

Original Research Article

Cost Effective Analysis on Mathematical Modelling of HIV/AIDS with Optimal Control Strategy

Abstract

In this paper, a deterministic model of Human Immunodeficiency Virus has been formulated to describe the transmission dynamics of the disease. The well posedness of the model equations was proved and the equilibrium points of the model have been identified. Both local and global stability of the disease free equilibrium and endemic equilibrium point of the model equation was established using basic reproduction number. The results show that if the basic reproduction is less than one then the solution converges to the disease free steady state and the disease free equilibrium is locally asymptotically stable. On the other hand, if the basic reproduction number is greater than one then the solution converges to endemic equilibrium point and the endemic equilibrium is locally asymptotically stable. Also, sensitivity analysis of the model equation was performed on the key parameters to find out their relative significance and potential impact on the transmission dynamics of Human Immunodeficiency Virus. The results of simulation show that treatment minimizes the risk of Human Immunodeficiency Virus transmission from the community and the stability of disease free equilibrium is achievable when basic reproduction is less one. The findings from the analysis of cost-effectiveness revealed that a combination of prevention and screening are the most effective strategy to eradicate the disease from the community.

Keywords: Model, Stability, Optimal control, Simulation.

1. Introduction

Human Immunodeficiency Virus is the causative agent of Acquired Immunodeficiency Syndrome [1]. The target cell of HIV is the CD4 T cells. A healthy human body has about $1000/\text{mm}^3$ CD4 T cells. When the CD4 T cells of the patient decrease to $200 / \text{mm}^3$ or less, this person is classified as AIDS [2]. When CD4 T cells are dwindling, they cannot give a strong response. This translates into low responses of CTLs and antibodies that cannot remove infection

[3].HIV is mainly transmitted by unprotected sex with an infected person, through the exchange of infected blood or blood products, or to the newborn from an infected mother. However, antiretroviral treatment (art) improves health, prolongs life and significantly reduces the risk of HIV transmission. More than 90% of sub-Saharan Africa acquires HIV infection of unprotected sexual relationship with infected partners [4].

According to updated statistics on the state of the epidemic from UNAIDS, 36.9 million people, globally, were living with HIV in 2017, of which 21.7 million people had access to antiretroviral treatment (antiretroviral therapy) and 1.8 million people were newly infected with HIV in 2017. A total of 77.3 million people have been infected with HIV since the epidemic began in 1981. The numbers of death indicate that 940,000 people died of diseases serving in 2017, with a total of 4 million people deceased for AIDS-related illnesses from the beginning of the epidemic [5].

Several mathematical models have played a major role in increasing our understanding of the dynamics of sexually transmitted diseases. Several models have been proposed to study the effects of some factors on the transmission dynamics of these sexually transmitted diseases, including HIV/AIDS, and to provide guidelines on how to control their spread. Among these models Anderson et al [6] presented a simple mathematical HIV transmission model study the effects of various factors on the general evolution of the AIDS epidemic. Stilianakis et al [7] who proposed and provided a detailed analysis of a dynamic model describing the pathogenesis of HIV, and Tripathiet al [8] who proposed a model to study the effects of screening of unaware infective on the transmission dynamics of HIV/AIDS. K.O.Okosun [9] presented the impact of optimal control on the treatment of HIV/AIDS and screening of unaware infective on the transmission dynamics of disease in a homogeneous population with a constant immigration of susceptible individuals integrating the use of condoms, the screening of unconscious infected persons and the treatment of infected persons. In [10] a mathematical model for the transmission of HIV/AIDS was proposed, as well as a control problem in which the aim was to determine the pre-exposure prophylaxis (PrEP) strategy that minimizes the number of individuals with pre-AIDS HIV infection, balanced against the costs associated with PrEP. The paper by Mukandavire et al [11] compares the impact of increasing condom use or HIV PrEP use among sex workers. The authors found that condom promotion interventions should remain the mainstay HIV prevention strategy for female sex workers (FSWs), with PrEP only being

implemented once condom interventions have been maximized or to fill prevention gaps where condoms cannot be used. In [12], the authors develop a model of HIV risk and compare HIV-risk estimates before and after the introduction of PrEP to determine the maximum tolerated reductions in condom use with regular partners and clients for HIV risk not to change. With a case study of FSWs in South Africa, in [12] it is found that PrEP is likely to be of benefit in reducing HIV risk, even if reductions in condom use do occur.

However, few mathematical studies have been undertaken to model Human Immunodeficiency Virus mathematically, but they did not considered protected compartment in their studies.

2. Model Description and Formulation

The model divides the total population into six subclasses with respect to their disease status in the system. Protected individuals $P(t)$, is the class of individuals which are protected against the disease over a period of time. Susceptible individuals $S(t)$, is the class of individuals who are healthy but can contract the disease. Exposed individuals $E(t)$, is the class of individuals which are infected but not yet infectious. Asymptomatic individuals $A_s(t)$, is the class of an infectious without symptoms of disease. Infectious individuals $I(t)$, is the class of an infectious with symptoms of disease and individuals with AIDS $D(t)$, is the class of individuals with AIDS.

The model assumes that a fraction of the population has been protected before the disease outbreak at rate of $\theta\Pi$ and $(1 - \theta)\Pi$ fraction of population susceptible. The susceptible class is increased from protected class by losing protection with φ rate. Susceptible individuals are exposed to HIV infection with force of infection $\lambda = \frac{\beta(I+qA)}{N}$ where β is contact rate and q is transmission coefficient for the asymptomatic. If $q > 1$ then, the asymptomatic infect susceptible more likely than infective. If $q = 1$, then both asymptomatic and infective have equal chance to infect the susceptible, but if $q < 1$ then, the infective have good chance to infect susceptible than asymptomatic. Exposed individuals progress to infectious class with probability $p\eta$ and to the asymptomatic infectious class with probability $(1 - p)\eta$, where η is the per capita rate of becoming infectious. The asymptomatic individuals can develop disease symptom or can screen them selves and join the infectious class with a rate ϕ and others join the AIDS class with rate γ . Individuals in infectious class join the AIDS class with rate α . All infected individuals ξ is the

disease induced mortality rate due to infection. Also, in all class μ is the natural mortality rate of individuals and all parameters in the model are positive.

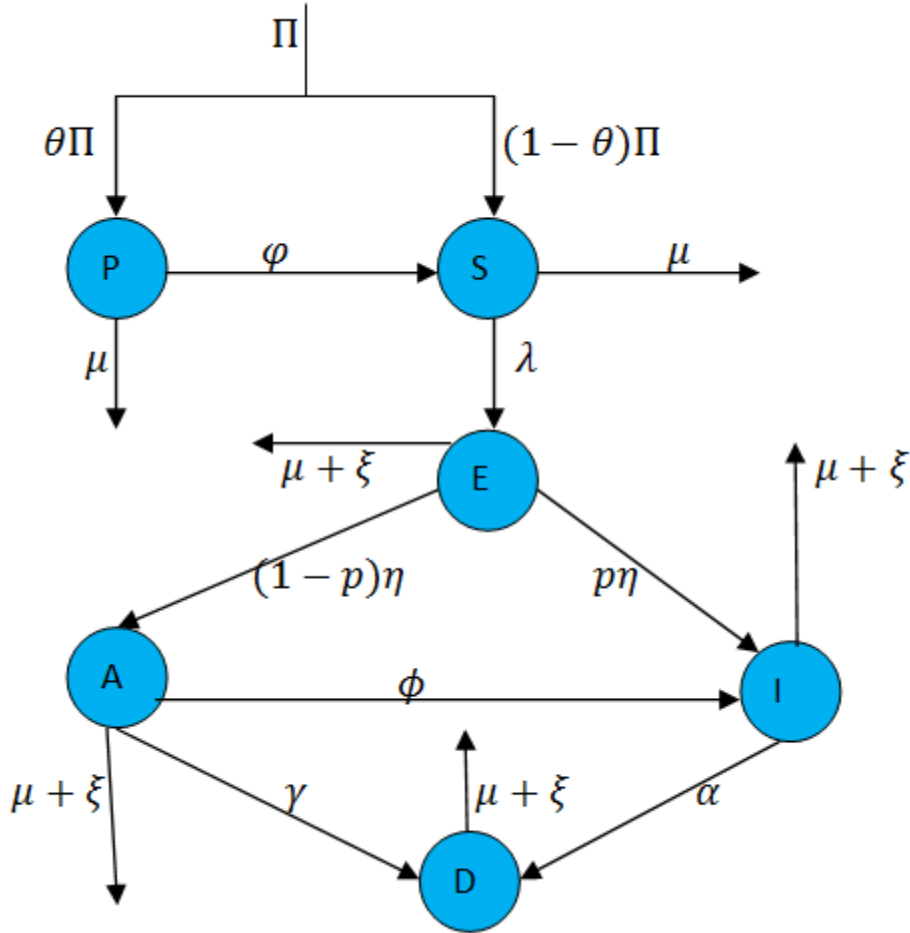


Figure 1: Schematic diagram of HIV/AIDS model.

Based on the model assumptions and the schematic diagram, the model equations are formulated and given as follows:

$$\begin{cases} \frac{dP(t)}{dt} = \theta\Pi - (\varphi + \mu)P \\ \frac{dS(t)}{dt} = (1 - \theta)\Pi + \varphi P - (\lambda + \mu)S \\ \frac{dE(t)}{dt} = \lambda S - (\eta + \mu + \xi)E \\ \frac{dA(t)}{dt} = (1 - p)\eta E - (\phi + \gamma + \mu + \xi)A \\ \frac{dI(t)}{dt} = p\eta E + \phi A - (\alpha + \mu + \xi)I \\ \frac{dD(t)}{dt} = \gamma A + \alpha I - (\mu + \xi)D \end{cases} \quad (1)$$

With initial condition $P(0) = P_0, S(0) = S_0, E(0) = E_0, A(0) = A_0, I(0) = I_0, D(0) = D_0$.

3. Mathematical Analysis of the Model

3.1 Invariant Region

In the model equation 1 that governs human population, all the variables and parameters used in the model equation are non-negative. We consider a biologically-feasible region $\{\Omega = \{(P, S, E, A, I, D) \in \mathbb{R}_+^6 : N \leq \frac{\Pi}{\mu}\}$.

We adhere to the following steps to show the positive invariance of Ω , that is all the solution of model equation 1 that initiate in Ω remains in the region Ω and is bounded in Ω . We have the total population

$$N(t) = P(t) + S(t) + E(t) + A(t) + I(t) + D(t)$$

The rate of change of the total population by adding all the equations considered in model equation 1 is given by

$$\frac{dN}{dt} = \Pi - \mu N - \xi(E(t) + A(t) + I(t) + D(t))$$

In the absence of mortality due to disease it becomes

$$\frac{dN}{dt} \leq \Pi - \mu N$$

Thus, the particular solution can be expressed as

$$0 \leq N(t) \leq \frac{\Pi}{\mu} + (N_0 - \frac{\Pi}{\mu})e^{-\mu t} \quad (2)$$

As $t \rightarrow \infty$ in equation (2), the population size $N \rightarrow \frac{\Pi}{\mu}$ which implies that $0 \leq N \leq \frac{\Pi}{\mu}$.

Thus the feasible solution set of the model equation remain in the the region

$$\Omega = \{(P, S, E, A, I, D) \in \mathbb{R}_+^6 : N \leq \frac{\Pi}{\mu}\}.$$

Therefore, the basic model is wellposed epidemiologically and mathematically. Hence, it is sufficient to study the dynamics of the basic model in region Ω .

3.2 Existence and Uniqueness of the Solutions of the Model

The validity and authenticity of any mathematical model depends on whether the given system of equations has a solution, and if the solution exists then it is unique. We shall use the Lipchitz condition to verify the existence and uniqueness of solution for the system of equation 1.

Theorem 1 Let Ω denote th region $1 \leq \alpha \leq \mathbb{R}$. Then the model equations (1) together with the initial conditions $P(0) > 0, S(0) > 0, E(0) \geq 0, A(t)(0) \geq 0, I(t)(0) \geq 0, D(t)(0) \geq 0$ exist in \mathbb{R}_+^6 and has a unique solution. i.e., the model variables $P(t), S(t), E(t), A(t), I(t)$ and $D(t)$ exist for all t and will remain in \mathbb{R}_+^6 .

Proof : We have to show that $\frac{\partial f_i}{\partial x_j}, i, j = 1, 2, 3, 4, 5, 6$ are continues and bounded in Ω . Let the right

hand side of the system of equation (1) can be expressed as follows:

$$\begin{cases} f_1(P, S, E, A, I, D) = \theta\Pi - (\varphi + \mu)P \\ f_2(P, S, E, A, I, D) = (1 - \theta)\Pi + \varphi P - (\lambda + \mu)S \\ f_3(P, S, E, A, I, D) = \lambda S - (\eta + \mu + \xi)E \\ f_4(P, S, E, A, I, D) = (1 - p)\eta E - (\phi + \gamma + \mu + \xi)A \\ f_5(P, S, E, A, I, D) = p\eta E + \phi A - (\alpha + \mu + \xi)I \\ f_6(P, S, E, A, I, D) = \gamma A + \alpha I - (\mu + \xi)D \end{cases} \quad (3)$$

According to Derrick and Groosman theorem, let Ω denote the region $\Omega = (P, S, E, A, I, D) \in \mathbb{R}_+^6; N \leq (\Pi/\mu)$. Then equations (1) have a unique solution if $(\partial f_i)/(\partial x_j), i, j = 1, 2, 3, 4, 5, 6$ are continuous and bounded in Ω . Here, $x_1 = P, x_2 = S, x_3 = E, x_4 = A, x_5 = I, x_6 = D$ and $\lambda = \frac{\beta}{N}(I + qA)$.

3.3. Positivity of the solution of the model

In this section we aim to obtain the non negative solution when dealing with human populations. Therefore, the next discussion below targets on the conditions under which the model being studied has a non negative solution.

Theorem 2. Let $\Omega = \{(P, S, E, A, I, D) \in \mathbb{R}_+^6: P_0 > 0, S_0 > 0, E_0 \geq 0, A_0 \geq 0, I_0 \geq 0, D_0 \geq 0.\}$ then the solution of $\{P, S, E, A, I, D\}$ are positive for all $t \geq 0$.

Proof: From the system of differential equation(1),

let us take the first equation such that.

$$\frac{dP}{dt} = \theta\Pi - (\varphi + \mu)P, \text{ eliminating the positive terms } \theta\Pi \text{ we get}$$

$$\frac{dP}{dt} \geq -(\varphi + \mu)P, \text{ using variables separable method we get,}$$

$$\frac{dP}{P} \geq -(\varphi + \mu)dt \text{ integrating both side we can get,}$$

$$\int \frac{dP}{P} \geq -\int (\varphi + \mu)dt \text{ we obtain:}$$

$$\ln(S) \geq -(\varphi + \mu)t + \ln(C) \text{ where } \ln(C) \text{ is any arbitrary constant.}$$

Then after solving for P we obtain:

$$P(t) \geq P e^{-(\varphi + \mu)t}.$$

Recall that an exponential function is always non-negative irrespective of the sign of the exponent, i.e., the exponential function $e^{-(\varphi + \mu)t}$ is a non-negative quantity. Hence, it can be concluded that $S(t) > C e^{-(\varphi + \mu)t} \geq 0$.

Therefore $P(t) > 0$ for all $t \geq 0$.

From the system of differential equation(1),

let us take the second equation such that.

$$\frac{dS}{dt} = (1 - \theta)\Pi + \varphi P - (\lambda + \mu)S, \text{ eliminating the positive terms } (1 - \theta)\Pi + \varphi P \text{ we get}$$

$$\frac{dS}{dt} \geq -(\lambda + \mu)S, \text{ using variables separable method we get,}$$

$$\frac{dS}{S} \geq -(\lambda + \mu)dt \text{ integrating both side we can get,}$$

$$\int \frac{dS}{S} \geq - \int (\lambda + \mu)dt \text{ we obtain:}$$

$$\ln(S) \geq -(\lambda + \mu)t + \ln(C) \text{ where } \ln(C) \text{ is any arbitrary constant.}$$

Then after solving for S we obtain:

$$S(t) \geq C e^{-(\lambda+\mu)t}.$$

Recall that an exponential function is always non-negative irrespective of the sign of the exponent, i.e., the exponential function $e^{-(\lambda+\mu)t}$ is a non-negative quantity. Hence, it can be concluded that $S(t) > C e^{-(\lambda+\mu)t} \geq 0$.

Therefore $S(t) > 0$ for all $t \geq 0$.

From the system of differential equation 1, let us take the third equation such that:

$$\frac{dE}{dt} = \lambda S - (\eta + \mu + \xi)E, \text{ eliminating the positive terms } \lambda S \text{ we get}$$

$$\frac{dE}{dt} \geq -(\eta + \mu + \xi)E \text{ using variables separable method we get,}$$

$$\frac{dE}{E} \geq -(\eta + \mu + \xi)dt \text{ integrating both side we can get,}$$

$$\int \frac{dE}{E} \geq - \int (\eta + \mu + \xi)dt \text{ we obtain:}$$

$$\ln(E) \geq -(\eta + \mu + \xi)t + \ln(C) \text{ where } \ln(C) \text{ is any arbitrary constant.}$$

Then after solving for E we obtain:

$$E(t) \geq C e^{-(\eta+\mu+\xi)t}.$$

Recall that an exponential function is always non-negative irrespective of the sign of the exponent, i.e., the exponential function $e^{-(\eta+\mu+\xi)t}$ is a non-negative quantity. Hence, it can be concluded that $E(t) > C e^{-(\eta+\mu+\xi)t} \geq 0$.

Therefore $E(t) \geq 0$ for all $t \geq 0$.

From the system of differential equation(1), let us take the fourth equation such that:

$$\frac{dA}{dt} = (1 - p)\eta E - (\phi + \gamma + \mu + \xi)A, \text{ eliminating the positive terms } (1 - p)\eta E \text{ we get}$$

, $\frac{dA}{dt} \geq -(\phi + \gamma + \mu + \xi)A$ using variables separable method we get,

$\frac{dA}{A} \geq -(\phi + \gamma + \mu + \xi)dt$ integrating both side we can get,

$\int \frac{dA}{A} \geq -\int (\phi + \gamma + \mu + \xi)dt$ we obtain:

$\ln(A) \geq -(\phi + \gamma + \mu + \xi)t + \ln(C)$ where $\ln(C)$ is any arbitrary constant.

Then after solving for A we obtain:

$$A(t) \geq Ce^{-(\phi+\gamma+\mu+\xi)t}.$$

Recall that an exponential function is always non-negative irrespective of the sign of the exponent, i.e., the exponential function $e^{-(\phi+\gamma+\mu+\xi)t}$ is a non-negative quantity. Hence, it can be concluded that $A(t) \geq Ce^{-(\phi+\gamma+\mu+\xi)t} \geq 0$.

Therefore $A(t) \geq 0$ for all $t \geq 0$.

From the system of differential equation(1), let us take the fifth equation such that:

$\frac{dI}{dt} = p\eta E + \phi A - (\alpha + \mu + \xi)I$, eliminating the positive terms $p\eta E + \phi A$ we get

, $\frac{dI}{dt} \geq -(\alpha + \mu + \xi)I$ using variables separable method we get,

$\frac{dI}{I} \geq -(\alpha + \mu + \xi)dt$ integrating both side we can get,

$\int \frac{dI}{I} \geq -\int (\alpha + \mu + \xi)dt$ we obtain:

$\ln(I) \geq -(\alpha + \mu + \xi)t + \ln(C)$ where $\ln(C)$ is any arbitrary constant.

Then after solving for I we obtain:

$$I(t) \geq Ce^{-(\alpha+\mu+\xi)t}.$$

Recall that an exponential function is always non-negative irrespective of the sign of the exponent, i.e., the exponential function $e^{-(\alpha+\mu+\xi)t}$ is a non-negative quantity. Hence, it can be concluded that $I(t) \geq Ce^{-(\alpha+\mu+\xi)t} \geq 0$.

Therefore $I(t) \geq 0$ for all $t \geq 0$

From the system of differential equation 1, let us take the sixth equation such that:

$\frac{dD}{dt} = \gamma A + \alpha I - (\mu + \xi)D$, eliminating the positive terms $\gamma A + \alpha I$ we get

, $\frac{dD}{dt} \geq -(\mu + \xi)D$ using variables separable method we get,

$\frac{dD}{D} \geq -(\mu + \xi)dt$ integrating both side we can get,

$\int \frac{dD}{D} \geq -\int (\mu + \xi)dt$ we obtain:

$\ln(D) \geq -(\mu + \xi)t + \ln(C)$ where $\ln(C)$ is any arbitrary constant.

Then after solving for D we obtain:

$$D(t) \geq Ce^{-(\mu+\xi)t}.$$

Recall that an exponential function is always non-negative irrespective of the sign of the exponent, i.e., the exponential function $e^{-(\mu+\xi)t}$ is a non-negative quantity. Hence, it can be concluded that $D(t) \geq Ce^{-(\mu+\xi)t} \geq 0$.

Therefore $D(t) \geq 0$ for all $t \geq 0$.

3.4. Disease Free Equilibrium Points (DFE)

Disease free equilibrium points are steady state solutions where there is no disease in the population. In the absence of disease in the population, implies that $E(t) = 0, A(t) = 0, I(t) = 0$ and $D(t) = 0$ and the equilibrium points require that the right hand side of the model equation set equal to zero. We denote disease-free equilibrium point by E_1 .

These requirements reflect in reducing the model equations(1) as

$$\begin{cases} \theta\Pi - (\varphi + \mu)P = 0 \\ (1 - \theta)\Pi + \varphi P - (\lambda + \mu)S = 0 \\ \lambda S - (\eta + \mu + \xi)E = 0 \\ (1 - p)\eta E - (\phi + \gamma + \mu + \xi)A = 0 \\ p\eta E + \phi A - (\alpha + \mu + \xi)I = 0 \\ \gamma A + \alpha I - (\mu + \xi)D = 0 \end{cases} \quad (4)$$

Then solving the system of differential equation 4 simultaneously, we obtain

$$E_0 = \{P^0, S^0, E^0, A^0, I^0, D^0\} = \left\{ \frac{\theta\Pi}{(\varphi+\mu)}, \frac{\Pi(\varphi+\mu-\theta)}{(\varphi+\mu)(\lambda+\mu)}, 0, 0, 0, 0 \right\}.$$

3.5. The Basic Reproduction Number (R_0)

The basic reproduction number denoted by R_0 is the average number of secondary infections caused by an infected individual throughout its period of infectivity (Diekmann et. al) [13]. The basic reproduction number is an important dimensionless quantity in epidemiology because it sets the threshold in the study of disease both for predicting its outbreak and for evaluating its control strategies [13]. Therefore, the persistence or disappearance of a disease in a community depends on the value of the reproduction number, R_0 . In addition, the stability of the scale point can be analyzed using R_0 . If $R_0 > 1$ every infectious individual will cause more than one secondary infection and hence the disease will invade the population. Obtained by taking the

largest (dominant) eigenvalue (spectral radius)

$$R_0 = \left[\frac{\partial F_i(E_0)}{\partial x_j} \right] \left[\frac{\partial V_i(x_0)}{\partial x_j} \right]^{-1}$$

where f_i be the rate of appearance of new criminal in compartments, v_i is the transfer of individuals out of the compartment by another means, E_0 is the disease free equilibrium point. We compute the basic reproduction number using the next generation matrix approach.

Thus the associated matrices F and V for the new infectious terms and the remaining transition terms are respectively given by:

$$F_i = \begin{bmatrix} \frac{\beta(I+qA)S}{N} \\ 0 \\ 0 \\ 0 \end{bmatrix}, V_i = \begin{bmatrix} (\eta + \mu + \xi)E \\ -(1-p)\eta E + (\phi + \gamma + \mu + \xi)A \\ -p\eta E - \phi A + (\alpha + \mu + \xi)I - \gamma A - \alpha I + (\mu + \xi)D \end{bmatrix}$$

Thus the jacobian matrix of F and V at the disease free equilibrium point E_0 takes the form respectively as:

$$F(E_0) = \begin{bmatrix} 0 & \beta q & \beta & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{bmatrix} \text{ and}$$

$$V(E_0) = \begin{bmatrix} a & 0 & 0 & 0 \\ -(1-p)\eta & b & 0 & 0 \\ -p\eta & -\phi & c & 0 \\ 0 & -\gamma & -\alpha & d \end{bmatrix}$$

where $a = \eta + \mu + \xi$, $b = \phi + \gamma + \mu + \xi$, $c = \alpha + \mu + \xi$, $d = \mu + \xi$.

It can be verified that that the matrix $V(E_0)$ is non-singular as its determinant $\det(V(E_0)) = abcd \neq 0$ is non-zero. That is $V(E_0) \neq 0$ then it is invertable and the inverse is given by .

$$(V(E_0))^{-1} = \frac{Adj(V)}{\det(V)} \quad (5)$$

Then after some algebraic computations the inverse matrix is constructed as follows:

$$[V(E_0)]^{-1} = \begin{bmatrix} \frac{1}{a} & 0 & 0 & 0 \\ \frac{(1-p)\eta}{ab} & \frac{1}{b} & 0 & 0 \\ \frac{(1-p)\eta + bp\eta}{abc} & \frac{-\phi}{bc} & \frac{1}{c} & 0 \\ \frac{(1-p)\eta(\phi\alpha + \gamma c) - b\alpha p\eta}{abcd} & \frac{\phi\alpha + c\gamma}{bcd} & \frac{\alpha}{cd} & \frac{1}{d} \end{bmatrix} \quad (6)$$

Now,

$$[F(E_0)][V(E_0)]^{-1} = \begin{bmatrix} \frac{\beta\eta q(1-p)(cq+1) + \beta bq\eta}{abc} & \frac{\beta q}{b} - \frac{\beta\phi}{bc} & \frac{\beta}{c} & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{bmatrix} \quad (7)$$

Thus the eigenvalues of the matrix in equation (7) are: $\lambda_1 = \frac{\beta\eta q(1-p)(cq+1) + \beta bq\eta}{abc}$, $\lambda_2 = 0$, $\lambda_3 = 0$, $\lambda_4 = 0$. Then from $\lambda_1, \lambda_2, \lambda_3, \lambda_4$ the dominant eigenvalue is $\lambda_1 = \frac{\beta\eta q(1-p)(cq+\phi) + \beta bq\eta}{abc}$.

Therefore the basic reproduction number is given by

$$R_0 = \frac{\beta\eta q(1-p)(cq+\phi) + \beta bq\eta}{abc}.$$

3.6. Local Stability of Disease Free Equilibrium Points (DFE)

Theorem 3: The DFE E_0 of the system (1) is locally asymptotically stable if $R_0 < 1$ and unstable if $R_0 > 1$.

Proof Consider the right hand side expressions of the equations (1) as functions so as to find the Jacobian matrix as follows:

Thus, the Jacobian matrix J of model at the disease free equilibrium E_0 is given by

$$J(E_0) = \begin{bmatrix} -(\varphi + \mu) & 0 & 0 & 0 & 0 & 0 \\ \varphi & -\mu & 0 & -\beta q & -\beta & 0 \\ 0 & 0 & -a & \beta q & \beta & 0 \\ 0 & 0 & (1-p)\eta & -b & 0 & 0 \\ 0 & 0 & p\eta & \phi & -c & 0 \\ 0 & 0 & 0 & \gamma & \alpha & -d \end{bmatrix} \quad (8)$$

The eigenvalues of the jacobian matrix $J(E_0)$ are required to be found as follows.

$$\begin{vmatrix} -(\varphi + \mu) - \lambda & 0 & 0 & 0 & 0 & 0 \\ \varphi & -\mu - \lambda & 0 & -\beta q & -\beta & 0 \\ 0 & 0 & -a - \lambda & \beta q & \beta & 0 \\ 0 & 0 & (1-p)\eta & -b - \lambda & 0 & 0 \\ 0 & 0 & p\eta & \phi & -c - \lambda & 0 \\ 0 & 0 & 0 & \gamma & \alpha & -d - \lambda \end{vmatrix} = 0$$

The characteristic equation of the Jacobian matrix at the disease free equilibrium point is

$$(-(\varphi + \mu) - \lambda)(-\mu - \lambda)(-d - \lambda)(\lambda^3 + e_1\lambda^2 + e_2\lambda + e_3) = 0$$

Where $e_1 = (a + b + c)$, $e_2 = (ac + bc + ab - \beta q(1-p)\eta - \beta p\eta)$, $e_3 = abc(1 - R_0)$

Then, $\lambda_1 = -(\varphi + \mu)$, $\lambda_2 = -\mu$, $\lambda_3 = -d$. From this the first three eigenvalues $\lambda_1, \lambda_2, \lambda_3$ are real, distinct and negative, which is stable. To determine the sign of the eigenvalues we use the Routh-Hurwitz criterion for the cubic equation; $\lambda^3 + e_1\lambda^2 + e_2\lambda + e_3 = 0$.

According to the Routh-Hurwitz criteria the three roots of a polynomial of order three of type $p(\lambda) = \lambda^3 + e_1\lambda^2 + e_2\lambda + e_3$, are real distinct and negative if the coefficients satisfy the conditions $e_1 > 0, e_2 > 0, e_3 > 0$ and $e_1e_2 > e_3$.

It is straight forward to verify that this conditions are satisfied and hence the last three eigenvalues are real distinct and negative.i.e

$$\begin{aligned} e_1 &> 0 \text{ if } a + b + c > 0 \\ e_2 &> 0 \text{ if } ac + cb + ab > (\beta q(1-p)\eta - \beta p\eta) \\ e_3 &> 0 \text{ if } R_0 < 1 \end{aligned}$$

Clearly it can be observed that the first three conditions of the Routh-Hurwitz criteria are satisfied and the fourth condition is satisfied provided that : $a_1a_2 > a_3$ if $(a + b + c)(ac + bc + ab - \beta q(1-p)\eta + \beta p\eta) > abc(1 - R_0)$.

Therefore the disease free equilibrium point of the system of ordinary differential equation (1) is locally asymptotically stable if $R_0 < 1$.

3.7. Global stability of the disease free equilibrium point (DFE)

Theorem 4: The disease free equilibrium point E_0 of the model equation (1) is globally asymptotically stable if $R_0 < 1$.

proof To establish the global stability of the disease-free equilibrium point, we construct a Lyapunov function. let $\Omega \subseteq \mathbb{R}_+^6$ be an open neighborhood of the disease free equilibrium point E_0 .

Then the function $L: \Omega \rightarrow \mathbb{R}_+^6$ defined by:

$$L(P, S, E, A, I, D) = \frac{B_1}{2}(E(t))^2 + \frac{B_2}{2}(A(t))^2 + \frac{B_3}{2}(I(t))^2 + \frac{B_4}{2}(D(t))^2 \quad (9)$$

where B_i , for $i = 1, 2, 3, 4$ are some positive constants to be chosen later.

Then $L(P, S, E, A, I, D)$ should satisfy the following properties:

- i) L is continuously differentiable.
- ii) $L > 0, \forall x \in \Omega: E_0$ and $L(E_0) = 0$, as $(E(t))^2 \geq 0, (A(t))^2 \geq 0, (I(t))^2 \geq 0, (D(t))^2 \geq 0$.
- iii) $\frac{dL}{dt} \leq 0$ in Ω , then E_0 is stable.

The first two conditions hold, as L is continuously differentiable and $L > 0, \forall x \in \Omega: E_0$

and $L(E_0) = 0$. Now let us check the third condition $\frac{dL}{dt} \leq 0$ in Ω .

$$\begin{aligned} \frac{dL}{dt} &= B_1 \frac{dE}{dt} + B_2 \frac{dA}{dt} + B_3 \frac{dI}{dt} + B_4 \frac{dD}{dt} \\ &= B_1(\lambda S - aE) + B_2((1-p)\eta E - bA) + B_3(p\eta E + \phi A - cI) + B_4(\gamma A + \alpha I - dD) \\ &= B_1\left(\frac{\beta(I+qA)}{N}S - aE\right) + B_2((1-p)\eta E - bA) + B_3(p\eta E + \phi A - cI) + B_4(\alpha I - \\ & dD), S \leq N \text{ at } E_0. \\ &= B_1(\beta(I+qA) - aE) + B_2((1-p)\eta E - bA) + B_3(p\eta E + \phi A - cI) + B_4(\alpha I - dD) \\ &= B_1\beta I + B_1\beta qA - B_1aE + B_2(1-p)\eta E - B_2bA + B_3p\eta E + B_3\phi A - B_3cI + B_4\gamma A \\ & \quad + B_4\alpha I - B_4dD \\ &= (B_2(1-p)\eta + B_3p\eta - B_1a)E + (B_1\beta q - B_2b + B_3\phi + B_4\gamma)A + (B_1\beta - B_3c \\ & \quad + B_4\alpha)I - B_4dD \\ &= B_1a\left(\frac{(B_2(1-p)\eta + B_3p\eta)}{B_1a} - 1\right)E + B_3\phi A - B_3cI + B_4\gamma A + B_4\alpha I - B_4dD \end{aligned}$$

Now choosing $B_1 = bc, B_2 = \beta(cq + \phi), B_3 = \beta b, B_4 = 0$. Then,

$$\begin{aligned} \frac{dL}{dt} &= abc\left(\frac{\beta(cq + \phi)(1-p)\eta + \beta b p \eta}{abc} - 1\right)E + (bcq\beta - bcq\beta - \beta b\phi + \beta b\phi)A + (bc\beta \\ & \quad - \beta bc)I \\ &= abc\left(\frac{\beta(cq + \phi)(1-p)\eta + \beta b p \eta}{abc} - 1\right)E \\ &= abc(R_0 - 1)E \end{aligned}$$

Therefore $\frac{dL}{dt} \leq bcd(R_0 - 1)E < 0$ if $R_0 < 1$ which implies that $\frac{dL}{dt} \leq 0$. Therefore the largest compact invariant set in Ω is singleton set E_0 . Hence LaSalle's invariant principle implies that E_0 is globally asymptotically stable.

3.8. Endemic Equilibrium Points

The endemic equilibrium point denoted by $E_1 = \{P^*, S^*, E^*, A^*, I^*, D^*\}$ is a steady state solution where the disease persists in the population. The endemic equilibrium point is obtained by setting rates of changes of variables with respect to time in model equations (1) equal to zero. That is, setting

$$\begin{cases} \theta\Pi - (\varphi + \mu)P = 0 \\ (1 - \theta)\Pi + \varphi P - (\lambda + \mu)S = 0 \\ \lambda S - (\eta + \mu + \xi)E = 0 \\ (1 - p)\eta E - (\phi + \gamma + \mu + \xi)A = 0 \\ p\eta E + \phi A - (\alpha + \mu + \xi)I = 0 \\ \gamma A + \alpha I - (\mu + \xi)D = 0 \end{cases} \quad (10)$$

Then solving they system of differential equation 10 by substitution and after some algebraic simplification we obtain $E_1 = \{P^*, S^*, E^*, A^*, I^*, D^*\}$ where:

$$\begin{aligned} P^* &= \frac{\theta\Pi}{(\varphi + \mu)} \\ S^* &= \frac{\Pi(\varphi + \mu - \theta\mu)}{(\lambda^* + \mu)} \\ E^* &= \frac{\lambda^* S^*}{(\eta + \mu + \xi)} \\ A^* &= \frac{(1 - p)\eta E^*}{(\phi + \gamma + \mu + \xi)} \\ I^* &= \frac{p\eta E^* + \phi A^*}{(\alpha + \mu + \xi)} \\ D^* &= \frac{\gamma A^* + \alpha I^*}{\mu + \xi}. \end{aligned}$$

On substituting the expression for A^* and I^* into the force of infection, that is, $\lambda^* = \frac{\beta(I^* + qA^*)}{N}$ obtained as

$$\begin{aligned} \lambda^* &= \mu[R_0(\varphi + \mu - \theta\mu) - 1] \\ \lambda^* &\leq 0, \text{ if } R_0(\varphi + \mu - \theta\mu) < 1, \text{ i.e } R_0 < \frac{1}{\varphi + \mu - \theta\mu} \end{aligned}$$

From this, we see that, there is no endemic equilibrium for this model. Therefore, this condition shows that it is not possible for backward bifurcation in the model if $R_0 < 1$.

Lemma: A unique endemic equilibrium point E_1 exists and positive if $R_0 > 1$.

3.9. Global Stability of Endemic Equilibrium

Theorem: 5 The endemic equilibrium point of the model equation(1) is globally asymptotically stable whenever $R_0 > 1$.

Proof: To prove the global stability of the endemic equilibrium we use the method of Lyapunov functions. Define

Define:

$$L(P^*, S^*, E^*, A^*, I^*, D^*) = [P - P^* - P^* \ln(\frac{P}{P^*})][S - S^* - S^* \ln(\frac{S}{S^*})] + [E - E^* - E^* \ln(\frac{E}{E^*})] + [A - A^* - A^* \ln(\frac{A}{A^*})] + [I - I^* - I^* \ln(\frac{I}{I^*})] + [D - D^* - D^* \ln(\frac{D}{D^*})] \quad (11)$$

Then by taking the time derivative of $L(P^*, S^*, E^*, A^*, I^*, D^*)$, we obtain:

$$\begin{aligned} \frac{dL}{dt} &= (P' - \frac{P^*}{P}P') + (S' - \frac{S^*}{S}S') + (E' - \frac{E^*}{E}E') + (A' - \frac{A^*}{A}A') + (I' - \frac{I^*}{I}I') + (D' - \frac{D^*}{D}D') \\ &= (1 - \frac{P^*}{P})\frac{dP}{dt} + (1 - \frac{S^*}{S})\frac{dS}{dt} + (1 - \frac{E^*}{E})\frac{dE}{dt} + (1 - \frac{A^*}{A})\frac{dA}{dt} + (1 - \frac{I^*}{I})\frac{dI}{dt} + (1 - \frac{D^*}{D})\frac{dD}{dt} \end{aligned}$$

By substituting the value $\frac{dD}{dt}, \frac{dS}{dt}, \frac{dE}{dt}, \frac{dA}{dt}, \frac{dI}{dt}, \frac{dD}{dt}$ from model equation1 we obtain

$$\begin{aligned} \frac{dL}{dt} &= (1 - \frac{P^*}{P})[\theta\Pi - (\varphi + \mu)P] + [1 - \frac{S^*}{S}][(1 - \theta)\Pi + \varphi P - (\lambda + \mu)S] + [1 - \frac{E^*}{E}][\lambda S - (\eta \\ &\quad + \mu + \xi)E] + [1 - \frac{A^*}{A}][(1 - p)\eta E - (\phi + \gamma + \mu + \xi)A] + [1 - \frac{I^*}{I}][p\eta E + \phi A \\ &\quad - (\alpha + \mu + \xi)I] + [1 - \frac{D^*}{D}][\gamma A + \alpha I - (\mu + \xi)D] \\ &= (\pi + \theta R + \lambda S^* + \mu S^* - \lambda S - \mu S - \pi \frac{S^*}{S} - \theta R \frac{S^*}{S}) + (\lambda S + \mu E^* + \eta E^* + \phi E^* - \mu E - \eta E \\ &\quad - \phi E - \lambda S \frac{E^*}{E}) + (\eta E + \mu A^* + \gamma A^* + \frac{A^*}{A} p\eta E - p\eta E - \mu A - \gamma A - \frac{A^*}{A} \eta E) \\ &\quad + (p\eta E \mu I^* + \alpha I^* - \mu I - \alpha I - \frac{I^*}{I} P\eta E) + (\alpha I + \gamma I + \phi E + \theta R^* + \mu R^* - \theta R \\ &\quad - \mu R - \alpha I \frac{R^*}{R} - \gamma A \frac{R^*}{R} - \phi E \frac{R^*}{R}) \end{aligned}$$

Now after some simplifications i.e cancelling like terms which is opposite in sign we obtain:

$$\begin{aligned} &= \underbrace{[\Pi + P^* \varphi + \lambda^* S^* + \eta E^* + (\phi + \gamma) A^* + \alpha I^* + \mu(N^* - N) + \xi[(E^* + A^* + I^* + D^*) - (E + A + I + D)]]}_Q \\ &\quad - \underbrace{[\theta \Pi \frac{P^*}{P} + ((1 - \theta)\Pi + \varphi P) \frac{S^*}{S} + \lambda^* S \frac{E^*}{E} + ((1 - p)\eta E) \frac{A^*}{A} + (p\eta E + \phi A) \frac{I^*}{I} + (\gamma A + \alpha I) \frac{D^*}{D}]}_K \end{aligned}$$

$$\frac{dL}{dt} = Q - K$$

Thus if $Q < K$, then $\frac{dL}{dt} \leq 0$. Noting that $\frac{dL}{dt} = 0$ if and only if $P = P^*, S = S^*, E = E^*, A = A^*, I = I^*, D = D^*$. Therefore, the largest compact invariant set in $\{(P^*, S^*, E^*, A^*, I^*, D^*) \in \Omega; \frac{dL}{dt} = 0\}$ is the singleton E_1 is the endemic equilibrium of the system 1. By LaSalle's invariant principle (LaSalle's,1976),it implies that E_1 is globally asymptotically stable in Ω if $Q < K$.

4.Sensitivity Analysis of Model Parameters

One of the most important concerns about any infectious disease is its ability to invade a population. The basic reproduction number, R_0 is a measure of the potential for disease spread in a population, and is inarguably 'one of the foremost and most valuable ideas that mathematical thinking has brought to epidemic theory' [14]. A large value of R_0 may indicate the possibility of a major epidemic. We thus, carried out sensitivity analysis of the basic reproduction number, R_0 with respect to the model parameters in order to determine the relative importance of the different factors responsible for the transmission and prevalence of the disease. This will assist in curtailing the transmission of the disease by using appropriate intervention strategies. There are more than a dozen ways of conducting sensitivity analysis, all resulting in a slightly different sensitivity ranking [15]. Following [14], we used the normalized forward sensitivity index also called elasticity as it is the backbone of nearly all other sensitivity analysis techniques [15] and are computationally efficient[16]. The normalized forward sensitivity index of the basic reproduction number, R_0 with respect to a parameter value, P is given by:

$$S_p^{R_0} = \frac{\partial R_0}{\partial P} \times \frac{P}{R_0} \quad (12)$$

The sensitivity indices of the basic reproductive number with respect to main parameters are arranged orderly in Table 1. Those parameters that have positive indices show that they have great impact on expanding the disease in the community if their values are increasing. Due to the reason that the basic reproduction number increases as their values increase, it means that the average number of secondary cases of infection increases in the community. Furthermore, those parameters in which their sensitivity indices are negative have an influence of minimizing the burden of the disease in the community as their values increase while the others are left constant. And also as their values increase, the basic reproduction number decreases, which leads to

minimizing the endemicity of the disease in the community.

Table 1: Sensitivity indices Table.

Parameter symbol	Sensitivity indices
β	+ve
η	+ve
q	+ve
μ	-ve
p	-ve
α	-ve
ϕ	-ve
γ	-ve
ξ	-ve

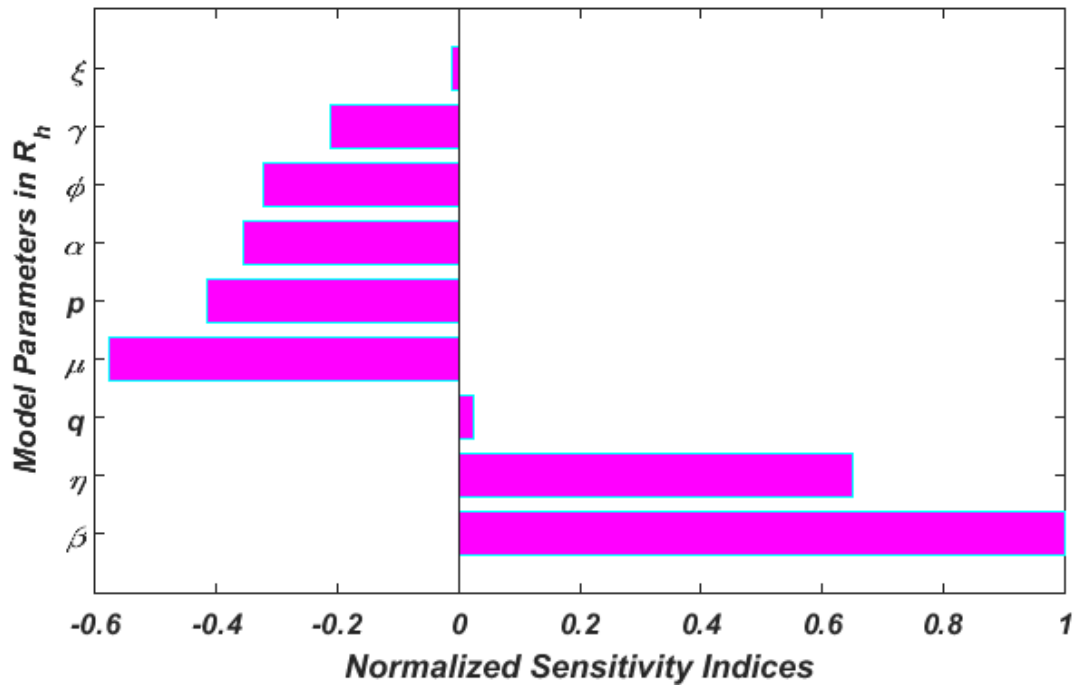


Figure 2: Sensitivity indices of basic reproduction number

5. Formulation of an optimal control problem

The purpose of this section is to extend model equation (1) into an optimal control problem. The controls are defined as follows:

1. u_1 is the control variable for prevention of the recruitment to susceptible individuals.
2. u_2 is the control variable for reduction of the spread/contact of HIV infection.
3. u_3 is the control variable for screen of the exposed individuals.
4. u_4 is the control variable for treatment of the asymptomatic and infected individuals

After incorporating the controls, the corresponding state system for model equation1 is given as:

$$\begin{cases} \frac{dP(t)}{dt} = \theta\Pi - (1 - u_1)\varphi P - \mu P \\ \frac{dS(t)}{dt} = (1 - \theta)\Pi + (1 - u_1)\varphi P - (1 - u_2)\lambda S - \mu S \\ \frac{dE(t)}{dt} = (1 - u_2)\lambda S - (1 - u_3)\eta E - (\mu + \xi)E \\ \frac{dA(t)}{dt} = (1 - u_3)(1 - p)\eta E - (1 - u_4)(\phi + \gamma)A - (\mu + \xi)A \\ \frac{dI(t)}{dt} = (1 - u_3)p\eta E + (1 - u_4)\phi A - (1 - u_4)\alpha I - (\mu + \xi)I \\ \frac{dD(t)}{dt} = (1 - u_4)\gamma A + (1 - u_4)\alpha I - (\mu + \xi)D \end{cases} \quad (13)$$

With initial condition $P(0) \geq 0, S(0) \geq 0, E(0) \geq 0, A(0) \geq 0, I(0) \geq 0, D(0) \geq 0$ with a bounded Lebesgue measurable control set is represented as

$$U = \{u = (u_1, u_2, u_3, u_4), 0 \leq u_i \leq u_{i_{max}}, i = 1, 2, 3, 4, \} \text{ and } t \in [0, T]$$

The aim objective is to minimize the number of infected population while minimizing the rate of interventions u_1, u_2, u_3 and u_4 on a fixed time period T . Therefore, the optimal control problem for the model equation (13) is to minimize the objective functional:

$$J(u) = \int_0^T [g(\phi, u)]dt = \int_0^T [M_1S + M_2E + M_3A + M_4I + + \frac{1}{2}\sum_{i=1}^4 k_i u_i^2(t)]dt \rightarrow \min \quad (14)$$

where, $i = 1, 2, 3, 4$ and $\phi = (P, S, E, A, I, D)$ solves equation 13 for the specified control u .

In the intervention of controls the solution $\phi = (P, S, E, A, I, D)$ depends on the controls. The constants w_1, w_2, w_3 and w_4 measures the cost or effort required for the implementation of each of the four control measures adopted while M_1, M_2, M_3 and M_4 measures the relative importance of reducing the associated classes on the spread of the disease. Thus, we need to find the optimal controls $u^* = (u_1^*, u_2^*, u_3^*, u_4^*)$ such that

$$J(u^*) = \min_U J(u_1, u_2, u_3, u_4) \quad (15)$$

Hence, the basic setup of the optimal control problem is to check the existence and uniqueness of the optimal controls and to characterize them.

5.1. Existence of an optimal controls

Theorem: 6 Given $J(u)$ subject to system 13 with $P(0) \geq 0, S(0) \geq 0, E(0) \geq 0, A(0) \geq 0, I(0) \geq 0, D(0) \geq 0$, then there exists an optimal control u^* and corresponding $(P^*, S^*, E^*, A^*, I^*, D^*)$, that minimizes $J(u)$ over U . The proof is based on the following assumption and by Fleming and Rishel's [17] theorem.

1. The set of controls and corresponding state variable is nonempty.
2. The measurable control set is convex and closed.
3. All the right hand sides of equations of the state system is continuous, bounded above by a sum of bounded control and state, and can be written as a linear function of u with coefficients depending on time and state.
4. The integrand $g(\phi, u)$ of the objective functional is convex.
5. There exist constants $c_1, c_2, c_3, c_4, c_5 \geq 0$ and $\tau^* \geq 1$ such that the integrand of the objective functional satisfies $(\phi, u) \geq c_1 + c_2|u_1|^\tau + c_3|u_2|^\tau + c_4|u_3|^\tau + c_5|u_4|^\tau$.

Proof:

1. U is a nonempty set of measurable functions on $0 \leq T$ with values in real numbers \mathbb{R} . The system 13 has bounded coefficients and hence any solutions are bounded on $[0, T]$. The corresponding solutions for the system (13) exists.
2. Assume that $u_1, u_2, u_3, u_4 \in U$ such that $\|u_i\| \leq 1, i = 1, 2, 3, 4$. Now, let us take any controls $u_1, u_2 \in U$ and $\lambda \in [0, 1]$, then $0 \leq \lambda u_1 + (1 - \lambda)u_2$. Additionally, we observe that

$$\|\lambda u_1\| \leq \lambda \|u_1\| \leq \lambda \text{ and } \|(1 - \lambda)u_2\| \leq (1 - \lambda) \|u_2\| \leq (1 - \lambda).$$

Then for any $\lambda \in [0, 1]$,

$$\begin{aligned} & \|\lambda u_1 + (1 - \lambda)u_2\| \\ & \leq \|\lambda u_1\| + \|(1 - \lambda)u_2\| \\ & \leq \lambda \|u_1\| + (1 - \lambda) \|u_2\| \\ & \leq \lambda + (1 - \lambda) = 1 \end{aligned}$$

Hence, $0 \leq \lambda u_1 + (1 - \lambda)u_2 \leq$, for all $u_1, u_2 \in U$ and $\lambda \in [0,1]$.

Therefore, the control space $U = \{u = (u_1, u_2, u_3, u_4), 0 \leq u_i \leq u_{i_{max}}, i = 1,2,3,4, \}$ and $t \in [0, T]$ is convex and closed by definition.

3. By definition, each right hand side of system 13 is continuous. All variables P, S, E, A, I, D and u are bounded on $[0, T]$. To prove the boundedness we use the method in []. To do so we use the fact the super-solutions of system 13 is written as:

$$\begin{cases} \frac{dP(t)}{dt} = \theta\Pi \\ \frac{dS(t)}{dt} = (1 - \theta)\Pi + (1 - u_1)\varphi P \\ \frac{dE(t)}{dt} = (1 - u_2)\lambda S \\ \frac{dA(t)}{dt} = (1 - u_3)(1 - p)\eta E \\ \frac{dI(t)}{dt} = (1 - u_3)p\eta E + (1 - u_4)\phi A \\ \frac{dD(t)}{dt} = (1 - u_4)\gamma A + (1 - u_4)\alpha I \end{cases} \quad (16)$$

are bounded on a finite time interval. System 17 can be written as;

$$\phi = \begin{bmatrix} P' \\ S' \\ E' \\ A' \\ I' \\ D' \end{bmatrix} = \begin{bmatrix} 0 & 0 & 0 & 0 & 0 & 0 \\ (1 - u_1)\varphi & 0 & 0 & 0 & 0 & 0 \\ 0 & (1 - u_2)\lambda & 0 & 0 & 0 & 0 \\ 0 & 0 & (1 - u_3)\eta & 0 & 0 & 0 \\ 0 & 0 & (1 - u_3)\eta p & (1 - u_4)\phi & 0 & 0 \\ 0 & 0 & 0 & (1 - u_4)\gamma & (1 - u_4)\alpha & 0 \end{bmatrix} \begin{bmatrix} \bar{P} \\ \bar{S} \\ \bar{E} \\ \bar{A} \\ \bar{I} \\ \bar{D} \end{bmatrix} + \begin{bmatrix} \theta\Pi \\ (1 - \theta)\Pi \\ 0 \\ 0 \\ 0 \\ 0 \end{bmatrix} \quad (17)$$

The system is linear in finite time with bounded coefficients, then the super-solutions $\bar{P}, \bar{S}, \bar{E}, \bar{A}, \bar{I}$ and \bar{D} is uniformly bounded. Since the solution to each state equation is bounded, we observe that,

$$|f(t, \phi, u)| \leq$$

$$\begin{bmatrix} 0 \\ (1-u_1)\varphi \\ 0 \\ 0 \\ 0 \\ 0 \end{bmatrix} + \begin{bmatrix} 0 \\ 0 \\ (1-u_2)\lambda \\ 0 \\ (1-u_3)\eta \\ (1-u_3)\eta\mu \\ 0 \end{bmatrix} + \begin{bmatrix} 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \end{bmatrix} + \begin{bmatrix} 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \end{bmatrix} + \begin{bmatrix} 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \end{bmatrix} + \begin{bmatrix} \bar{P} \\ \bar{S} \\ \bar{E} \\ \bar{A} \\ \bar{I} \\ \bar{D} \end{bmatrix} \quad (18)$$

$$\begin{bmatrix} \theta\Pi \\ (1-\theta)\Pi \\ 0 \\ 0 \\ 0 \\ 0 \end{bmatrix} + \begin{bmatrix} S \\ E \\ A \\ I \end{bmatrix} \begin{bmatrix} 0 \\ u_1 \\ u_2 \\ u_3 \\ u_4 \\ 0 \end{bmatrix} \leq K|\phi| + M|u| + N$$

Where K depends on the coefficients of the system. Thus, the assumption holds.

4. The integrand in the objective functional, which is a cost function $g(\phi, u)$ is an affine function. Recall that any affine function is a convex and the sum of a convex function is a convex. Therefore, $g(\phi, u)$ is convex on U .
5. Assume that there exists constants $c_1, c_2, c_3, c_4, c_5 \geq 0$ and $\tau^* \geq 1$ such that $g(\phi, u)$ satisfies $g(\phi, u) \geq c_1 + c_2|u_1|^\tau + c_3|u_2|^\tau + c_4|u_3|^\tau + c_5|u_4|^\tau$. Thus, the state variables are being bounded.

Let $c_1 = \inf_{t \in [0, T]} [M_1 S + M_2 E + M_3 A + M_4 I]$, $c_2 = \frac{w_1}{2}$, $c_3 = \frac{w_2}{2}$, $c_4 = \frac{w_3}{2}$, $c_5 = \frac{w_4}{2}$ and $\tau = 2$ then it follows that

$$g(\phi, u) \geq c_1 + c_2|u_1|^\tau + c_3|u_2|^\tau + c_4|u_3|^\tau + c_5|u_4|^\tau$$

Thus, this assumption is justified. Therefore, the optimal control u exists.

5.2. Characterization of an optimal control

In order to determine the necessary conditions for the optimal control the Pontryagin's maximum principle [18] is used. To apply this we need to convert the optimal control problem into a problem of minimizing point wise a Hamiltonian, H , with respect to u . The Hamiltonian associated to our problem is:

$$H(\phi, u, \lambda) = M_1 S + M_2 E + M_3 A + M_4 I + \frac{w_1 u_1^2}{2} + \frac{w_2 u_2^2}{2} + \frac{w_3 u_3^2}{2} + \frac{w_4 u_4^2}{2} \quad (19)$$

$$+ \lambda_1 [\theta\Pi - (1-u_1)\varphi P - \mu P] + \lambda_2 [(1-\theta)\Pi + (1-u_1)\varphi P - (1-u_2)\lambda S - \mu S]$$

$$\begin{aligned}
& +\lambda_3[(1-u_2)\lambda S - (1-u_3)\eta E - (\mu + \xi)E] + \lambda_4[(1-u_3)(1-p)\eta E - (1-u_4)(\phi + \gamma)A \\
& \quad - (\mu + \xi)A] \\
& +\lambda_5[(1-u_3)p\eta E + (1-u_4)\phi A - (1-u_4)\alpha I - (\mu + \xi)I] + \lambda_6[(1-u_4)\gamma A + (1-u_4)\alpha I \\
& \quad - (\mu + \xi)D]
\end{aligned}$$

Based on [18], if the control u^* and the corresponding state ϕ^* are an optimal couple, necessarily there exists a non trivial adjoint vector $\lambda = (\lambda_1, \lambda_2, \lambda_3, \lambda_4, \lambda_5, \lambda_6)$ satisfying the following equality

$$\begin{cases} \frac{d\phi}{dt} = \frac{\partial H(\phi, u, \lambda)}{\partial \lambda} \\ \frac{d\lambda}{dt} = -\frac{\partial H(\phi, u, \lambda)}{\partial \phi} \\ \frac{\partial H(\phi, u, \lambda)}{\partial u} = 0 \end{cases} \quad (20)$$

Which gives after derivation

$$\begin{cases} u_i^* = 0, \text{ if } \frac{\partial H}{\partial u_i} < 0 \\ 0 \leq u_i^* \leq u_{imax}, \text{ if } \frac{\partial H}{\partial u_i} = 0 \\ u_i^* = u_{imax}, \text{ if } \frac{\partial H}{\partial u_i} > 0 \end{cases} \quad (21)$$

Now we apply the necessary conditions to the Hamilton function, H.

Theorem: 7 Given an optimal control u^* and a solution to the corresponding state ϕ , then there exist an adjoint vector λ and this satisfies the following adjoint equation:

$$\begin{cases} \frac{d\lambda_1}{dt} = \lambda_1[(1-u_1)\phi + \mu] - \lambda_2(1-u_1)\phi \\ \frac{d\lambda_2}{dt} = -M_1 + \lambda_2[(1-u_2)\lambda^* + \mu] - \lambda_3(1-u_2)\lambda^* \\ \frac{d\lambda_3}{dt} = -M_2 + \lambda_3[(1-u_3)\eta + (\mu + \xi)] - \lambda_4[(1-u_3)(1-p)\eta] - \lambda_5[(1-u_3)p\eta] \\ \frac{d\lambda_4}{dt} = -M_3 + \lambda_2[(1-u_2)\frac{\beta q S}{N}] - \lambda_3[(1-u_2)\frac{\beta q S}{N}] + \lambda_4[(1-u_4)(\gamma + \phi) + (\mu + \xi)] - \lambda_5[(1-u_4)\phi] \\ \quad - \lambda_6[(1-u_4)\gamma] \\ \frac{d\lambda_5}{dt} = -M_4 + \lambda_2[(1-u_2)\frac{\beta S}{N}] - \lambda_3[(1-u_2)\frac{\beta S}{N}] + \lambda_5[(1-u_4)\alpha + (\mu + \xi)] - \lambda_6[(1-u_4)\alpha] \\ \frac{d\lambda_6}{dt} = \lambda_6(\mu + \xi) \\ \lambda_i(T) = 0, i = 1, 2, 3, 4, 5, 6. \end{cases}$$

$\lambda_i(T) = 0$ is the transversality condition. Moreover, the optimal control u^* given by

$$\begin{cases} u_1^* = \min\{\max\{\frac{(\lambda_2 - \lambda_1)\varphi P}{w_1}, 0\}, u_{1max}\} \\ u_2^* = \min\{\max\{\frac{(\lambda_3 - \lambda_2)\lambda^* S}{w_2}, 0\}, u_{2max}\} \\ u_3^* = \min\{\max\{\frac{(\lambda_4(1-p) - \lambda_3)\eta E + \lambda_5 p \eta E}{w_3}, 0\}, u_{3max}\} \\ u_4^* = \min\{\max\{\frac{(\lambda_6 - \lambda_4)\gamma A + (\lambda_5 - \lambda_4)\phi A + (\lambda_6 - \lambda_5)\alpha I}{w_4}, 0\}, u_{4max}\} \end{cases} \quad (22)$$

Proof: The adjoint equation is obtained by differentiating the Hamiltonian equation 19 with respect to $\phi = (P, S, E, A, I, D)$. That is $\frac{d\lambda}{dt} = -\frac{\partial H(\phi, u, \lambda)}{\partial \phi}$. Assuming that the final states $P(T), S(T), E(T), A(T), I(T), D(T)$ are free we get the transversality conditions $\lambda(T) = 0$. The optimal controls u are found from the optimality conditions and using the property of the control space U . The optimality condition of the Hamiltonian gives $\frac{\partial H}{\partial u} = 0$. That is

$$\begin{cases} \frac{\partial H}{\partial u_1} = 0 \Rightarrow u_1^* = \frac{(\lambda_2 - \lambda_1)\varphi P}{w_1} \\ \frac{\partial H}{\partial u_2} = 0 \Rightarrow u_2^* = \frac{(\lambda_3 - \lambda_2)\lambda^* S}{w_2} \\ \frac{\partial H}{\partial u_3} = 0 \Rightarrow u_3^* = \frac{(\lambda_4(1-p) - \lambda_3)\eta E + \lambda_5 p \eta E}{w_3} \\ \frac{\partial H}{\partial u_4} = 0 \Rightarrow u_4^* = \frac{(\lambda_6 - \lambda_4)\gamma A + (\lambda_5 - \lambda_4)\phi A + (\lambda_6 - \lambda_5)\alpha I}{w_4} \end{cases} \quad (23)$$

And using the property of the control space U , the controls are given as

$$\begin{cases} u_1^* = 0, \text{ if } (\lambda_2 - \lambda_1)\varphi P < 0, \\ u_1^*, \text{ if } 0 \leq (\lambda_2 - \lambda_1)\varphi P \leq w_1 u_{1max} \\ u_{1max}, \text{ if } (\lambda_2 - \lambda_1)\varphi P > w_1 u_{1max} \end{cases} \quad (24)$$

$$\begin{cases} u_2^* = 0, \text{ if } (\lambda_3 - \lambda_1)\lambda^* S < 0, \\ u_2^*, \text{ if } 0 \leq (\lambda_3 - \lambda_1)\lambda^* S \leq w_2 u_{2max} \\ u_{2max}, \text{ if } (\lambda_3 - \lambda_1)\lambda^* S > w_2 u_{2max} \end{cases} \quad (25)$$

$$\begin{cases} u_3^* = 0, \text{ if } (\lambda_4(1-p) - \lambda_3)\eta E + \lambda_5 p \eta E < 0, \\ u_3^*, \text{ if } 0 \leq (\lambda_4(1-p) - \lambda_3)\eta E + \lambda_5 p \eta E \leq w_3 u_{3max} \\ u_{3max}, \text{ if } (\lambda_4(1-p) - \lambda_3)\eta E + \lambda_5 p \eta E > w_3 u_{3max} \end{cases} \quad (26)$$

$$\begin{cases} u_4^* = 0, \text{ if } (\lambda_6 - \lambda_4)\gamma A + (\lambda_5 - \lambda_4)\phi A + (\lambda_6 - \lambda_5)\alpha I < 0, \\ u_4^*, \text{ if } 0 \leq (\lambda_6 - \lambda_4)\gamma A + (\lambda_5 - \lambda_4)\phi A + (\lambda_6 - \lambda_5)\alpha I \leq w_4 u_{4max} \\ u_{4max}, \text{ if } (\lambda_6 - \lambda_4)\gamma A + (\lambda_5 - \lambda_4)\phi A + (\lambda_6 - \lambda_5)\alpha I > w_4 u_{4max} \end{cases} \quad (27)$$

5.3. The Optimality System

The optimality system consists of the state system (13) with its initial conditions coupled

with the adjoint system (22) with its transversality conditions together with the characterization of the optimal controls. It is written as follows:

$$\left\{ \begin{array}{l} \frac{dP(t)}{dt} = \theta\Pi - (1 - u_1)\varphi P - \mu P \\ \frac{dS(t)}{dt} = (1 - \theta)\Pi + (1 - u_1)\varphi P - (1 - u_2)\lambda S - \mu S \\ \frac{dE(t)}{dt} = (1 - u_2)\lambda S - (1 - u_3)\eta E - (\mu + \xi)E \\ \frac{dA(t)}{dt} = (1 - u_3)(1 - p)\eta E - (1 - u_4)(\phi + \gamma)A - (\mu + \xi)A \\ \frac{dI(t)}{dt} = (1 - u_3)p\eta E + (1 - u_4)\phi A - (1 - u_4)\alpha I - (\mu + \xi)I \\ \frac{dD(t)}{dt} = (1 - u_4)\gamma A + (1 - u_4)\alpha I - (\mu + \xi)D \\ \frac{d\lambda_1}{dt} = \lambda_1[(1 - u_1)\varphi + \mu] - \lambda_2(1 - u_1)\varphi \\ \frac{d\lambda_2}{dt} = -M_1 + \lambda_2[(1 - u_2)\lambda^* + \mu] - \lambda_3(1 - u_2)\lambda^* \\ \frac{d\lambda_3}{dt} = -M_2 + \lambda_3[(1 - u_3)\eta + (\mu + \xi)] - \lambda_4[(1 - u_3)(1 - p)\eta] - \lambda_5[(1 - u_3)p\eta] \\ \frac{d\lambda_4}{dt} = -M_3 + \lambda_2[(1 - u_2)\frac{\beta q S}{N}] - \lambda_3[(1 - u_2)\frac{\beta q S}{N}] + \lambda_4[(1 - u_4)(\gamma + \phi) + (\mu + \xi)] - \lambda_5[(1 - u_4)\phi] \\ - \lambda_6[(1 - u_4)\gamma] \\ \frac{d\lambda_5}{dt} = -M_4 + \lambda_2[(1 - u_2)\frac{\beta S}{N}] - \lambda_3[(1 - u_2)\frac{\beta S}{N}] + \lambda_5[(1 - u_4)\alpha + (\mu + \xi)] - \lambda_6[(1 - u_4)\alpha] \\ \frac{d\lambda_6}{dt} = \lambda_6(\mu + \xi) \end{array} \right.$$

Where $\lambda^* = \frac{\beta(I+qA)}{N}$, $\lambda_i(T) = 0, i = 1,2,3,4,5,6$. (28)

5.4. Uniqueness of the optimality system

In order to successively discuss uniqueness of the optimality system we notice that the adjoint system is also linear in λ_i for $i = 1,2,3,4,5,6$ with bounded coefficients. Thus, there exists a $M > 0$ such that $|\lambda_i(t)| < M$ for $i = 1,2,3,4,5,6$ on $[0, T]$.

Theorem 8. [18] For T sufficiently small the solution to the optimality system is unique.

6. Numerical Simulation

In this section, the result obtained by numerically solving the optimality system was presented. In our control problem, we have initial conditions for the state variables and terminal conditions for the adjoints. That is, the optimality system is a two-point boundary value problem with separate boundary conditions at times $i = 0$ and $i = T$. The simulations are consistent for all

the scenarios under consideration, varying only in the margins of growth and reduction. As a result, we only have the results of the most effective combination.

To conduct the study, a set of physically meaningful values are assigned to the model parameters and using the software MATLAB R2015b with ODE45 solver. These values are either taken from literature or assumed on the basis of reality. Using the parameter values given in Table 2 and the initial conditions $P(0) = 100, S(0) = 80, E(0) = 50, A(0) = 25, I(0) = 15$ and $D(0) = 30$ a simulation study is conducted and the results are given in the following Figures.

Table 2: Parameter values

Parameter	Value	Source
θ	0.007	Assumed
Π	0.004	[19]
β	0.067	Assumed
μ	0.054	[19]
γ	0.015	Assumed
α	0.16	[19]
η	0.012	Assumed
p	0.06	Assumed
ξ	0.0001	[19]
ϕ	0.04	[19]
φ	0.03	Assumed
q	0.01	Assumed

A. Control strategy with prevention only

We simulated the optimality control system by incorporating prevention intervention only. Figures 3, 4 and 5 shows that the decrease of all infectious individuals in the specified time but they did not go to zero over the period of implementation of this intervention strategy. The reason is that due to lack of prevention susceptible individuals still get infected. Therefore, we conclude that applying optimized prevention only as control intervention decreases the burden of the disease but it is not eradicate HIV from the community.

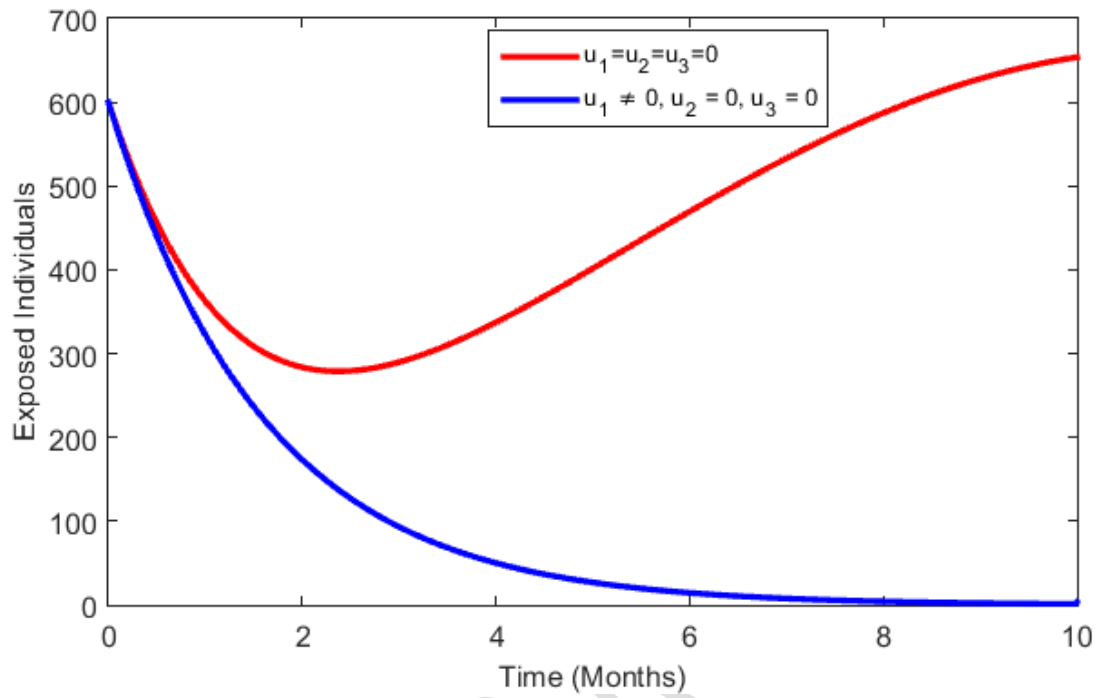


Figure 3: Simulations of exposed individuals with prevention only

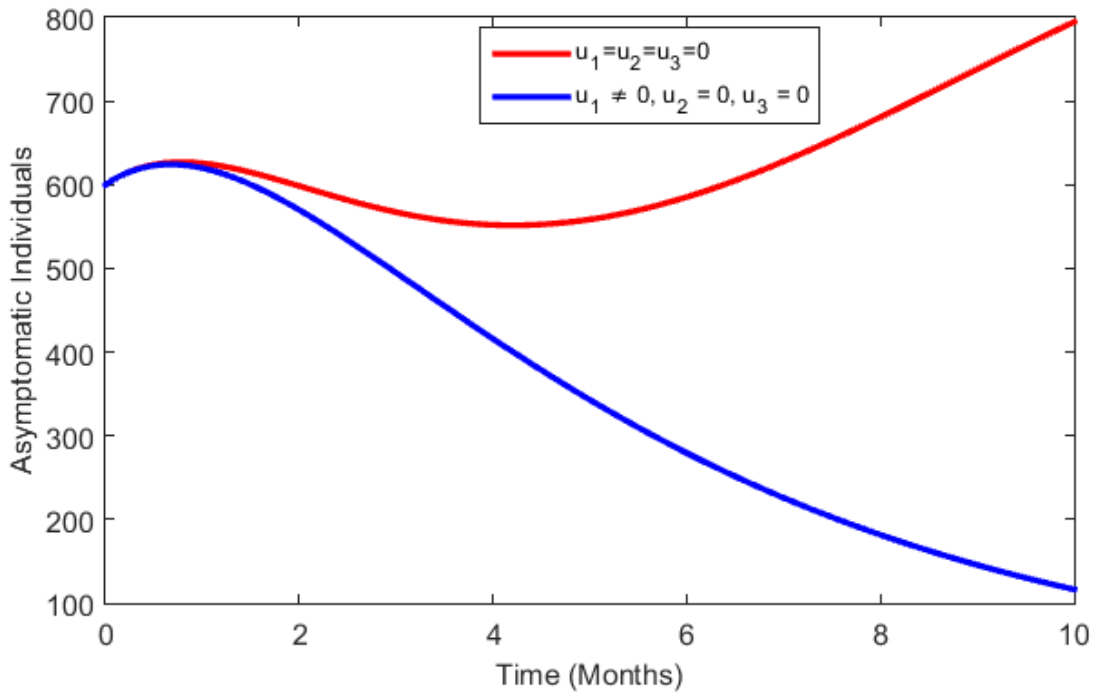


Figure 4: Simulations of asymptomatic individuals with prevention only

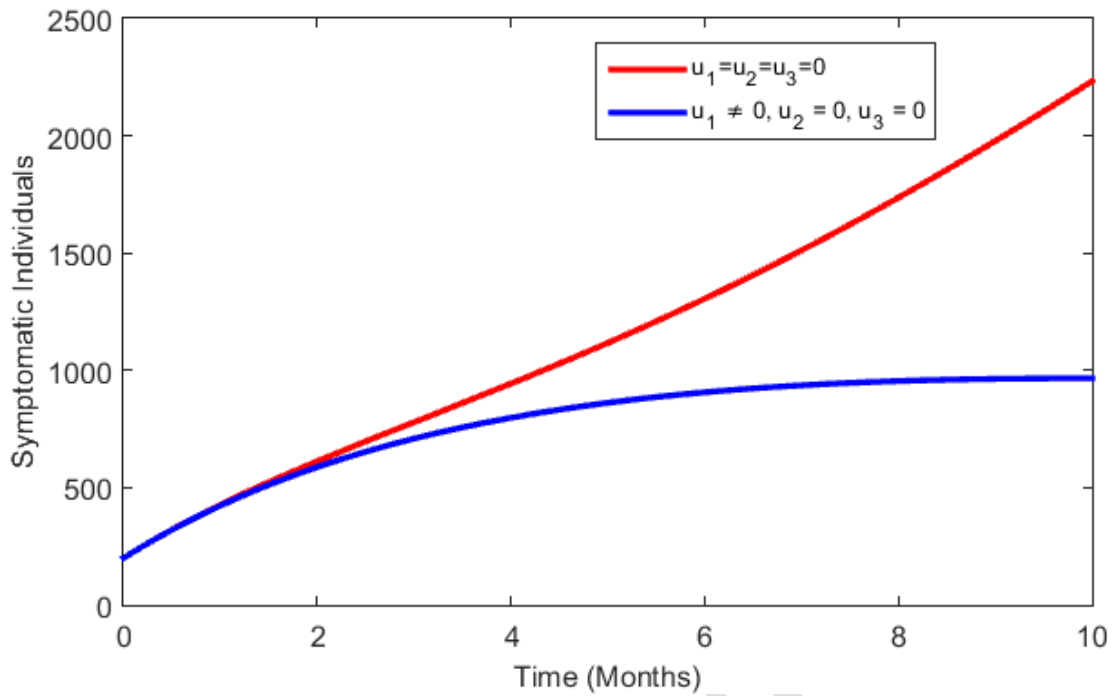


Figure 5: Simulations of symptomatic individuals with prevention only

B. Control strategy with treatment only

We applied treatment only as intervention that is treating individuals who develop disease symptom. Figures 6, 7 and 8 clearly show that all infectious individuals have gone to zero at the end of the implementation period. Therefore, we conclude that this strategy is effective in eradicating the HIV from the community in a specified period of time.

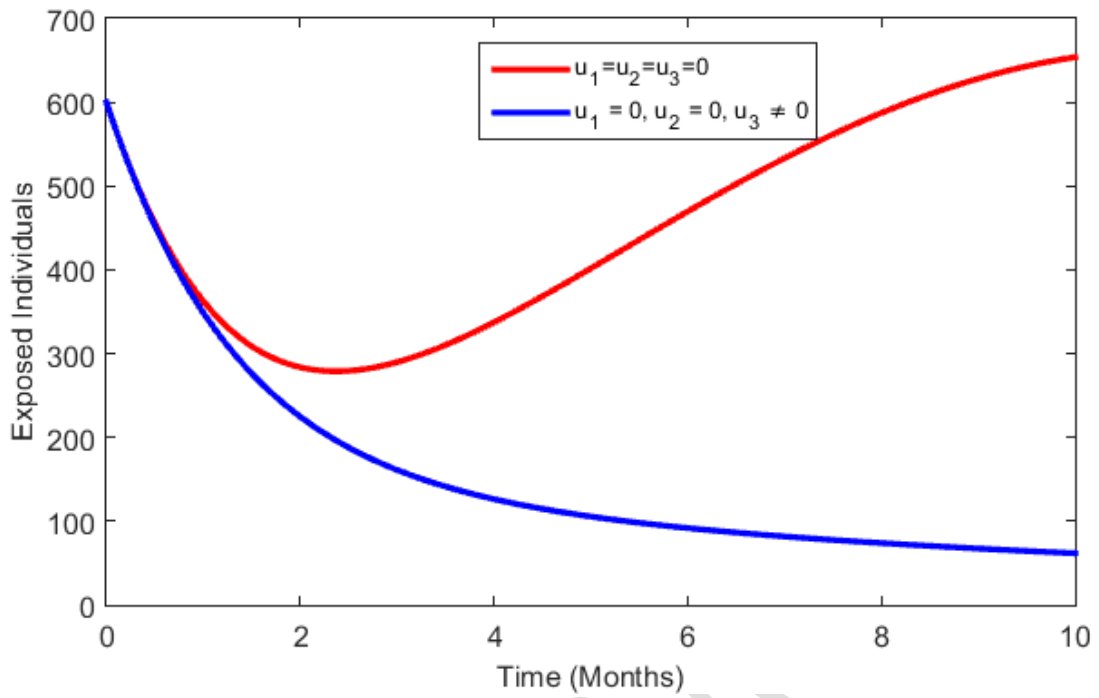


Figure 6: Simulations of exposed individuals with treatment only

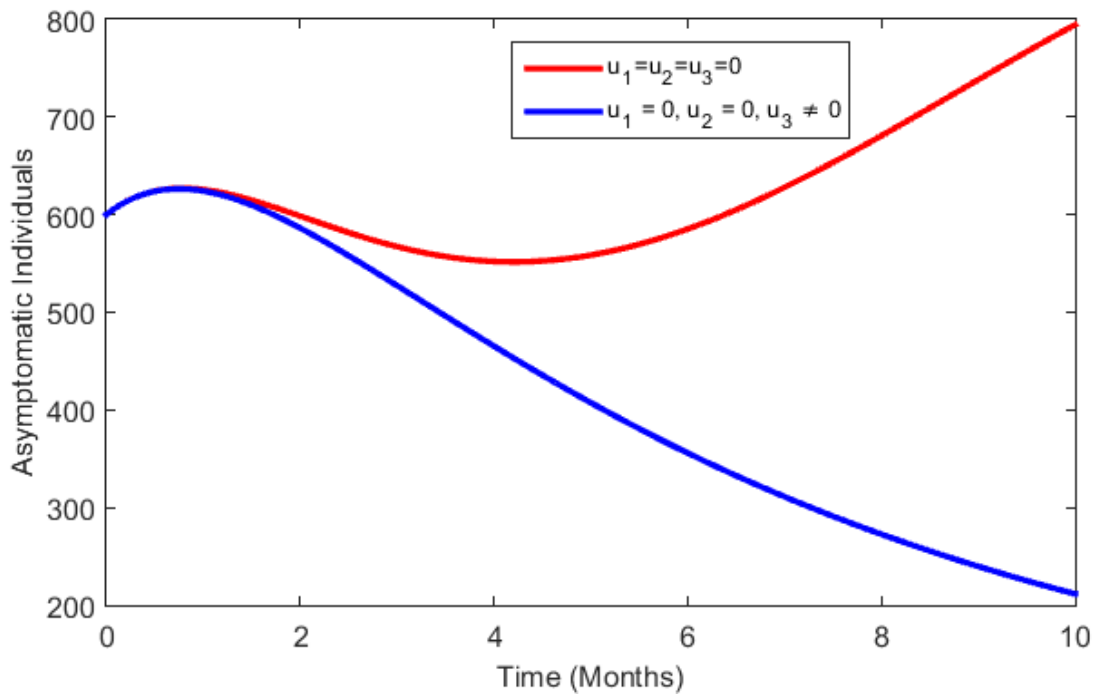


Figure 7: Simulations of asymptomatic individuals with treatment only

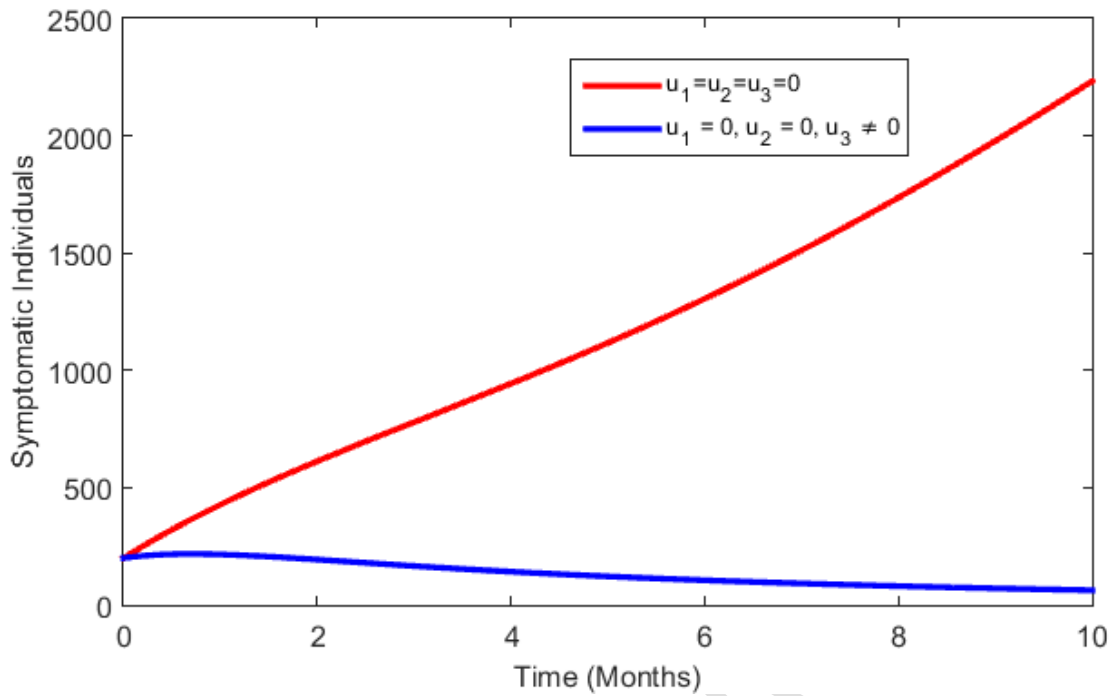


Figure 8: Simulations of symptomatic individuals with treatment only

C. Control strategy with prevention and Screening only

In this strategy, we applied prevention and screening as intervention to control HIV. Figures 9, 10 and 11 shows that infectious individuals did goes to zero over the period of implementation of this intervention strategy. Therefore, control with prevention and screening reduces the burden to some extent but it is not eradicate HPV totally from the community.

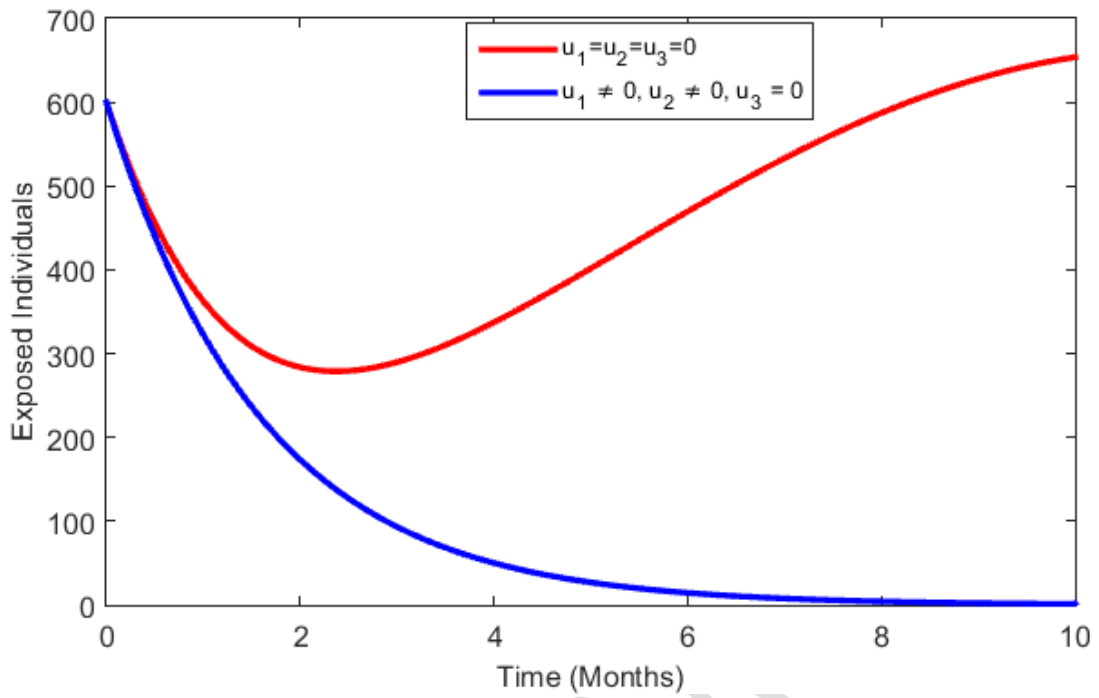


Figure 9: Simulations of exposed individuals with prevention and screening only

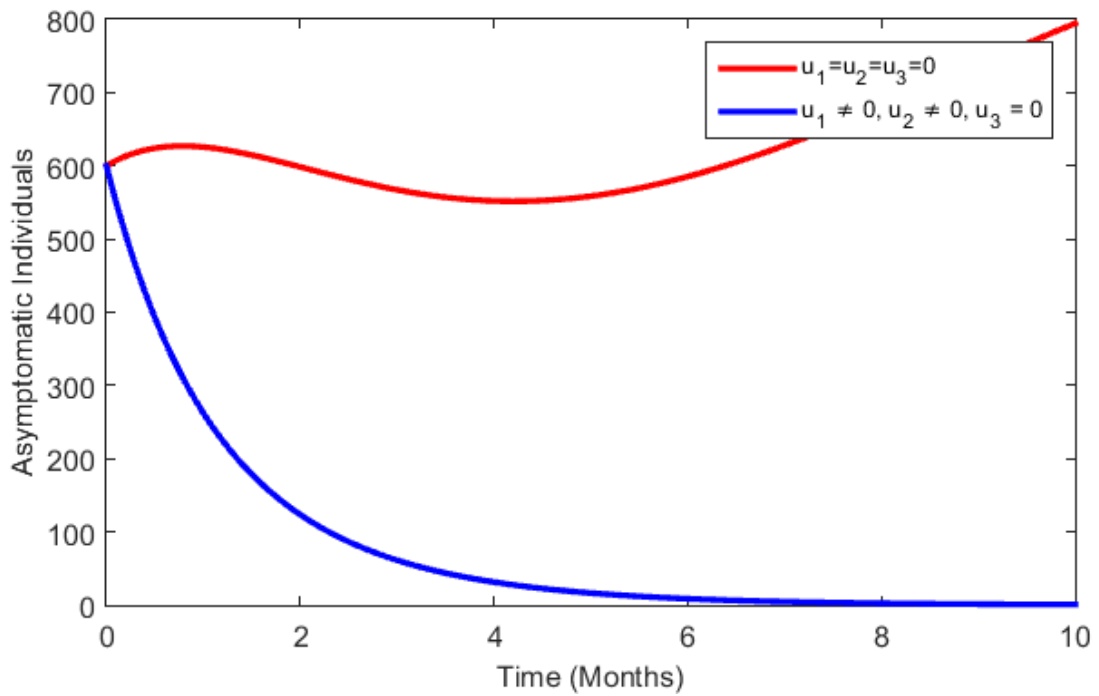


Figure 10: Simulations of asymptomatic individuals with prevention and screening only

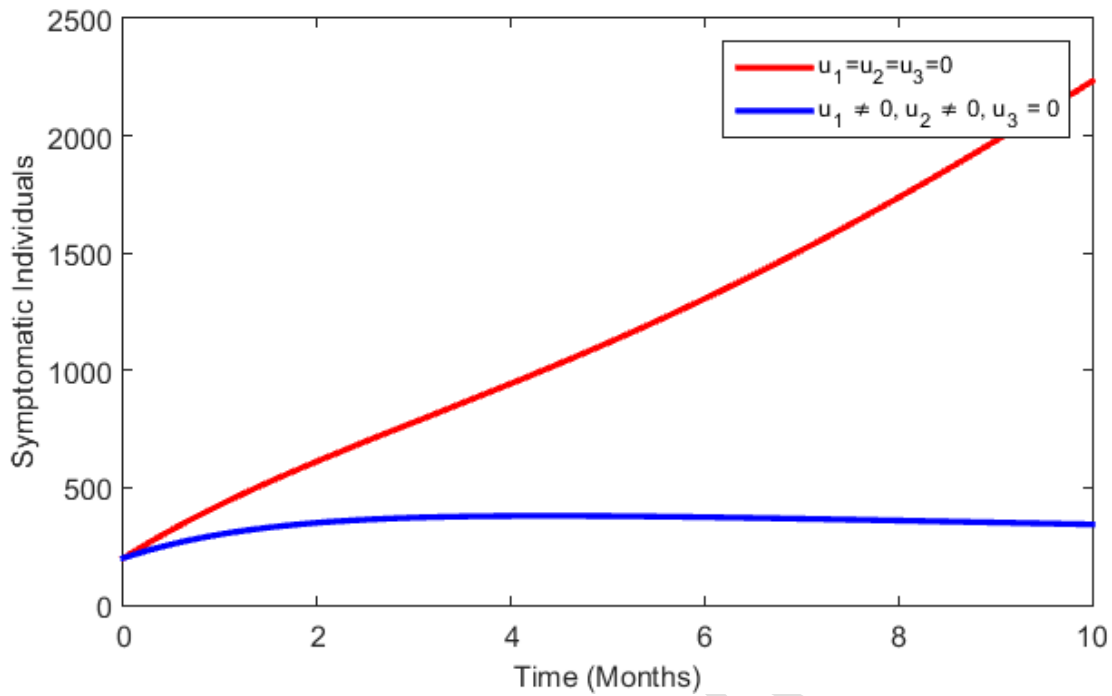


Figure 11: Simulations of symptomatic individuals with prevention and screening only

D. Control strategy with prevention and treatment only

We simulate the model using a combination of prevention and treatment as intervention strategy for control of HIV in the community. Figures 12, 13 and 14 shows that an infectious individual goes to zero over the period of implementation of this intervention strategy. Therefore, this strategy is effective in eradicating the HIV in the specified period of time.

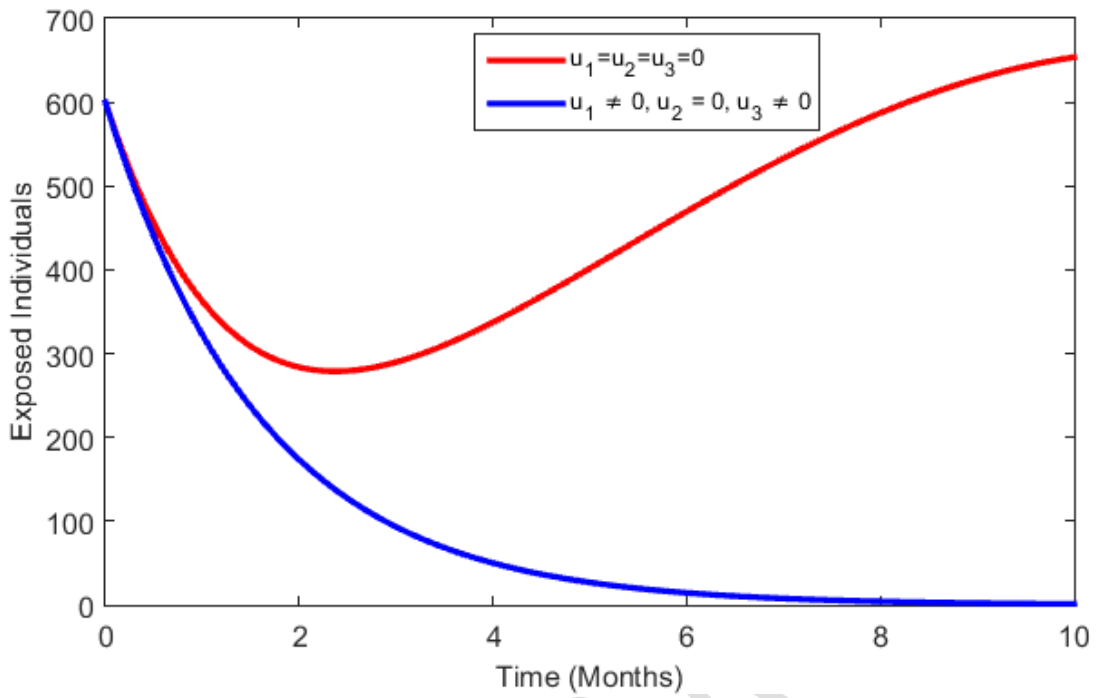


Figure 12: Simulations of exposed individuals with prevention and treatment only

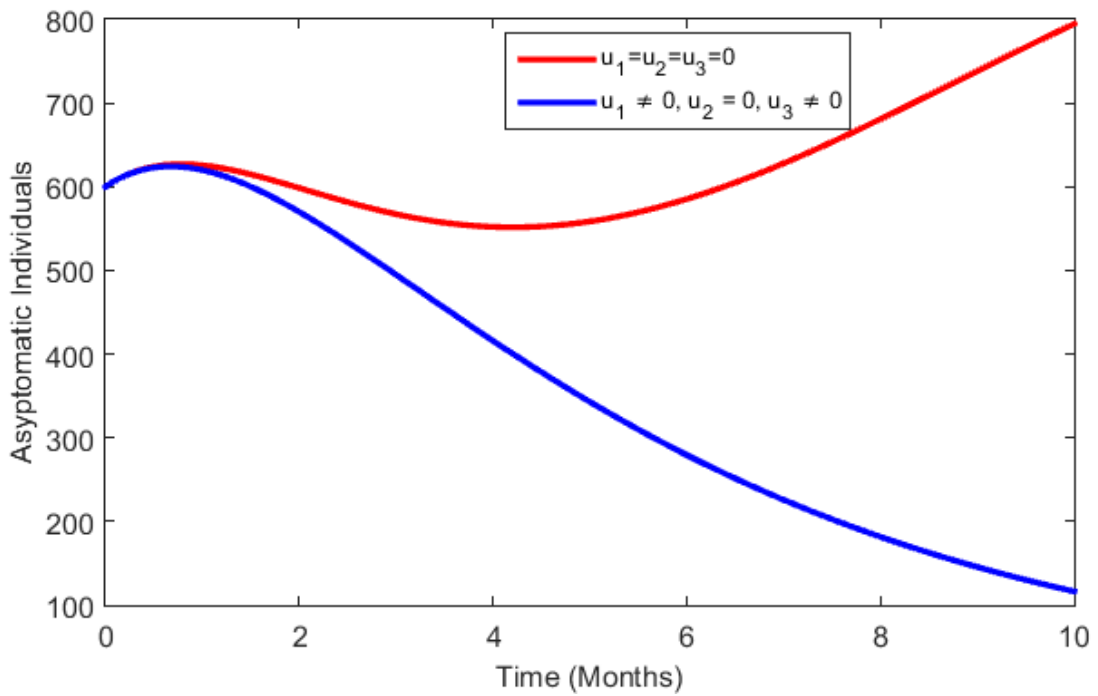


Figure 13: Simulations of asymptomatic individuals with prevention and treatment only

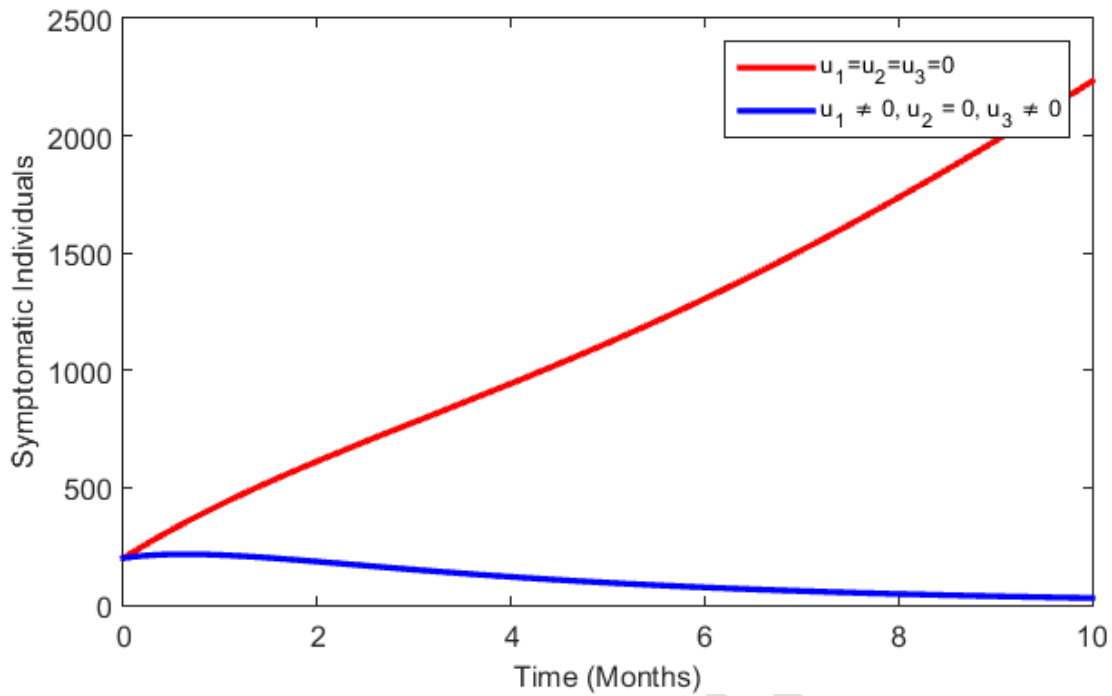


Figure 14: Simulations of symptomatic individuals with prevention and treatment only

E. Control strategy with prevention, screening and treatment

In this strategy, we implemented all the three controls (prevention, screening and treatment) as intervention to eradicate HIV from the community. Figures 15, 16 and 17 shows that an infectious individual goes to zero at the end of the implementation period. Therefore, applying this strategy is effective in eradicating HIV from the community in a specified period of time.

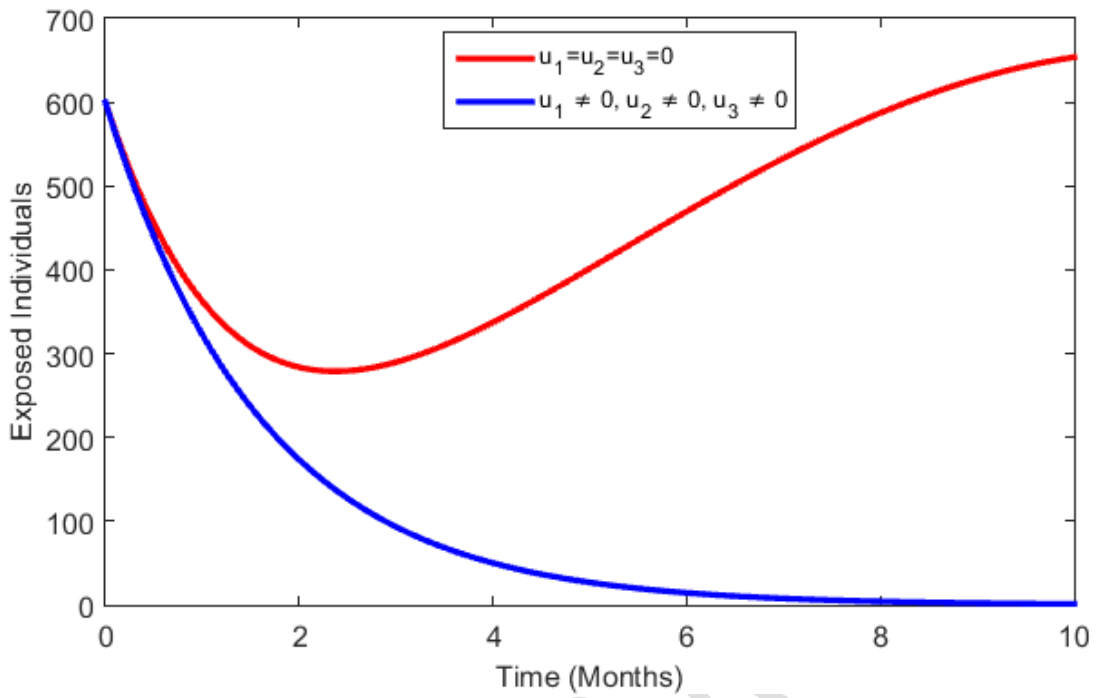


Figure 15: Simulations of exposed individuals with prevention, screening and treatment

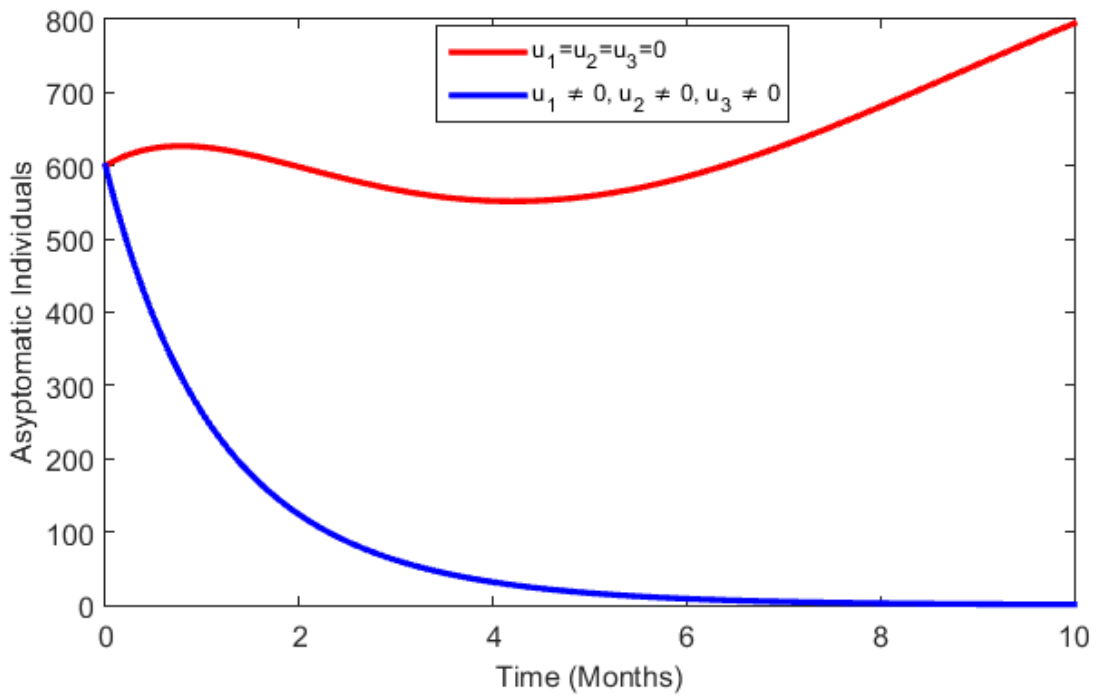


Figure 16: Simulations of asymptomatic individuals with prevention, screening and treatment

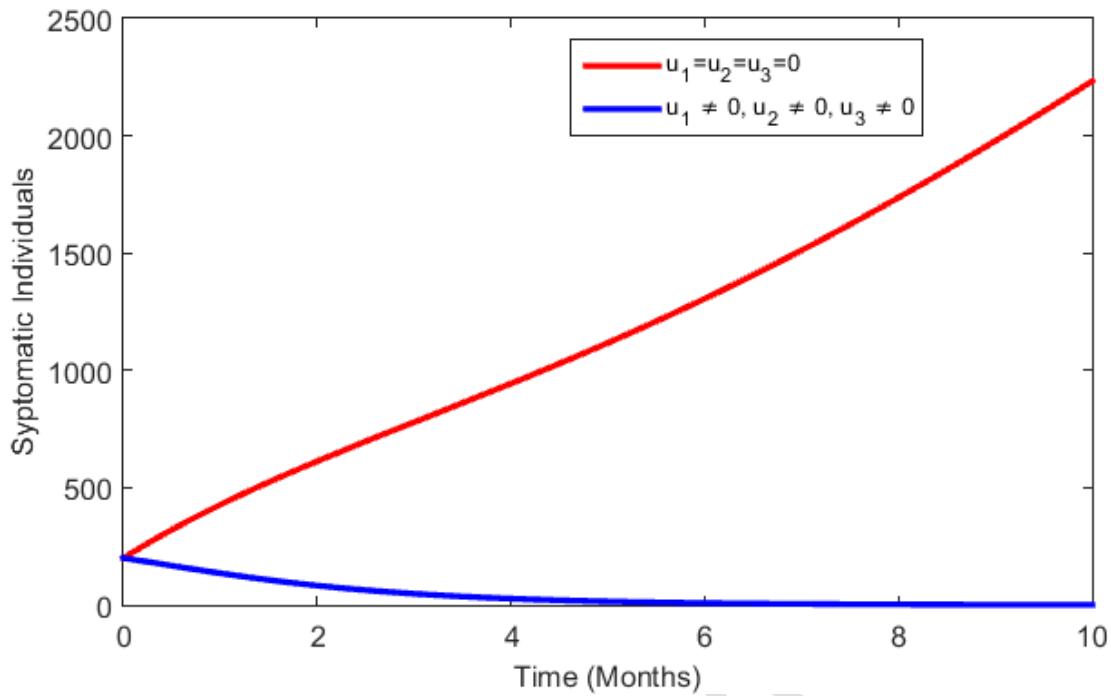


Figure 17: Simulations of symptomatic individuals with prevention, screening and treatment

7. Cost Effective Analysis

Cost-effectiveness analysis is directly linked to the financial and scientific implications of different control interventions. We evaluate the cost using the incremental cost-effectiveness ratio (ICER) which is used to compare the differences between the costs and health outcomes of the two competing intervention strategies. Each intervention is compared with the next less effective alternative [9]. The infection averted is calculated by taking the difference between the total number of individuals of species without control and the total number of individuals of species with control. The control strategies are ranked in order of increasing infection averted as presented in Table 3.

Strategies	Total infectious averted	Total Cost	ICER
Strategy A	15.87	100	6.30
Strategy B	133.86	99.9939	-0.00005169
Strategy D	149.11	200	6.55777
Strategy C	475.53	199.4593	-0.001656
Strategy E	605.88	298.7859	0.761999

Table 3: Total number of infection averted and total cost with their ICER

The comparison between ICER (A) and ICER (B) shows a cost saving of \$0.00005169 for strategy B over strategy A. There is an additional \$6.3 per infection averted as we move from strategy A to B. The small value ICER for strategy B indicates the strategy A is "strongly dominated". That is, strategy A is more costly and less effective than strategy B. Therefore, strategy A, the strongly dominated is excluded. Exclude strategy A, we now compare strategy B with D, C and E. From the numerical results we get as follows in table 4.

Strategies	Total infectious averted	Total Cost	ICER
Strategy B	133.86	99.9939	0.747
Strategy D	149.11	200	6.55777
Strategy C	475.53	199.4593	-0.001656
Strategy E	605.88	298.7859	0.761999

Table 4: Total number of infection averted and total cost with their ICER

The comparison between ICER (B) and ICER (D) shows a cost saving of \$0.747 for strategy B over strategy D. The small ICER for strategy B indicates the strategy D is "strongly dominated". That is, strategy D is more costly and less effective than strategy B. Therefore, strategy D, the strongly dominated is excluded from the set of alternatives so it does not consume limited resources. We exclude strategy D and compare strategy B with C and E. From the numerical results we get as follows in table 5.

Strategies	Total infectious averted	Total Cost	ICER
Strategy B	133.86	99.9939	0.747
Strategy C	475.53	199.4593	0.291
Strategy E	605.88	298.7859	0.761999

Table 5: Total number of infection averted and total cost with their ICER

The comparison between ICER (B) and ICER (C) shows a cost saving of \$0.29111 for strategy B over strategy C. There is an additional \$0.747 per infection averted as we move from strategy B to C. The small value ICER for strategy C indicates the strategy B is "strongly dominated". That is, strategy B is more costly and less effective than strategy C. Therefore, strategy B, the strongly dominated is excluded. Exclude strategy B, we now compare strategy C with E. From the numerical results we get as follows in table 6.

Strategies	Total infectious averted	Total Cost	ICER
Strategy C	475.53	199.4593	0.41944
Strategy E	605.88	298.7859	0.761999

Table 6: Total number of infection averted and total cost with their ICER

The comparison between ICER (C) and ICER (E) shows a cost saving of \$0.41944 for strategy C over strategy E. There is an additional \$0.761999 per infection averted as we move from strategy C to E. Similarly, the small value ICER for strategy C indicates the strategy E is "strongly dominated". That is, strategy E is more costly and less effective than strategy C. Therefore, strategy E, the strongly dominated is excluded.

With this result therefore, it is found that strategy C (combination of prevention with screening is most cost-effective of all the strategies for HIV disease control. This result agrees with the results obtained in figure 20.

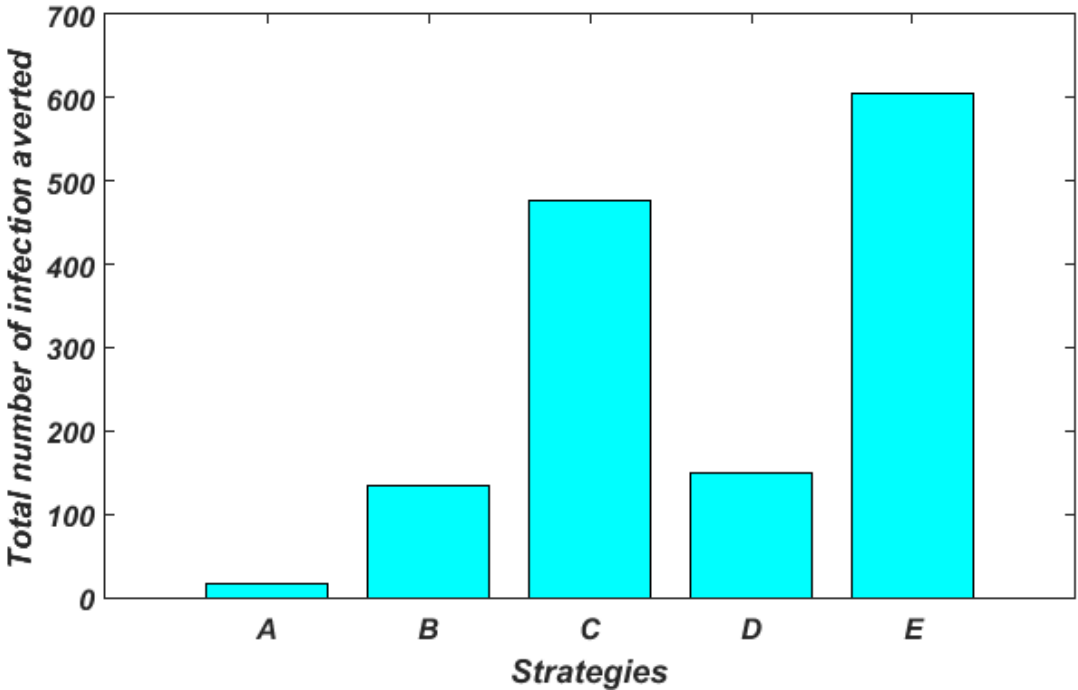


Figure 18: Total infectious averted plots indicating the effect of control strategies A, B, C, D and E

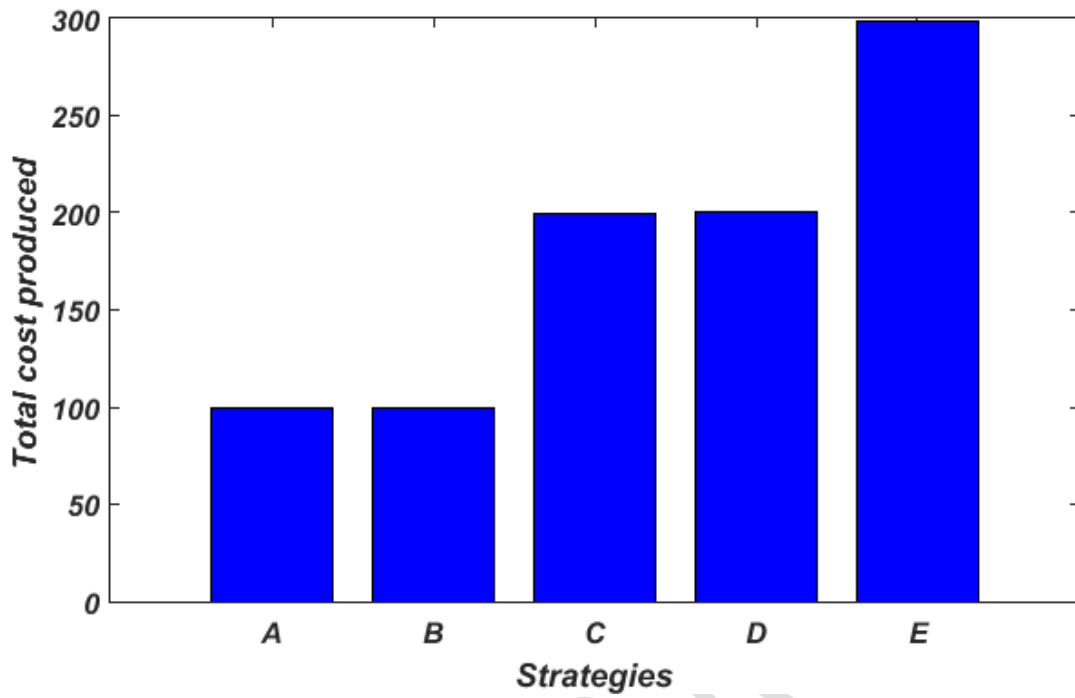


Figure 19: The objective functional plots indicating the effect of control strategies a, B, C, D and E

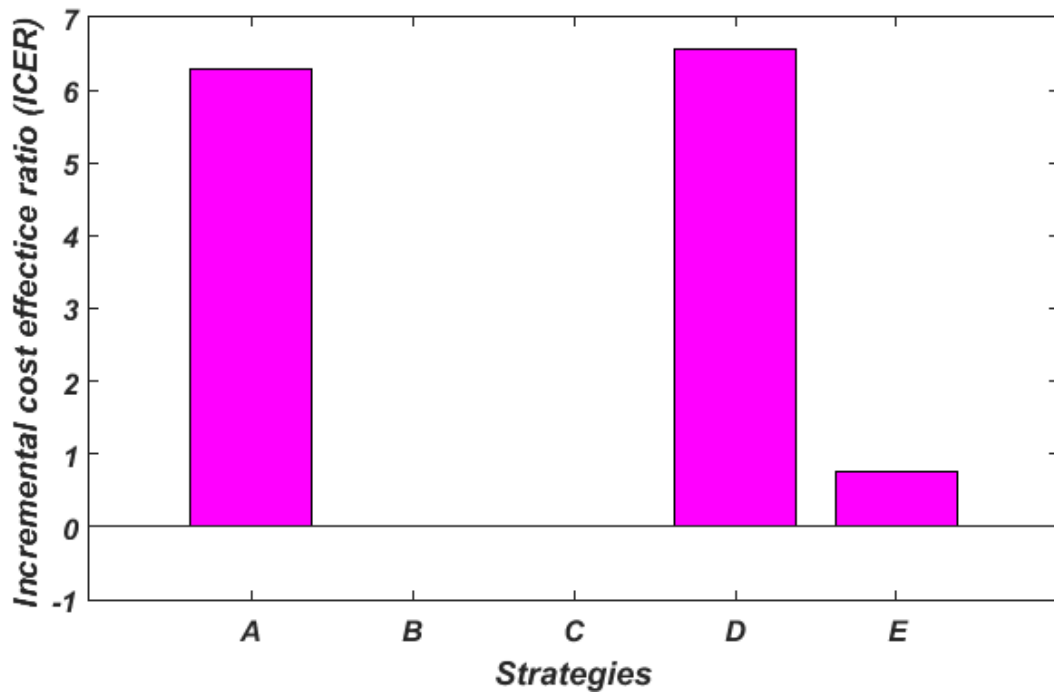


Figure 20: Incremental cost effective ration (ICER) plots indicating the effect of control strategies A, B, C, D and E

8. Conclusion

In this chapter, a mathematical model of HIV/AIDS with an optimal control strategy was formulated and analyzed using the stability theory of differential equations. First, we analyzed the invariant region and the positivity solution of the model. The basic reproduction number representing the epidemic indicator is obtained using the next generation matrix. Both local and global stability of the disease-free equilibrium and endemic equilibrium point of the model equation was established. The results show that, if the basic reproduction number is less than one, then the solution converges to the disease-free steady-state, and the disease-free equilibrium is asymptotically stable. Sensitivity analysis of the model equation was performed on the key parameters in order to determine their impact on the disease transmission dynamics. Second, we apply optimal control theory to describe the model that incorporates three controls, namely using prevention of HIV/AIDS, screening of asymptomatic populations, and treatment of infected populations. Pontryagin's maximum principle is introduced to obtain the necessary condition for the optimal control problem. Finally, the simulation result of optimal control problem and analysis of cost-effectiveness show that a combination of using prevention and screening is the most effective and least-cost strategy to prevent the HIV/AIDS disease.

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