until they become AIDS sick before we give them the treatment (Figures 8–10). The expenses that will be incurred by starting ARV treatment earlier will be compensated for by the remarkable reduction in the prevalence and incidence in the later years. Thus, it will be cheaper in the long run to commence ARV treatment at the pre-AIDS stage for the infected population.

Remark 1 The two scenarios simulated were specifically chosen to demonstrate that the case where ARV treatment is given to patients after they have developed full-blown AIDS, as practised in most resource-limited settings. This may not be helpful in reducing the spread of the disease. Rather, an alternative approach of starting the treatment as soon as the patients progress to the pre-AIDS stage of the disease would be better.

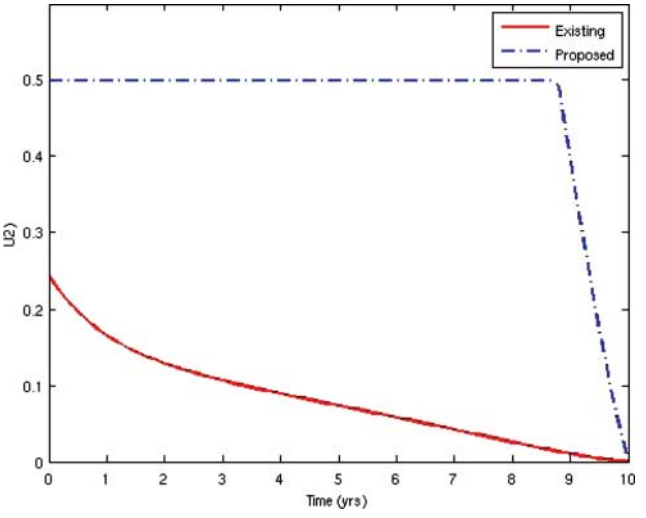

Figure 9. Control u_2 for the two scenarios.

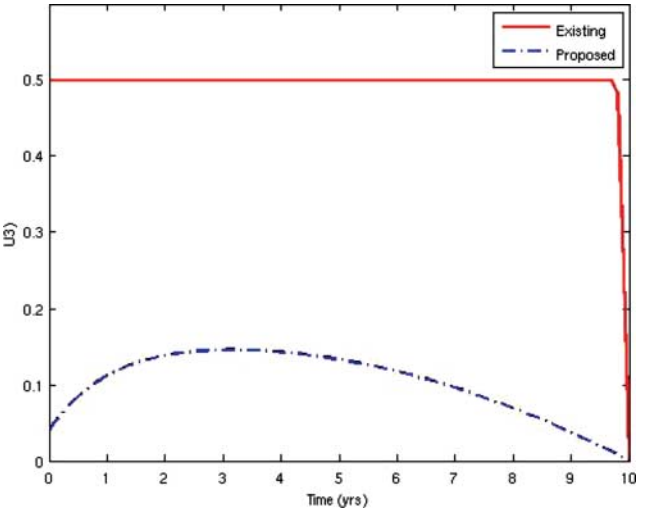

Figure 10. Control u_3 for the two scenarios.

7. Conclusion

We presented a deterministic model for controlling the sexual spread of HIV/AIDS disease. We established that the model disease-free equilibrium is locally and globally asymptotically stable, if the basic reproduction number is less than unity. We formulated an optimal control problem subject to the model dynamics with change in the susceptible individuals' sexual habits due to education/enlightenment campaigns and the administration of ARV treatment to the pre-AIDS and the AIDS-sick individuals as controls. Our aim is to find an optimal strategy that will minimize the cost of implementing the combined control programmes as well as the incidence of the disease.

We proved the existence and uniqueness of the optimal control and we characterized the controls using PMP. The resulting optimality system was solved numerically; the results show that the optimal way to mitigate the spread of the disease is for susceptible individuals to consistently

practise safe sex as much as possible, while ARV treatment should be initiated for patients as soon as they progress to the pre-AIDS stage of the disease. This strategy may be expensive at the outset, but it is optimally cost effective in the long run and it portends more benefits for the HIV/AIDS individuals and the society at large.

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