Application of Optimal Control Strategies for the Spread of HIV in a Population

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ABSTRACT
This paper presents an application of optimal control theory to assess the effectiveness of control measures on the spread of HIV in a population. This paper formulates and analyzes a deterministic mathematical model with use of condom, screening and therapy as control variables using optimal control theory and Pontryagin’s Maximum Principle. It formulates the appropriate optimal control problem and investigate the necessary conditions for the disease control in order to determine the role of unaware infectives in the spread of HIV using of condom, screening of unaware infective and antiretroviral therapy are used as the control items. The optimality system is derived and solved numerically.

Keyword: Optimal control; HIV; unaware infective; Pontryagin’s maximum principle.

INTRODUCTION
HIV (Human Immunodeficiency) and AIDS (Acquired Immune Deficiency Syndrome) is one of the health problems. Currently, the development effectiveness of screening control and antiretroviral therapy have not been adequate despite increased coverage. Many aspects of the response is not yet known, for example, the phenomenon of the spread of the HIV epidemic. The number of cases of unaware infective very urgent and need to know the important parameters in the spread and develop optimal strategies and effective way to prevent and control the spread of HIV/AIDS.

Mathematical models have been used to help understand the transmission dynamics of HIV infections, for example Anderson (2001) presented a theoretical framework for transmission of HIV/AIDS with screening of unaware infectives. Modelling the effect of screening of unaware infectives and treatment on the spread of HIV infection (Tripathi et al., 2007 and Safiel et al., 2012). Marsudi et al. (2014, 2016) studied the impact of educational campaign, screening and HIV Therapy on the Dynamics of Spread of HIV. On the other hand, optimal control theory has been applied extensively in HIV model, for example Joshi et al. (2006) 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. Okosun et al. (2013) used optimal control approach to determine impact of screening of unaware infectives and treatment of HIV/AIDS.

The model we consider in this paper was developed from Marsudi et al. (2014) by adding the condom use control, the control on screening of unaware infectives and the control on antiretroviral therapy as a time dependent control parameters. Our objective functional balances the effect of minimizing the number of unaware infectives in the spread of HIV/AIDS and minimizing the cost of implementing the control.

The paper is organized as follows: In section two describes material and methods. Section three describes results and discussions that contains mathematical model, the optimal control problem and numerical
simulations. Finally, the conclusion are summarized in section four.

**MATERIAL AND METHODS**

This paper considers the HIV model used in Marsudi et al. (2014). The population (N) is divided into five subclass: susceptible individuals or HIV negative (S), unaware infective individuals or HIV positive who do not know they are infected (I1), screened infective individuals or HIV positive who know they are infected after a screening method (I2), therapy infective or HIV positive and accept HIV therapy after being screened (T), and AIDS patient or full blown AIDS (A). We assume that an individual can be infected only through the sexual contacts with third types of infective. This model is governed by the following nonlinear system of differential equations.

\[
\begin{align*}
\frac{dS}{dt} &= \lambda - \lambda S - \mu S \\
\frac{dI_1}{dt} &= \lambda S - (\theta + \sigma_1 + \mu)I_1 \\
\frac{dI_2}{dt} &= \theta I_1 - (\delta + \sigma_2 + \mu)I_2 \\
\frac{dT}{dt} &= \delta_2 - (\sigma + \mu)T \\
\frac{dA}{dt} &= \sigma I_1 + \sigma I_2 + \sigma T - (\gamma + \mu)A
\end{align*}
\]

Where:
\[
\lambda = \frac{c_1 \beta_1 I_1 + c_2 \beta_2 I_2 + c_3 \beta_3 T}{N}
\]

N = S + I_1 + I_2 + T + A.

The definitions of above model parameters are listed in Table 1.

The model considered in this paper is an improved model (1) by the inclusion of time dependent control parameters (use of condoms, screening of unaware infectives and antiretroviral therapy). This paper analyzed and applied optimal to the improved model to determine the impact of condom use, optimal screening of unaware infectives and antiretroviral therapy of HIV on the spread of HIV with the following steps:

1. Describing proposed model and we estimate the model stated initial conditions and parameter values.
2. Formulating an optimal control problem subject to the model dynamics, characterize the optimal controls, and constitute its optimality using Pontryagin’s Maximum Principle.
3. Solving the resulting optimality system numerically using a fourth order iterative Runge-Kutta scheme (forward-backward sweep method).

**RESULT AND DISCUSSION**

1. **Mathematical Model.**

This paper introduces into the model (1), condom use (u1), screening of unaware infectives (u2) and antiretroviral therapy (u3) as time dependent control to reduce the spread of HIV/AIDS. The model (1) becomes.

\[
\begin{align*}
\frac{dS}{dt} &= \lambda - (1-u_1)\lambda S - \mu S \\
\frac{dI_1}{dt} &= (1-u_1)\lambda S - (u_1\theta + \sigma_1 + \mu)I_1 \\
\frac{dI_2}{dt} &= u_1\theta I_1 - (u_2\delta + \sigma_2 + \mu)I_2 \\
\frac{dT}{dt} &= u_2\delta I_2 - (\sigma + \mu)T \\
\frac{dA}{dt} &= \sigma I_1 + \sigma I_2 + \sigma T - (\gamma + \mu)A
\end{align*}
\]

Where:
\[
S(0) = S_0, I_1(0) = I_{10}, I_2(0) = I_{20}, T(0) = T_0, A(0) = A_0
\]

are given. Here, the condom use control is bounded \((0 \leq u_1 \leq 1)\) the control on screening of unaware infective is bounded \((0 \leq u_2 \leq 1)\) and the control on antiretroviral therapy is bounded \((0 \leq u_3 \leq 1)\).

The description of parameters of HIV/AIDS model (2), together with the baseline values used in numerical analysis, are given in Table 1.
Table 1. Description of variables and parameters of HIV/AIDS model (2).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Description</th>
<th>Values</th>
<th>Sources</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\beta_1$</td>
<td>probability of susceptible individuals with unaware infectives</td>
<td>0.86</td>
<td>Safiel et al. [3]</td>
</tr>
<tr>
<td>$\beta_2$</td>
<td>probability of susceptible individuals with screened infectives</td>
<td>0.15</td>
<td>Tripathi et al. [1]</td>
</tr>
<tr>
<td>$\beta_3$</td>
<td>probability of susceptible individuals with therapy infectives</td>
<td>0.10</td>
<td>Safiel et al. [3]</td>
</tr>
<tr>
<td>$\theta$</td>
<td>rate of screening of unaware infectives</td>
<td>0.6</td>
<td></td>
</tr>
<tr>
<td>$\delta$</td>
<td>rate of therapy of infectives</td>
<td>0.99</td>
<td>Safiel et al. [3]</td>
</tr>
<tr>
<td>$\sigma_1$</td>
<td>the rate at which unaware infectives develop full blown AIDS</td>
<td>0.20</td>
<td>Safiel et al. [3]</td>
</tr>
<tr>
<td>$\sigma_2$</td>
<td>the rate at which screened infectives develop full blown AIDS</td>
<td>0.01</td>
<td>Safiel et al. [3]</td>
</tr>
<tr>
<td>$\sigma$</td>
<td>the rate at which therapy infectives develop full blown AIDS</td>
<td>0.001</td>
<td>Safiel et al. [3]</td>
</tr>
<tr>
<td>$\mu$</td>
<td>natural mortality rate</td>
<td>0.1</td>
<td>Safiel et al. [3]</td>
</tr>
<tr>
<td>$\gamma$</td>
<td>AIDS related death rate</td>
<td>1</td>
<td>Tripathi et al. [1]</td>
</tr>
<tr>
<td>$c_1$</td>
<td>average number of sexual partners per unit time for unaware infectives</td>
<td>3</td>
<td>Safiel et al. [3]</td>
</tr>
<tr>
<td>$c_2$</td>
<td>average number of sexual partners per unit time for screened infectives</td>
<td>2</td>
<td>Safiel et al. [3]</td>
</tr>
<tr>
<td>$c_3$</td>
<td>average number of sexual partners per unit time for therapy of infective</td>
<td>1</td>
<td>Safiel et al. [3]</td>
</tr>
<tr>
<td>$\Lambda$</td>
<td>the recruitment rate into the susceptible class</td>
<td>700</td>
<td>Assumed</td>
</tr>
</tbody>
</table>

2. The Optimal Control Problems

The problem is to minimize the number of unaware infectives and the cost of applying the control on the objective functional

$$J(u_1, u_2, u_3) = \min_{u_1, u_2, u_3} \int_0^T \left[ w_1 I_1 + \frac{1}{2} (w_2 u_1^2 + w_3 u_2^2 + w_4 u_3^2) \right] dt \quad (3)$$
subject to the system of equations (2) with appropriate state initial conditions, and \( t_f \) is the final time, while the control set \( U \) is defined as:

\[
U = \left\{ (u_1, u_2, u_3) \mid 0 \leq u_1 \leq 1, 0 \leq u_2 \leq 1, 0 \leq u_3 \leq 1 \text{ for } t \in t_f \right\}
\]

(4)

where \( w_1, w_2, w_3 \) and \( w_4 \) are positive weights. The weight constants, \( w_i \), is the relative measure of the importance of reducing the unaware infectives on the spread of HIV/AIDS, while \( w_2, w_3 \) and \( w_4 \) are the relative measures of the cost or effort required to implement each of the associated controls. Our target is to minimize the objective functional defined in equation (3) by minimizing the number of the unaware infectives. In other words, this paper was seeking optimal control triple \( u_1^*, u_2^* \) and \( u_3^* \) such that:

\[
J(u_1^*, u_2^*, u_3^*) = \min \{ J(u_1, u_2, u_3) \mid u_1, u_2, u_3 \in U \}
\]

(5)

Pontryagin’s Maximum Principle (Lenhart and Workman, 2007) provides necessary conditions for an optimal control problem. This principle converts (1), (3), and (5) into a problem of minimizing a Hamiltonian pointwisely with respect to \( u_1, u_2 \) and \( u_3 \)

\[
H = f(x,u,t) - \sum \lambda_i g_i(x,u,t)
\]

\[
= w_1 l_1 + \frac{1}{2} (w_2 u_1^2 + w_3 u_2^2 + w_4 u_3^2)
\]

\[
+ \lambda_3 \left[ \Lambda - (1 - u_1) \left( \frac{c_1 \beta_1 l_1 + c_2 \beta_2 l_2 + c_3 \beta_3 T S}{S + l_1 + l_2 + T + A} + \mu S \right) \right]
\]

\[
+ \lambda_i \left[ (1 - u_1) \frac{c_1 \beta_1 l_1 + c_2 \beta_2 l_2 + c_3 \beta_3 T S}{S + l_1 + l_2 + T + A} - (u_3 \theta + \sigma_1 + \mu) l_1 \right]
\]

\[
+ \lambda_i (u_3 \theta - (u_3 \sigma + \sigma_2 + \mu) l_2)
\]

\[
+ \lambda_i (\sigma_1 l_2 + \sigma_2 l_2 + \sigma T - (\gamma + \mu) A)
\]

where \( \lambda_3, \lambda_i, \lambda_\gamma, \lambda_\Sigma, \lambda_\eta \) and \( \lambda_\nu \) are adjoint (co-state) variables. By applying Pontryagin’s Maximum Principle and the existence result for the optimal control from (Fleming and Rishel, 1975), we obtain the following theorem.

**Theorem 1.** There exists an optimal control \( u_1^*, u_2^* \) and \( u_3^* \) and corresponding solution \( S^*(t), l_1^*(t), l_2^*(t), T^*(t) \) and \( A^*(t) \), that minimizes \( J(u_1, u_2, u_3) \) over \( u_1, u_2 \) and \( u_3 \). Then, there exists adjoint functions \( \lambda_3, \lambda_i, \lambda_\gamma, \lambda_\Sigma, \lambda_\eta \) and \( \lambda_\nu \) satisfying the equations:

\[
\frac{d\lambda_3}{dt} = \left( \lambda_3 - \lambda_i \right) \left[ \frac{(1-u_1)(c_1 \beta_1 l_1^* + c_2 \beta_2 l_2^* + c_3 \beta_3 T^*)}{S^* + l_1^* + l_2^* + T^* + A^*} - \frac{(1-u_1)(c_1 \beta_1 l_1^* + c_2 \beta_2 l_2^* + c_3 \beta_3 T^*)}{S^* + l_1^* + l_2^* + T^* + A^*} \right]
\]

\[
\frac{d\lambda_i}{dt} = -\mu \lambda_3
\]

\[
\frac{d\lambda_i}{dt} = \left( \lambda_3 - \lambda_i \right) \left[ \frac{(1-u_1)(c_1 \beta_1 S^* + c_2 \beta_2 l_2^* + c_3 \beta_3 T^*)}{S^* + l_1^* + l_2^* + T^* + A^*} - \frac{(1-u_1)(c_1 \beta_1 l_1^* + c_2 \beta_2 l_2^* + c_3 \beta_3 T^*)}{S^* + l_1^* + l_2^* + T^* + A^*} \right]
\]

(7)
\begin{align*}
\frac{d\lambda_i}{dt} &= (\lambda_i - \lambda_i) \left[ \frac{(1-u_i)c_i \beta_i S^*}{S^* + I^*_i + I^*_2 + T^* + A} - \frac{(1-u_i)(c_i \beta_i l^*_i + c_2 \beta_2 l^*_2 + c_3 \beta_3 T^*)S^*}{(S^* + I^*_1 + I^*_2 + T^* + A)^2} \right] \\
&\quad + (\lambda_i - \lambda_i) u_2 \theta + (\lambda_i - \lambda_i) \sigma_1 \lambda_i + \lambda_i \mu_i, \\
\frac{d\lambda_t}{dt} &= (\lambda_t - \lambda_t) \left[ \frac{(1-u_t)c_t \beta_t S^*}{S^* + I^*_1 + I^*_2 + T^* + A} - \frac{(1-u_t)(c_t \beta_t l^*_1 + c_2 \beta_2 l^*_2 + c_3 \beta_3 T^*)S^*}{(S^* + I^*_1 + I^*_2 + T^* + A)^2} \right] \\
&\quad + (\lambda_t - \lambda_t) \sigma + \lambda_t \mu_t, \\
\frac{d\lambda_s}{dt} &= (\lambda_s - \lambda_s) \left[ \frac{(1-u_s)c_s \beta_s S^*}{S^* + I^*_1 + I^*_2 + T^* + A} - \frac{(1-u_s)(c_s \beta_s l^*_1 + c_2 \beta_2 l^*_2 + c_3 \beta_3 T^*)S^*}{(S^* + I^*_1 + I^*_2 + T^* + A)^2} \right] + \lambda_s (\gamma + \mu).
\end{align*}

and transversality conditions:
\begin{equation}
\lambda_i (t_f) = \lambda_i (t_f) = \lambda_t (t_f) = \lambda_s (t_f) = 0.
\end{equation}

with the optimal control is given by
\begin{align*}
\hat{u}_1 &= \max \left\{ 0, \min \left\{ \frac{\lambda_i - \lambda_s}{w_1 (S^* + I^*_1 + I^*_2 + T^* + A)} \right\} \right\}, \\
\hat{u}_2 &= \max \left\{ 0, \min \left\{ \frac{\lambda_t - \lambda_t}{w_2 (S^* + I^*_1 + I^*_2 + T^* + A)} \right\} \right\}, \\
\hat{u}_3 &= \max \left\{ 0, \min \left\{ \frac{\lambda_s - \lambda_s}{w_3 (S^* + I^*_1 + I^*_2 + T^* + A)} \right\} \right\}.
\end{align*}

\textbf{Proof.}

Due to the convexity of integrand of $J(u_1,u_2,u_3)$ with respect to $u_1,u_2$ and $u_3$, a priori boundedness of the state solutions, and the Lipschitz property of the state system with the respect to the state variables. The existence of an optimal control has been given by Fleming and Rishel (1975). The adjoint equations and transversality conditions can be obtained by using Pontryagin’s Maximum Principle such that:
\begin{align*}
\frac{d\lambda_x}{dt} &= -\frac{\partial H}{\partial S}, \quad \lambda_x (t_f) = 0, \\
\frac{d\lambda_i}{dt} &= -\frac{\partial H}{\partial l_i}, \quad \lambda_i (t_f) = 0, \\
\frac{d\lambda_t}{dt} &= -\frac{\partial H}{\partial l_t}, \quad \lambda_t (t_f) = 0, \\
\frac{d\lambda_s}{dt} &= -\frac{\partial H}{\partial l_s}, \quad \lambda_s (t_f) = 0, \\
\frac{d\lambda_x}{dt} &= -\frac{\partial H}{\partial T}, \quad \lambda_x (t_f) = 0, \\
\frac{d\lambda_i}{dt} &= -\frac{\partial H}{\partial A}, \quad \lambda_i (t_f) = 0.
\end{align*}
The Hamiltonian is maximized with respect to the controls at the optimal control \( u^* = (u_1^*, u_2^*, u_3^*) \), thus we differentiate \( H \) with respect to \( u_1, u_2 \) and \( u_3 \) on \( U \), respectively, to obtain:

\[
\frac{\partial H}{\partial u_1} = w_1 u_1 + (\lambda - \lambda_1) \left[ \frac{(c_1 + c_2 l_1 + c_3 l_1) S}{S + l_1 + l_2 + T + A} \right] = 0 \quad \text{at } u_1 = u_1^*,
\]
\[
\frac{\partial H}{\partial u_2} = w_2 u_2 + (\lambda - \lambda_2) \theta l_1 = 0 \quad \text{at } u_2 = u_2^*,
\]
\[
\frac{\partial H}{\partial u_3} = w_3 u_3 + (\lambda - \lambda_3) \delta l_2 = 0 \quad \text{at } u_3 = u_3^*.
\]

Hence, solving for \( u_1^*, u_2^* \) and \( u_3^* \) on the interior sets gives:

\[
u_1^* = \max \left\{ 0, \min \left[ 1, \frac{(\lambda - \lambda_1)(c_2 l_1 + c_2 l_2 + c_3 l_2) S^*}{w_2 (S^* + l_1^* + l_2^* + T^* + A^*)} \right] \right\}
\]
\[
u_2^* = \max \left\{ 0, \min \left[ 1, \frac{(\lambda - \lambda_2) l_1^*}{w_3} \right] \right\}
\]
\[
u_3^* = \max \left\{ 0, \min \left[ 1, \frac{(\lambda - \lambda_3) l_2^*}{w_4} \right] \right\}.
\]


The optimal control system thus, is a coupled forward state equation and a backward adjoint equation, along with the regular control. This problem, being nonlinear and coupled in nature, needs to be solved using concurrent and iterative numerical procedures. In this paper, the optimal strategy is simulated by solving the state and adjoint systems and the transversality conditions based on Runge-Kutta fourth order 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 (12). This computational procedure is done iteratively until a convergence is attained. Details on the forward-backward sweep procedure are given in Lenhart and Workman (2007).

The numerical simulations are carried out using Matlab. The parameter values we used are given in Table 1. The cost coefficients \( w_1=200, w_2=35, w_3=55, \) and \( w_4=75 \) and the initial conditions is taken to be \( S(0)=25.000.000, I_1(0)=200.000, I_2(0)=25.000, T(0)=5000, \) and \( A(0)=2000 \). Using model parameter values shown in Table 1 is obtained the effective reproduction numbers, \( R_{ef} = 3.1035 \). Because \( R_{ef} > 1 \), the HIV infection will persist in population.

Figure 1 (a)-(b) shows the comparison between the numbers of unaware infectives \( (I_1) \) with and without control. In Figure 1 (a), we observe that in presence of control efforts on condom use \( (u_1) \), screening of unaware infectives \( (u_2) \) and the antiretroviral therapy \( (u_3) \) results in a significant decrease in the number of unaware infectives compared with the case without control. The numbers of unaware infectives initially increases rapidly then reaches the maximum number of \( I_1 \) would be \( 6.737x10^5 \) \((t=4.4)\) in the case without control and \( 2408 \) \((t=0)\) with control (Figure 1(b)). From the point of maximum value is then starts to decreases then reaches at the final
time $t_f = 20$ (years) is 716.6 in the case without control and $7.04 \times 10^{-7}$ with control. It is nearly 99.99% of the effectiveness of the combinations of the strategies in the control HIV.

$7 \times 10^5$ (a)

Unaware Infective

0 1 2 3 4 5
0 5 10 15 20

with control

without control

Time

Figure 1. The comparison between the number of unaware infectives with and without control.

Similarly, the comparison between the numbers of AIDS patient ($A$) with and without control is shown in Figure 2. From Figure 2, we know that the optimal control can make the AIDS patient far more than that without control, which show that the HIV has been effectively controlled based on our optimal control strategy. The numbers of unaware infectives initially increases rapidly then reaches the maximum number of $A$ is $4.059 \times 10^5$ ($t = 5.1$) in the case without control and $1130$ ($t = 0.3$) with control (Figure 2b). It reaches 531 at the end of this control against 1.835 in the absence of control, i.e. a reduction of 529.165 cases.

Finally, the control profile of the combination of the three kinds of the control strategies is shown in Figure 3. The control of condom use ($u_1$) is at the upper bound till the final time (Figure 3-a), the screening control ($u_2$) never reached the upper limit dropped gradually from the upper bound to the lower bound after $t = 5.5$ (Figure 3-b) and the antiretroviral therapy control ($u_3$) is at $1.455 \times 10^{-11}$ at the beginning of the period then increases rapidly reaches the maximum at $4.366 \times 10^{-11}$ and then decreases gradually while oscillating up to $9.095 \times 10^{-13}$ and to zero at the final time.

$5 \times 10^5$ (a)

AIDS Patient

0 1 2 3 4 5
0 5 10 15 20

with control

without control

Time

Figure 2. The comparison between the number of HIV patient with and without control.
CONCLUSION

This paper presented a deterministic model for controlling the impact of condom use, screening of unaware infectives and antiretroviral therapy of HIV on the spread of HIV in a population. It formulates an optimal control problem subject to the model dynamics, investigates the necessary conditions for the disease control in order to determine the role of unaware infectives in the spread of HIV and proves the uniqueness of the optimal control using Pontryagin’s Maximum Principle.

The numerical simulations of both the systems i.e. with control and without control, shows that this strategy helps to reduce the number of unaware infectives and the number of AIDS patient greatly. The results obtained shows also that the effectiveness of the combinations of condom use, screening of unaware infectives and antiretroviral therapy in the control HIV can reach 99.99%.

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