

Herpes Simplex Virus Type -2 (HSV-2) and HIV Co-infection Dynamics with Optimal Control

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ABSTRACT

Herpes Simplex Virus type-2 (HSV-2) is a member of the human Herpes virial family, a set of viruses that produce viral infection in majority of humans. It is frequently unrecognized lifelong infection which may facilitate the Human Immunodeficiency Virus (HIV) transmission. In this paper, a deterministic co-infection model of HSV-2 and HIV was considered. The model was qualitatively analysed and numerically simulated. Optimal control theory was applied. We proved existence of the optimal control and characterized the controls. The controls represent monitoring and counselling of individuals infected with HSV-2 only and also represent monitoring and counselling of individuals dually infected with HSV-2 and HIV. It was revealed that efforts should be devoted to individuals dually infected with HSV-2 and HIV as compared to those infected with HSV-2 only.

1. Introduction

Herpes simplex virus type 2 (HSV-2) infection is widespread throughout the world and almost exclusively sexually transmitted, causing genital herpes that is lifelong incurable. HIV is a retrovirus that infects cells of the human system that leads to acquired immune deficiency syndrome (AIDS). AIDS is a condition in humans in which progressive failure of the immune system allows life-threatening infections and cancers to thrive. Since HIV was first identified in the United States in 1983, over 60 million people have been infected and the WHO estimates that deaths due to AIDS exceeds 25 million people Abu-Raddad, (2008). HSV-2 is a double strand DNA virus, with human being as the only natural hosts.

Herpes simplex virus type 2 (HSV-2) and human immunodeficiency virus (HIV) are sexually transmitted infections (STIs) that are detrimental to human health.

There are 1.5 million new HSV-2 infections among 15-20years old in sub-Saharan Africa every year and an estimated 1.6 million infections annually in the USA. HSV-2 has been recognized as the most common cause of genital ulcer disease. HSV-2 is a significant factor for increased risk of acquisition and transmission of HIV (Bhunu *et al.*, 2009). In the United States of America (USA), annual health costs for STIs have reached US\$17 Billion, with HSV-2 taking \$541 million, making it the third most costly sexually transmitted infection (STI) after HIV and human papillomavirus (HPV) (Blower *et al.*, 2004).

New controls for the prevention of infection with HIV are necessary, especially in sub-Saharan Africa. The use of condoms remains low in the region, despite intensive educational campaigns, and sexually transmitted infections are highly prevalent, especially infection with HSV-2, with a prevalence of up to 80% (Bhunu *et al.*, 2009). HIV target cells and have been detected in herpetic lesions, and the presence of these cells could also increase susceptibility to HIV (Castillo- Chavez *et al.*, 2004). Researchers suggest that HSV-2 infection doubles the risk of acquiring HIV and may contribute to more than 50% of HIV infections in sub-Saharan Africa (Castillo-Chavez *et al.*, 2002). The epidemiological and biological relationship between HSV-2 and HIV has been the subject of many studies over the years, with more proves supporting the hypothesis that HSV-2 increase the risk of acquiring and transmission HIV (Feng *et al.*, 2009). This relationship between these two viruses has led researchers to consider HSV-2 suppressive treatment as a biomedical prevention control to reduce the risk of HIV transmission (Freeman *et al.*, 2006). Despite numerous research efforts that have been devoted to the study of HIV and HSV-2 co-infection, the aspect of poor HSV-2 treatment adherence and its impact on infection and spread of HIV has not yet been investigated. The global consensus currently is that, prevention of new infections is the key to reversing the HIV/AIDS epidemic, hence HSV-2 treatment with good treatment adherence can be another possible strategic method (Foss *et al.*, 2009).

With HSV-2 being a pathway for the transmission of HIV, this has motivated many authors to look at

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HIV/HSV-2 co-infections. A number of mathematical models have looked into mathematical modelling of HIV and HSV-2 co-infections from a number of different issues (Helton *et al.*, 1993). In contrast to other STIs such as chlamydia, gonorrhea and syphilis, infection with HSV-2 or HIV is lifelong and once established, there is currently no treatment to eliminate. We looked at the impact of poor HSV-2 treatment adherence on HIV/AIDS prevalence. The aim of this paper is to study an optimal control model of HIV and HSV-2 co-infection, by considering two control measures (namely: monitoring and counselling individuals infected with HSV-2 only and monitoring and counselling individuals dually infected with HIV and HSV-2) that try to reduce the number of individuals who quit HSV-2 anti-viral treatment before completion. To achieve our aim, we shall apply the optimal control theory which has proven to be a successful tool in understanding ways to curtail the spread of infectious diseases by devising the optimal disease intervention strategies. The method consists of minimizing the cost of infection or the cost of implementing the controls or both.

The paper is organized as follows. In the next section, the model is formulated. Section 3 is dedicated to the stability analysis of the model. The definition of an optimal control, model properties and proof of existence of optimal control, analysis and the numerical simulations are given in Section 4. The paper is concluded in Section 5.

2. The Model

The total sexual active population at time t , denoted by $\bar{N}$, is sub-divided into eleven (11) compartments, namely susceptible ($\bar{S}$), individuals infected with acute HSV-2 only and under antiviral treatment ($\bar{I}_1$), individuals with acute HSV-2 only and not under anti-viral treatment ($\bar{I}_2$), individuals infected with latent HSV-2 only after undergoing successful anti-treatment ($\bar{Q}_1$), individuals with latent HSV-2 only after undergoing natural healing ($\bar{Q}_2$), individuals infected with HIV only ($\bar{H}$), individuals dually infected with HIV and acute HSV-2, also under HSV-2 anti-viral treatment ($\bar{H}_{I1}$), individuals dually infected with HIV and latent HSV-2, also not under HSV-2 anti-viral treatment ($\bar{H}_{I2}$), individuals dually infected with HIV and latent HSV-2 after undergoing successful HSV-2 treatment ($\bar{H}_{Q1}$), individuals dually infected with HIV and latent HSV-2 after undergoing natural healing ($\bar{H}_{Q2}$) and the AIDS class ($\bar{A}$), so that

$$\bar{N} = \bar{S} + \bar{I}_1 + \bar{I}_2 + \bar{Q}_1 + \bar{Q}_2 + \bar{H} + \bar{H}_{I1} + \bar{H}_{I2} + \bar{H}_{Q1} + \bar{H}_{Q2} + \bar{A}. \quad (1)$$

The recruitment of susceptible is proportional to the population and is given by $\mu\bar{N}$ as applied in (Abu-Raddad, 2008). Both singly and dually infected individuals transmit either HSV-2 or HIV, not both at the same time. Susceptible individuals acquire infection following effective contact with HIV infected individuals at a rate $\bar{\lambda}_H$ and acquire HSV-2 infection following effective contact with HSV-2 infective at a rate $\bar{\lambda}_I$. Natural death rate occurs in all compartments at a rate μ and the AIDS induced death rate ν . The force of infection of HSV-2 is denoted by $\bar{\lambda}_I$, given by

$$\bar{\lambda}_I = \frac{\beta_I[(1-\alpha_1)(\bar{I}_2 + (1-\eta_1)\bar{I}_1) + (\bar{H}_{I2} + (1-\eta_2)\bar{H}_{I1})]}{\bar{N}} \quad (2)$$

Where, β_H is the effective contact rate for HSV-2 transmission, the modification parameter $\alpha_1 \in (0,1)$ for the relative infectiousness of individuals dually infected with HIV and HSV-2, as compared to those infected with HIV and HSV-2 only. The modification parameter $0 < \eta_1, \eta_2 < 1$ account for the assumed reduced likelihood for individuals in classes $\bar{I}_1$ and $\bar{H}_{I1}$ to pass on infection compared to classes $\bar{I}_2$ and $\bar{H}_{I2}$ respectively.

This is due to the fact that individuals in treatment have reduced viral load compared to those who have failed to adhere to anti-viral treatment guidelines. Also, susceptibles acquire HIV infection following effective contact with HIV infected individuals at a rate $\bar{\lambda}_H$, given by

$$\bar{\lambda}_H = \frac{\beta_H[(1-\alpha_2)(\bar{H} + \bar{H}_{Q1} + \bar{H}_{Q2}) + (\bar{H}_{I2} + (1-\tau)\bar{H}_{I1})]}{\bar{N}} \quad (3)$$

β_H is the effective contact rate for HIV infection, $\alpha_1 \in (0,1)$ is a modification parameter accounting for increased likelihood of infectiousness by individuals in classes $\bar{H}_{I1}$ and $\bar{H}_{I2}$ relative to those in classes $\bar{H}$, $\bar{H}_{Q1}$ and $\bar{H}_{Q2}$. $\tau \in (0,1)$ Captures the assumption that individuals who are dually infected with HIV and HSV-2 and under treatment have reduced likelihood of passing on the infection as compared to the individuals who are dually infected with HIV and HSV-2 and also not under HSV-2 treatment. Upon being infected with HSV-2, the individuals infected with HSV-2 only will become latent at constant rate k_1 , where as those dually infected with HIV and HSV-2 become latent at a rate k_2 . Following an appropriate stimulus in individuals with latent HSV-2 and those dually infected with HIV and latent HSV-2, re-activation may occur (Golin *et al.*, 2002). The anti-viral treatment for individuals with acute HSV-2 only and individuals dually infected with HIV and HSV-2 is denoted by ψ . Since the anti-viral medication will also suppress re-activation of latent HSV-2, we assume that the re-activation rate of people with latent HSV-2 only and those dually infected with HIV and latent HSV-2 is at rate $\gamma^{(1)}(\psi)$ and $\gamma^{(2)}(\psi)$, respectively. Both $\gamma^{(1)}(\psi)$ and $\gamma^{(2)}(\psi)$ are decreasing functions of ψ and $\gamma^{(1)}$. Hence

$$\gamma^{(1)} = \gamma_0^{(1)} \frac{\omega_1}{\omega_1 + \psi}, \gamma^{(2)} = \gamma_0^{(2)} \frac{\omega_2}{\omega_2 + \psi} \quad (4)$$

in which the factor $\frac{w_i}{w_i+\psi}$ for $i = 1, 2$ represents reduced re-activation treatment. In the case where there is no treatment for the individuals infected with HSV-2 only, we have that $\psi = 0$; thus $\gamma^{(1)}(\psi_0) \equiv \gamma^{(1)}(0) \equiv \gamma_0^{(1)}$. Similarly, for the case where there is no treatment for the individuals dually infected with HIV and HSV-2, we also have that $\psi = 0$; thus $\gamma_0^{(2)}(\psi_0) \equiv \gamma^{(2)}(0) \equiv \gamma_0^{(2)}$. A proportion $(1 - \theta_1)$ of individual infected with HSV-2 only fail to adhere to treatment at rate δ_1 HSV-2 only fail to adhere to treatment at rate δ_1 and then move to class I_2 . Furthermore, a proportion $(1 - \theta_2)$ of individuals dually infected with HIV and HSV-2 fail to adhere to HSV-2 anti-viral treatment at rate δ_2 , and they move to class H_{12} . $\sigma \geq 1$ denotes the enhanced susceptibility to HIV infection for individuals infected with acute HSV-2. $\varphi \geq 1$ denotes the enhanced susceptibility to HSV-2 infection for individuals infected with HIV only. It is worth noting that $\gamma^{(2)}$ and $\gamma^{(2)}$ do not mean squared or to the power 1 respectively, but will be used as our notation throughout the manuscript. The model flow diagram is depicted in Figure 1.

From the above descriptions and assumptions on the dynamics of the epidemic above, the following are the model equations.

$$\begin{cases} S' = \mu N - (\bar{\lambda}_H + \bar{\lambda}_I)S - \mu S, \\ I_1' = \bar{\lambda}_I S + \gamma^{(1)}\bar{Q}_1 - \sigma\bar{\lambda}_H I_1 - (\delta_1(1 - \theta_1) + k_1 + \psi + \mu)\bar{I}_1 \\ I_2' = \delta_1(1 - \theta_1)\bar{I}_1 - \sigma\bar{\lambda}_H I_2 + \gamma^{(1)}\bar{Q}_2 - (\mu + k_1)\bar{I}_2 \\ Q_1' = (k_1 + \psi)\bar{I}_1 - \bar{\lambda}_H Q_1 - (\gamma^{(1)} + \mu)\bar{Q}_1, \\ Q_2' = k_1\bar{I}_2 - \bar{\lambda}_H Q_2 - (\gamma_0^{(1)} + \mu)\bar{Q}_2, \\ H' = \bar{\lambda}_H S - \phi\bar{\lambda}_I H - (\mu + \varphi)\bar{H} \\ H_{I1}' = \phi\bar{\lambda}_I H - (\delta_2(1 - \theta_2) + \varphi + k_2 + \psi + \mu)\bar{H}_{I1} + \gamma^{(2)}\bar{H}_{Q1} + \sigma\bar{\lambda}_H I_1, \\ H_{I2}' = \delta_2(1 - \theta_2)\bar{H}_{I1} + \sigma\bar{\lambda}_H I_2 + \gamma_0^{(2)}\bar{H}_{Q2} - (\mu + k_2 + \varphi)\bar{H}_{I2} \\ H_{Q1}' = (k_2 + \psi)\bar{H}_{I1} - (\mu + \varphi + \gamma^{(2)})\bar{H}_{Q1} + \bar{\lambda}_H Q_1, \\ H_{Q2}' = \bar{\lambda}_H Q_2 + k_2\bar{H}_{I2} - (\mu + \varphi + \gamma_0^{(2)})\bar{H}_{Q2} \\ A' = \varphi(\bar{H} + \bar{H}_{I1} + \bar{H}_{I2} + \bar{H}_{Q1} + \bar{H}_{Q2}) - (\mu + v)\bar{A} \end{cases} \quad (5)$$

Rescaling model system (5) so that we have dimensionless variables.

$$S = \frac{\bar{S}}{N}, I_1 = \frac{\bar{I}_1}{N}, I_2 = \frac{\bar{I}_2}{N}, Q_1 = \frac{\bar{Q}_1}{N}, Q_2 = \frac{\bar{Q}_2}{N}, H = \frac{\bar{H}}{N}, \\ H_{I1} = \frac{\bar{H}_{I1}}{N}, H_{I2} = \frac{\bar{H}_{I2}}{N}, H_{Q1} = \frac{\bar{H}_{Q1}}{N}, H_{Q2} = \frac{\bar{H}_{Q2}}{N}, A = \frac{\bar{A}}{N}$$

We thus have the following re-scaled system

$$\begin{cases} S' = \mu - (\lambda_H + \lambda_I)S - \mu S, \\ I_1' = \lambda_I S + \gamma^{(1)}Q_1 - \sigma\lambda_H I_1 - (\delta_1(1 - \theta_1) + k_1 + \psi + \mu)I_1 \\ I_2' = \delta_1(1 - \theta_1)I_1 - \sigma\lambda_H I_2 + \gamma^{(1)}Q_2 - (\mu + k_1)I_2, \\ Q_1' = (k_1 + \psi)I_1 - \lambda_H Q_1 - (\gamma^{(1)} + \mu)Q_1, \\ Q_2' = k_1I_2 - \lambda_H Q_2 - (\gamma_0^{(1)} + \mu)Q_2, \\ H' = \lambda_H S - \phi\lambda_I H - (\mu + \varphi)H, \\ H_{I1}' = \phi\lambda_I H - (\delta_2(1 - \theta_2) + \varphi + k_2 + \psi + \mu)H_{I1} + \gamma^{(2)}H_{Q1} + \sigma\lambda_H I_1, \\ H_{I2}' = \delta_2(1 - \theta_2)H_{I1} + \sigma\lambda_H I_2 + \gamma_0^{(2)}H_{Q2} - (\mu + k_2 + \varphi)H_{I2}, \\ H_{Q1}' = (k_2 + \psi)H_{I1} - (\mu + \varphi + \gamma^{(2)})H_{Q1} + \lambda_H Q_1, \\ H_{Q2}' = \lambda_H Q_2 + k_2H_{I2} - (\mu + \varphi + \gamma_0^{(2)})H_{Q2} \\ A' = \varphi(H + H_{I1} + H_{I2} + H_{Q1} + H_{Q2}) - (\mu + v)A \end{cases} \quad (6)$$

where $\lambda_I = \beta_I[(1 - \alpha_1)(I_2 + (1 - \eta_1)I_1) + (H_{I2} + (1 - \eta_2)H_{I1})]$ and $\lambda_H = \beta_H[(1 - \alpha_2)(H + H_{Q1} + H_{Q2}) + (H_{I2} + (1 - \tau)H_{I1})]$.

Since model system (6) monitors human populations, all the state variables and parameters of the model are non-negative. Consider the biologically-feasible region

$$\Omega = \{(S_1, I_1, I_2, Q_1, Q_2, H, H_{I1}, H_{I2}, H_{Q1}, H_{Q2}, A) \in \mathbb{R}_+^{11}; N \leq 1\} \quad (7)$$

The following steps are followed to establish the positive invariance of Ω . The rate of change of the total population, obtained by adding all the equations in model system (6), is given by

$$\frac{dN}{dt} = \mu - \mu N - vA \leq \mu - \mu N \quad (8)$$

It is easy to see that whenever $N > 1$, then $\frac{dN}{dt} < 0$. Since $\frac{dN}{dt}$ is bounded by $\mu - \mu N$ a standard comparison theorem Carr (1981) can be used to show that

$$N(t) \leq N(0)\exp^{-\mu t} + (1 - \exp^{-\mu t}) \quad (9)$$

$N(t) \leq 1$ if $N(0) \leq 1$. Thus, every solution of the model system (6) with initial conditions in Ω is positive invariant and attracting. Hence it is sufficient to consider the dynamics of the flow generated by model system (6) in Ω . In this region, the model can be considered as been epidemiologically and mathematically well-posed

1. MODEL ANALYSIS

It is necessary to gain insights into the dynamics of the models for HIV only (HIV-only model) (Lakshmikantham *et al.*, 1989) and HSV-2 only (HSV-2 only model) (Lenhart and Workman, 2007).

3.1 HIV/HSV-2 model

Having explored the two sub-models, the full HIV/HSV-2 model system (6) is now considered.

3.1.1 Disease-free equilibrium and stability analysis

The disease-free equilibrium for model system (6) is given by

$$\xi_{H1}^0 = (S^0, I_1^0, I_2^0, Q_1^0, Q_2^0, h^0, H_{11}^0, H_{12}^0, H_{Q1}^0, H_{Q2}^0, A^0) = (1, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0) \quad (10)$$

Using the next-generation matrix method by Driessche and Watmough (2002). It can be shown that the reproduction number for the full HIV/HSV-2 model system (6) denoted by R_H is given by

$$R_{HI} = \max \left\{ \frac{\beta_H}{\mu + \theta}, \frac{\beta_1(\mu + \gamma)\delta_1(1 - \theta_1)(\mu + \gamma_0) + \mu(1 - \eta_1)(\mu + k_1 + \gamma_0)}{\mu(\mu + k_1 + \gamma_0)[\gamma(\delta_1(1 - \theta_1) + \mu) + \mu(\delta_1(1 - \theta_1)\mu + k_1 + \psi)]} \right\} \quad (11)$$

so that the following result follows from Theorem 2 in van den Driessche and Watmough (2002).

Theorem 1. The disease-free equilibrium ξ_{H1}^0 of model system (6) is locally asymptotically stable if $R_{H1} < 1$ and unstable if $R_{H1} > 1$.

Using a comparison theorem by (Lakshmikantham *et al.*, 1989), we can explore the global stability of the disease free equilibrium (DFE) in the case that the reproduction number is less than unity.

Theorem 2. The disease-free equilibrium ξ_{H1}^0 of model system (6) is globally asymptotically stable if $\mathfrak{R}_{H1} \leq 1$ and unstable if $\mathfrak{R}_{H1} \geq 1$.

3.1.2 Interior equilibrium point and its stability analysis

This equilibrium occurs when both infections coexist in the community. The interior equilibrium point is given by

$$\mathcal{E}_{HI}^* = (S^*, I_1, I_2, Q^*, Q_2^*, H^*, H_{11}^*, H_{12}^*, H_{Q1}^*, H_{Q2}^*, A^*), \quad (12)$$

where each of the corresponding components are in terms of the force of infection λ_H^* and λ_1^* . However, they are too cumbersome to be expressed explicitly, but we claim a biologically feasible interior equilibrium exists. In the following, we will present the local stability ξ_{H1}^* when the reproduction number R_{H1} is close to 1. We will apply the centre manifold theorem Mbopi-Keou (2007), but we first present the following lemma.

Lemma 1. Consider the following general system of ordinary differential equations with parameter θ

$$\begin{aligned} \frac{dx}{dt} &= f(x, \phi) f: \mathbb{R}^n \times \mathbb{R} \rightarrow \mathbb{R}, \text{ and} \\ f &\in \mathbb{C}^2(\mathbb{R}^n \times \mathbb{R}^n) \end{aligned} \quad (13)$$

where 0 is an equilibrium of the system, that is $f(0, \phi) = 0 \quad \forall \phi$, and assume

A1) $A = D_x f(0, 0) = \left(\frac{\partial f_1}{\partial x_j}(0, 0) \right)$ is the linearization of system (6) around the equilibrium 0 and ϕ evaluated at 0. Zero is a simple eigenvalue of A and other eigenvalues of A have negative real parts

A2) Matrix A has the right eigenvector u and a left eigenvector v corresponding to the zero eigenvalue let f_k be the k^{th} component of f and

$$\begin{aligned} a &= \sum_{k,i,j=1}^n v_k u_i u_j \frac{\partial^2 f_k}{\partial x_i \partial x_j}(0, 0) \\ b &= \sum_{k,i=1}^n v_k u_i \frac{\partial^2 f_k}{\partial x_i \partial \phi}(0, 0) \end{aligned} \quad (14)$$

The local dynamics of (13) around zero are totally governed by a and b. i. $a > 0, b > 0$. When $\phi < 0$ with $|\phi| < 1$, and there exist a positive unstable equilibrium, when $0 < \theta < 1, 0$ is unstable and there exists a negative and locally asymptotically stable equilibrium;

ii. $a < 0, b < 0$. When $\phi < 0$ with $|\phi| < 1$, unstable, when $0 < \theta < 1, 0$ is locally asymptotically stable and there exist a positive unstable equilibrium;

iii. $a > 0, b < 0$. When $\theta < 0$ with $|\theta| < 1, 0$ is unstable, and there exist a locally asymptotically stable negative equilibrium; when $0 < \phi < 1, 0$ is stable, and a positive unstable equilibrium appears;

iv. $a < 0, b > 0$. When ϕ changes from negative to positive, 0 changes its stability from stable to unstable. Corresponding a negative unstable equilibrium becomes positive and locally asymptotically stable;

Theorem 3. The unique endemic equilibrium $\mathcal{E}_{H1}^*$ is locally asymptotically stable if $R_{H1} > 1$ but close to 1.

3. Optimal Control Problem

In this section, we present an optimal control problem, describing our goal and the restrictions of the epidemics, in order to investigate an effective campaign on reducing HIV/AIDS and HIV/HSV-2 co-infections. HSV-2 anti-viral treatment adherence is low in some parts of the world especially in sub-Saharan Africa where HIV/AIDS is at its highest. Monitoring and counselling of individuals infected with HSV-2 only and those dually infected with HIV/HSV-2, to HSV-2 anti-viral treatment can be a possible aid in the reduction of HIV/AIDS. We will reconsider model system (6) and introduce two time-dependent control variables. We seek to reduce the number of individuals who quit HSV-2 treatment before completion. There will be a lot of costs generated during the control process. So it is advisable to balance between the costs and the non-adherence effects.

Assuming the control variables in the set

$$U = \{(u_1, u_2); [0, T] \rightarrow \mathbb{R}^2 | u_i(t) \text{ is a Lebesgue measure on } [0, U_i], i = 1, 2\} \quad (15)$$

in which all control variables are bounded and Lebesgue measurable and $U_i, i = 1, 2$ is denoted to be the upper bound of the control variables. In our controls, u_1 denotes a time-dependent control effort on counselling and monitoring individuals with HSV-2 only, while u_2 is the same but for individuals dually infected with HIV and HSV-2.

In view of this, our optimal control problem is to minimize the objective functional given by

$$J(u_1, u_2) = \int_0^T \left[z_1 I_2 + z_2 H_{12} + b_1 u_1 I_2 + b_2 u_2 H_{12} + \frac{1}{2} (c_1 u_1^2 + c_2 u_2^2) \right] dt \quad (16)$$

subject to the system

$$\begin{cases} S' = \mu - (\lambda_H + \lambda_I)S - \mu S, \\ I_1' = \lambda_I S + \gamma^{(1)} Q_1 - \sigma \lambda_H I_1 - (\delta_1(1 - u_1) + k_1 + \psi + \mu) I_1, \\ I_2' = \delta_1(1 - u_1) I_1 - \sigma \lambda_H I_2 + \gamma^{(1)} Q_2 - (\mu + k_1) I_2, \\ Q_1' = (k_1 + \psi) I_1 - \lambda_H Q_1 - (\gamma^{(1)} + \mu) Q_1, \\ Q_2' = k_1 I_2 - \lambda_H Q_2 - (\gamma_0^{(1)} + \mu) Q_2, \\ H' = \lambda_H S - \phi \lambda_1 H - (\mu + \varphi) H, \\ H_{11}' = \phi \lambda_1 H - (\delta_2(1 - u_2) + \varphi + k_2 + \psi + \mu) H_{11} + \gamma^{(2)} H_{Q1} + \sigma \lambda_H I_1, \\ H_{12}' = \delta_2(1 - u_2) H_{11} + \sigma \lambda_H I_2 + \gamma_0^{(2)} H_{Q2} - (\mu + k_2 + \varphi) H_{12}, \\ H_{Q1}' = (k_2 + \psi) H_{11} - (\mu + \varphi + \gamma^{(2)}) H_{Q1} + \lambda_H Q_1, \\ H_{Q2}' = \lambda_H Q_{12} + k_2 H_{12} - (\mu + \varphi + \gamma_0^{(2)}) H_{Q2} \\ A' = \varphi(H + H_{11} + H_{12} + H_{Q1} + H_{Q2}) - (\mu + \nu) A \end{cases} \quad (17)$$

where z_i, b_i and $c_i (i = 1, 2)$ are (positive) balancing coefficients transferring the integrals into a monetary quantity over a finite period of T months. The z_i values represent the weights of the individuals infected with acute HSV-2 only and not under anti-viral treatment and the individuals dually infected with HIV and HSV-2, also not under HSV-2 anti-viral treatment, respectively. The terms with b_1 and b_2 represent the costs associated with intervention strategies in monitoring and counselling. We assume that the costs are proportional to the quadratic form of their corresponding control functions. The objective functional in (16) also includes some quadratic terms with coefficients c_1 and c_2 to indicate potential nonlinearities in the costs to indicate potential nonlinearities in the costs.

Our objective is to find an optimal control pair $(u_1^*(t), u_2^*(t))$ in order to seek the minimum value of the objective functional $J(u_1^*(t), u_2^*(t))$, such that

$$J(u_1^*(t), u_2^*(t)) = \min \{J(u_1(t), u_2(t)) | u_1(t), u_2(t) \in U\} \quad (18)$$

subject to the system given by (17).

We now derive necessary conditions that the control pair and corresponding states must satisfy. By using the same method as in Sharomi and Gumel (2007), the existence of the optimal control can be proved. In the above minimizing problem, we can easily verify that the objective functional is convex on the closed, convex control set U . The optimal system is bounded, which determines the compactness needed for the existence of the optimal control.

In order to find an optimal solution of model system (17), first let us define the Hamiltonian functions H for the optimal control system (17) as

$$H(t, X, U, \lambda) = L + \lambda_1 \frac{dS}{dt} + \lambda_2 \frac{dI_1}{dt} + \lambda_3 \frac{dI_2}{dt} + \lambda_4 \frac{dQ_1}{dt} + \lambda_5 \frac{dQ_2}{dt} + \lambda_6 \frac{dH}{dt} + \lambda_7 \frac{dH_{11}}{dt} + \lambda_8 \frac{dH_{12}}{dt} + \lambda_9 \frac{dH_{Q1}}{dt} + \lambda_{10} \frac{dH_{Q2}}{dt} + \lambda_{11} \frac{dA}{dt} \quad (19)$$

where L is the Lagrangian function $L = z_1 I_1 + z_2 H_{11} + b_1 u_1 I_2 + b_2 u_2 H_{12} + \frac{1}{2} (c_1 u_1^2 + c_2 u_2^2)$.

With the existence of the optimal control system, we now present and discuss the adjoint system and the characterizations of the optimal control system.

For simplicity, we denote

$$X(t) = (S(t), I_1(t), I_2(t), Q_1(t), Q_2(t), H_{H1}(t), H_{12}(t), Q_{11}(t), Q_{12}(t), A(t)) \quad (20)$$

and $\lambda = (\lambda_1, \lambda_2, \lambda_3, \lambda_4, \lambda_5, \lambda_6, \lambda_7, \lambda_8, \lambda_9, \lambda_{10}, \lambda_{11})$.

Theorem 4. Let (X^*, U^*) be an optimal control solution of the proposed control system then there exists a vector function $\lambda = (\lambda_1, \lambda_2, \dots, \lambda_9)$ satisfying the following equalities:

$$\begin{cases} \lambda'_1 = \lambda_1[\lambda_1 - \lambda_2] + \lambda_H[\lambda_1 - \lambda_6]\lambda_6 + \mu\lambda_1, \\ \lambda'_2 = \beta_1(1 - \eta_1)(1 - \alpha_1)[\lambda_1 - \lambda_2] + \sigma\lambda_H[\lambda_2 - \lambda_7] + \phi\beta_1(1 - \alpha_1)(1 - \eta_1)H[\lambda_6 - \lambda_7] \\ + \delta_1(1 - u_1)[\lambda_2 - \lambda_3] + (k_1 + \psi)[\lambda_2 - \lambda_4] + \mu\lambda_2, \\ \lambda'_3 = -z_1 + \beta_1(1 - \alpha_1)S[\lambda_1 - \lambda_2] + \sigma\lambda_H[\lambda_3 - \lambda_8] + k_1[\lambda_3 - \lambda_5] + \\ \phi\beta_1(1 - \alpha_1)H[\lambda_6 - \lambda_7] + \mu\lambda_3, \\ \lambda'_4 = \sigma\lambda_H[\lambda_4 - \lambda_9]\lambda_H + \gamma[\lambda_4 - \lambda_2] + \mu\lambda_4, \\ \lambda'_5 = \gamma_0[\lambda_5 - \lambda_3] + \lambda_H[\lambda_5 - \lambda_{10}] + \mu\lambda_5, \\ \lambda'_6 = \beta_H(1 - \alpha_2)S[\lambda_1 - \lambda_6] + \sigma\beta_H(1 - \alpha_2)I_1[\lambda_2 - \lambda_7] + \sigma\beta_H(1 - \alpha_2) \\ I_2[\lambda_3 - \lambda_8] + \phi[\lambda_6 - \lambda_{11}] + \mu\lambda_6 + \beta_H(1 - \alpha_2)Q_1[\lambda_4 - \lambda_9] + \beta_H(1 - \alpha_2) \\ Q_2[\lambda_5 - \lambda_{10}] + \phi\lambda_1[\lambda_6 - \lambda_7], \\ \lambda'_7 = \beta_1(1 - \eta_2)S[\lambda_1 - \lambda_2] + \beta_H[\lambda_1 - \lambda_6](1 - \tau) + \sigma\beta_H(1 - \tau)I_1[\lambda_2 - \lambda_7] \\ + \sigma\beta_H(1 - \tau)I_2[\lambda_3 - \lambda_8] + \beta_H(1 - \tau)Q_1[\lambda_4 - \lambda_9] + \beta_H(1 - \tau)Q_2[\lambda_5 - \lambda_{10}] \\ + \phi\beta_1(1 - \eta_2)H[\lambda_6 - \lambda_7] + \delta(1 - u_2)[\lambda_7 - \lambda_8] + (k_2 + \psi)[\lambda_7 - \lambda_9] + \phi[\lambda_7 - \lambda_{11}] + \mu\lambda_7, \\ \lambda'_8 = -z_1 + \beta_1S[\lambda_1 - \lambda_6] + \sigma\beta_H(1 - \alpha_1)I_1[\lambda_2 - \lambda_7] + \sigma\beta_HI_2[\lambda_3 - \lambda_8] \\ + \beta_HQ[\lambda_4 - \lambda_9] + \beta_HQ_2[\lambda_5 - \lambda_{10}] + \phi[\lambda_8 - \lambda_{11}] + k_2[\lambda_8 - \lambda_{10}] + \mu\lambda_8 + \phi\beta_1H[\lambda_6 - \lambda_7], \\ \lambda'_9 = \beta_H(1 - \alpha_2)S[\lambda_1 - \lambda_6] + \sigma\beta_H(1 - \alpha_2)I_1[\lambda_2 - \lambda_7] + \sigma\beta_H(1 - \alpha_2)I_2[\lambda_3 - \lambda_8] + \\ \beta_H(1 - \alpha_2)Q_1[\lambda_4 - \lambda_9] + \beta_H(1 - \alpha_2)Q_2[\lambda_5 - \lambda_{10}] + \gamma^{(2)}[\lambda_9 - \lambda_7] + \phi[\lambda_9 - \lambda_{11}] + \mu\lambda_9, \\ \lambda'_{10} = \beta_H(1 - \alpha_2)S[\lambda_1 - \lambda_6] + \sigma\beta_H(1 - \alpha_2)I_1[\lambda_2 - \lambda_7] + \sigma\beta_H(1 - \alpha_2)I_2[\lambda_3 - \lambda_8] + \\ \beta_H(1 - \alpha_2)Q_1[\lambda_4 - \lambda_9] + \beta_H(1 - \alpha_2)Q_2[\lambda_5 - \lambda_{10}] + \phi[\lambda_9 - \lambda_{11}] + \mu\lambda_{10} \\ \lambda'_{11} = (\mu + \nu)\lambda_{11} \end{cases} \quad (21)$$

with transversality conditions (or boundary conditions)

$$\lambda_i = 0, i = 1, 2, \dots, 9.$$

Furthermore, an optimal control could be attained

$$\begin{cases} u_1^* = \max\left\{0, \min\left\{\frac{(\lambda_3 - \lambda_2)\delta_1 I_1 - b_1 I_2}{c_1}\right\}\right\}, \\ u_2^* = \max\left\{0, \min\left\{\frac{(\lambda_8 - \lambda_7)\delta_2 H_{11} - b_2 H_{12}}{c_2}\right\}\right\}. \end{cases}$$

Proof: The Pontryagin's Maximum Principle, Pontryagin (1962) is used to find an optimal solution,

$$\begin{cases} \frac{\partial H(t, X, U, \lambda)}{\partial U} = 0 \text{ at } U^* (\text{optimality condition}) \\ \lambda' = -\frac{\partial H(t, H, U, \lambda)}{\partial X} \text{ (adjoint condition)} \\ \lambda(T) = 0 \text{ (transversely condition)} \end{cases}$$

Applying the adjoint conditions to the Hamiltonian (20) with $X = X^*$, that is

$$\lambda'_1 = -\frac{\partial H}{\partial S}, \lambda'_2 = -\frac{\partial H}{\partial I_1}, \lambda'_3 = -\frac{\partial H}{\partial I_2}, \dots, \lambda'_{11} = -\frac{\partial H}{\partial A}, \quad (22)$$

we then obtain model system (21). The optimal conditions

at U^* could be calculated as follows,

$$\frac{\partial H}{\partial u_1} = 0, \frac{\partial H}{\partial u_2} = 0,$$

That is

$$\begin{cases} c_1 u_1 + \delta_1 I_1 \lambda_2 - \delta_1 I_1 \lambda_3 + b_1 I_2 = 0 \\ c_2 u_2 + \delta_2 H_{11} \lambda_7 - \delta_2 H_{11} \lambda_8 + b_2 H_{12} = 0 \end{cases} \quad (23)$$

Using the bounds on the controls, we obtain the optimal control solutions of system (23). The optimality system consists of the state system coupled with the adjoint system, the initial conditions, the transversality conditions and the characterization of the optimal control. Substituting u_1^* and u_2^* for $u_1(t)$ and $u_2(t)$ in equation (21) gives the optimality system. The state system and adjoint system have finite upper bounds. These bounds are needed in the uniqueness proof of the optimality system. Due to a priori boundedness of the state and adjoint functions and the resulting Lipschitz structure of the ODEs, we obtain the uniqueness of the optimal control. The uniqueness of the optimal control follows from the uniqueness of the optimality system.

4. Numerical Simulations

The numerical study of the control strategies against HIV and HSV-2 co-infection was considered in this section. Numerical results in this section were generated using the forward and backward sweep methods (FBSM) (Van den Driessche and Watmough, 2002)

In order to illustrate the results of the foregoing analysis, we have simulated model system (6) using the parameters in Table 1. Unfortunately, the scarcity of the data on HSV-2 and HIV/AIDS correlation with a focus on HSV-2 treatment adherence limits our ability to calibrate; nevertheless, we assume some of the parameters in the realistic range for illustrative purposes. We use parameters obtained from previous researches by Feng *et al.* (2013); Foss *et al.* (2009) and Abu-Raddad *et al.* (2008). Reliable data on HSV-2 and HIV/AIDS correlation with a focus on HSV-2 treatment adherence would enhance our understanding and aid in the possible intervention strategies to be implemented.

The estimated parameters, among which are the weights on costs c_1 and c_2 weights on I_2 (individuals infected with acute HSV-2 only and not under antiviral treatment) and H_{12} (individuals dually infected with HIV and acute HSV-2, also not under HSV-2 anti-viral treatment); have been chosen for illustrative purposes. Thus $z_1 = 5000$, $z_2 = 5000$, $b_1 = 1$, $c_1 = 0.5$, $c_2 = 0.5$, and the following initial population levels are used in all the simulations $S(0) = 0.6$, $I_1(0) = 0.25$, $I_2(0) = 0.0$, $Q_1(0) = 0.0$, $Q_2(0) = 0.0$, $H(0) = 0.01$, $H_{11}(0) = 0.0$, $Q_{11}(0) = 0.0$, $Q_{12}(0) = 0.0$, $A(0) = 0.0$ over a period of 36 months (3 years).

Table 1: Definition of Parameters

Definition	Symbol	Baseline values (Range)	Source
Effective contact rate for HSV-2 infection	βI	0.2	Abu-Raddad (2008)
Effective contact rate for HIV infection	βH	0.3(0.11-0.95)	Plummer (2010)
Rate of acute HSV-2 becoming latent	$\kappa 1$	2.3805(2.3803-2.678)	Mhlanga (2015)
Rate of acute HSV-2 and HIV infected becoming latent	$\kappa 2$	1.683(1.458- 1.875)	Mhlanga (2015)
Treatment quitting rate	$\delta 1$	0.3	Mushayabasa(2011)
Treatment quitting rate (dually infected)	$\delta 2$	0.3	Assumed
Proportion of HSV-2 patients who successfully complete treatment	$\theta 1$	0.7(0-1)	Assumed
Proportion of patients who successfully complete treatment (dually infected)	$\theta 2$	0.8(0-1)	Assumed
Reactivation rate with an effect of treatment (HSV-2 only)	$\gamma(1)(\psi)$	Varies	Abu-Raddad (2008)
Reactivation rate with an effect of treatment (dually infected)	$\gamma(2)(\psi)$	Varies	Abu-Raddad (2008)
Baseline reactivation rate of latent HSV-2	$\gamma 0(1)(\psi)$	0.339 – 0.436	Mhlanga et al., (2015)
Baseline reactivation rate of latent HSV-2 (dually infected)	$\gamma 0(2)(\psi)$	0.365 – 0.469	Mhlanga et al., (2015)
Enhance susceptibility of people with acute HSV-2 to HIV infection	Σ	2.7 – 3.1	Owusu-Edusei et al., (2008)
Enhanced susceptibility to HSV-2 infection by HIV infective	Φ	≥ 1	Abu-Raddad (2008)
Treatment rate of acute HSV-2	Ψ	Varied	Abu-Raddad (2008)
Rate of progression form HIV to AIDS	Φ	0.0104	Mhlanga et al., (2015)
Average sexual lifespan	M	0.004(0.003 – 0.005)	Mhlanga et al., (2015)
AIDS related death rate	V	0.03	Reynolds et al., (2005)
Modification parameter	$\alpha 1$	(0 - 1)	Assumed
Modification parameter	$\alpha 2$	(0 - 1)	Assumed
Modification parameter	$\eta 1$	(0 - 1)	Assumed
Modification parameter	$\eta 1$	(0 - 1)	Assumed
Modification parameter	T	(0 - 1)	Assumed

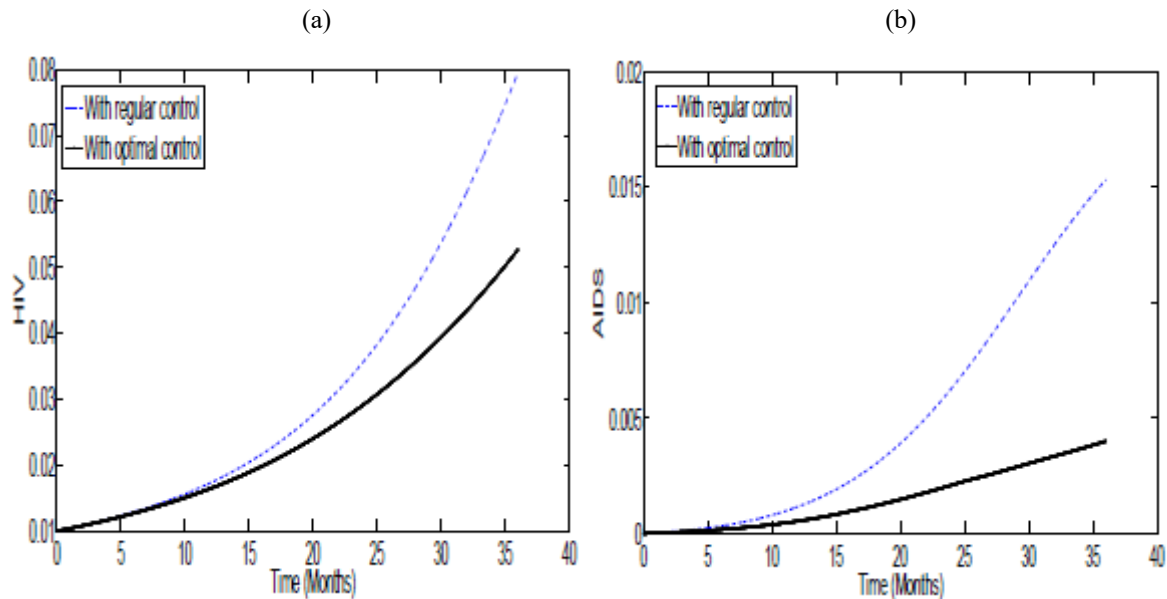


Figure 1. Graphs of the numerical simulation of the optimality system, showing the propagation of (a) HIV cases only (b) AIDS cases over a period of 36 months.

Figure 1(a) illustrates the impact of controls on the population of the individuals infected with HIV- only. The population of the HIV-only have moderate increases for the whole period under study for both cases in the presence and absence of controls. It is worth noting that the controls are effective for a period from 6 to 36 months. Further, we note that after 36 months, the control has an effect of reducing the HIV cases by approximately 35%.

Numerical result in figure 1(b) illustrate the impact of optimal counselling and monitoring on the individuals infected with HSV-2 only and those dually infected with HIV/HSV-2 on the AIDS cases. Overall we observe that the population of the AIDS cases increases for both cases (with and without the controls) for the whole period under review. For the period of 4 to 36 months, we observe an increase of AIDS cases in the absence of controls as compared to the presence of controls. Thus, the controls start showing some effectiveness on the AIDS cases after 4 months.

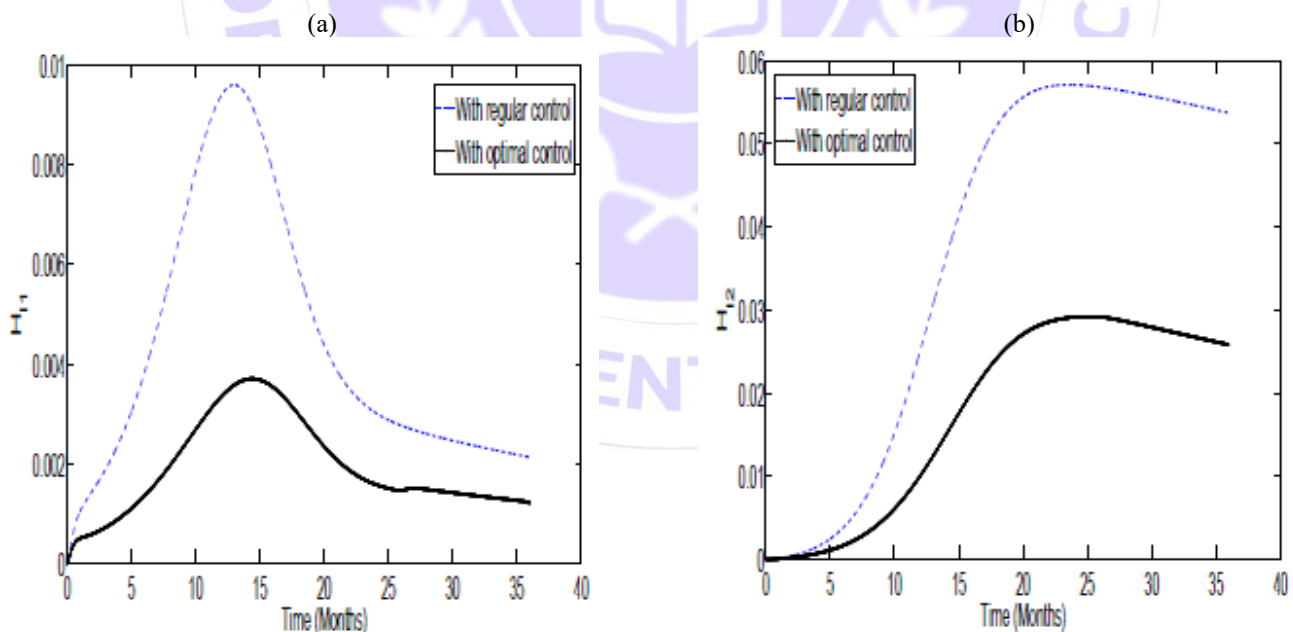


Figure 2. Graphs of the numerical simulation of the optimality system, showing the propagation of (a) individuals dually infected with HIV and acute HSV-2 also under HSV-2 anti-viral treatment and (b) individuals dually infected with HIV and acute HSV-2, also not under HSV-2 anti- viral treatment, over a period of 36 months.

Figure 2(a) illustrates the proportion of individuals who are dually infected with HIV and acute HSV-2, also under HSV-2 anti-viral treatment, in the presence and absence of controls. For both cases, in the absence and presence of controls, there is a sharp increase for the period of 0 – 15 months. It is worth noting that both cases reach maximum value at 15 month. The maximum proportion reached in the presence of controls is approximately 0.004 and the maximum proportion in the

absence of controls is approximately 0.1 for the period of 15 – 36 months for both cases, we note that they both drop uniformly with the H_{I1} proportion higher in the absence of controls as compared to their presence.

Figure 2(b) illustrates the proportion of individuals who are dually infected with HIV and acute HSV-2, also not under HSV-2 anti-viral treatment, in the presence and absence of controls. In the presence of controls, we observe that the population is lower, than in the absence of controls for the whole period under study. It is worth noting that, the controls start being effective after 2 months.

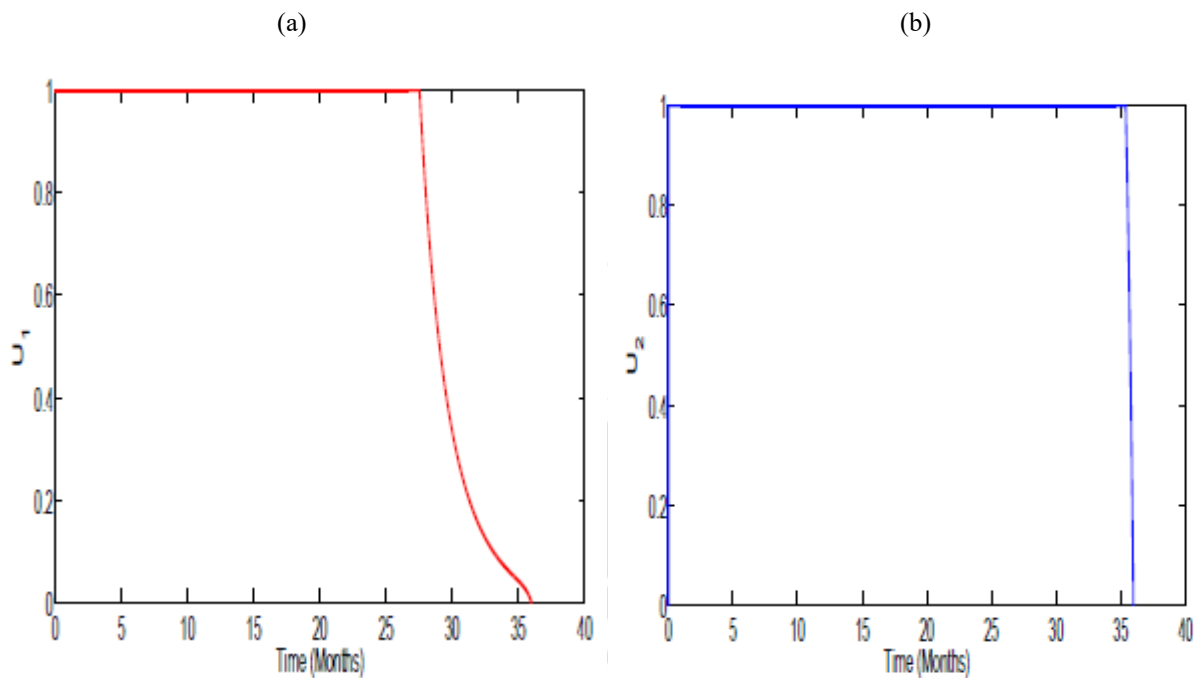


Figure 3 The optimal control graphs for the two controls, namely, monitoring and counselling individuals infected with HSV-2 only (u_1) and monitoring and counselling individuals dually infected with HSV-2 and HIV (u_2) over a period of 36 months.

Figure 3 shows the evolution of the control profiles over time. An interesting result is that the second control, u_2 starts at the lower bound, while u_1 starts at the upper bound. This can be explained by our assumption that, in a given community, an individual can be infected by either HIV or HSV-2 but not both at the same time. The result suggest that more effort should be devoted to optimal counselling and monitoring of individuals dually infected with HIV and acute HSV-2 control u_2 which is feasible for up to 36 months, as compared to individuals infected with acute HSV-2 only control u_1 which is feasible for about 27 months. However, if optimal counselling and monitoring is implemented for 27 months or less, then both controls can be feasible.

5. Discussion

HSV-2 is the most prevalent disease in most parts of the world especially in sub-Saharan Africa. HSV-2 is a significant factor of increased risk of acquisition and transmission of HIV and also being the leading disease in cause genital ulcers. Thus, Proper HSV-2 treatment adherence, might be beneficial in the reduction of HIV/AIDS. In this paper, we formulated and analyze a deterministic compartment model for the transmission dynamics of HIV and HSV-2. We considered the epidemiological synergy between sexually transmitted HIV and HSV-2. We calculate the basic reproduction number of model. Applying the comparison theorem by Lakshmikantham *et al.* (1989), we managed to prove the global stability of the disease-free equilibrium point is locally asymptotically stable when the associated reproduction number is greater than unity. Introducing two-time dependent controls to our model, we then formulated an optimal control problem for model system (6) to investigate optimal monitoring and counselling which seek to minimize the number of individuals infected with HIV/AIDS and those dually infected with HIV and HSV-2. Optimal monitoring and counselling is applied so as to try and reduce the number of individuals who quit HSV-2 anti-viral treatment before completion. We proved the existence of the optimal control and characterized the controls using pontryagin's Maximum principle. From the illustration in this study, it is clear that the time dependent intervention strategies can lead to the reduction of HIV/AIDS and those dually infected by HIV and HSV-2. It is worth noting that, as much as the HIV cases and the HIV/HSV-2 dual cases are reduced, they do not converge to zero since there are other factors influencing their prevalence within the population. Numerical analysis also suggests that the implementation of the controls should be devoted to both, since they are feasible for a longer period. Furthermore, the optimal control result suggest that more efforts should be devoted to monitoring and counselling of the individuals dually infected with HIV and HSV-2 compared to those infected with HSV-2 only. It would be importance to implement these controls at minimum cost, hence we suggest the monitoring and counselling can be disseminated at various health care centers. Various methods that target HIV and AIDS patients, can now involve some information on the dangers of poor HSV-2 treatment adherence.

The proposed model has several limitations, which should be acknowledge. Limited data exist on the co-infection of HSV-2 and HIV/AIDS, particularly, mathematical modelling study on HSV-2 is low. Therefore, some of our numerical estimates remain uncertain, particularly those data that are most sensitive to HSV-2 related parameters, which we took from other previous researches. More data sets and experimental studies are needed to include more realistic biological processes in the models. However just like any other model, we cannot say the model is complete it can be extended to include resource limited or resource given communities, with HIV treatment compartments included.

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