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Analysis of Optimal Control Strategy on Transmission Dynamics of HPV-HSV-II Coinfection Model

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Abstract

In this paper, optimal control problem is applied to Human Papillomavirus (HPV) and Herpes Simplex Virus type 2 (HSV-2) coinfection model formulated by a system of ordinary differential equations. Optimal control strategy is employed to study the effect of combining different intervention strategy on the transmission dynamics of HPV-HSV-II coinfection diseases. The necessary conditions for the existence of the optimal controls are established using Pontryagin's Maximum Principle. Optimal control systems were performed with help of Runge-Kutta forward-backward sweep numerical approximation method. Finally, numerical simulation illustrated that a combination of all controls is the most effective strategy to minimize the disease from the community. The results shows that the size of infectious population are minimized by using different control strategies.

Keywords: Coinfection, Model, Stability, Optimal control, Simulation.

1 | Introduction

Human Papillomavirus (HPV) is the most common sexually transmitted infection [1]. HPV is a double-stranded DNA virus belonging to the Papovaviridae family. There are more than 100 types of HPV and more than 40 of these viruses are the most common sexually transmitted disease in the world. HPV types 16 and 18 are responsible for about 70% of all cervical cancer cases worldwide [2], [3]. In worldwide, there are 18.1 million new cases, 9.6 million cancer related deaths, and 43.8 million people living with cancer in 2018. The number of new cases is expected to rise from 18 million to 22 million by 2030 and the number of global cancer deaths is projected to increase by 45% by 2030 [4], [5]. Herpes Simplex Virus Type 2 (HSV-2) infections is widespread throughout the world and is almost exclusively sexually transmitted, causing genital herpes [6]. Genital herpes infections frequently have no symptoms, or mild symptoms that go unrecognized. When symptoms do occur, genital herpes is characterized by one or more genital or anal blisters or open sores called ulcers. In addition to genital ulcers, symptoms of new genital herpes infections often include fever, body aches, and swollen lymph nodes.

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HSV-2 is mainly transmitted during sex, through contact with genital surfaces, skin, sores or fluids of someone infected with the virus. HSV-2 can be transmitted from skin in the genital or anal area that looks normal and is often transmitted in the absence of symptoms [7]. An estimated 491 million (13%) people aged 15 to 49 years worldwide were living with the infection in 2016. More women are infected with HSV-2 than men in 2016. It were estimated that 313 million women and 178 million men were living with the infection [8], [9].

Many mathematical models have been developed to analyze the dynamics of transmission of HPV and HSV-II infection and its associated health problems, and as well study the impact of some control strategies against the virus. It is an essential and effective way to totally understand the real-world problems by establishing mathematical models and analyzing their dynamical behaviors. Old and recent studies such as [17]-[21] amongst others have shown that mathematical modeling is a widely used tool for resolving questions on public health. Several SIR models [16], [19] have been developed to assess the potential impact of vaccination against HPV. Also, Naik et al. [22] and Ribassin-Majed and Lounes [23] formulated an SIS model for HPV transmission with vaccination as a control strategy and Taira et al. [24] developed a dynamic model for the heterosexual transmission of HPV types 16 and 18, which are covered by available vaccines.

The main objective of this work is to study the effect of incorporating optimal control strategies to mathematical model of HPV and HSV-II co-infection developed by Gurmu et al. [10].

2 | Model Assumption

The total human population N is subdivided into ten compartments, Susceptible (S), HPV infectious (I_p), HSV-II infectious (I_h), HPV-HSV-II co-infectious (I_{ph}), HSV-II-Cervical cancer co-infectious (I_{sc}), Cervical cancer infectious (C), Drug resistance compartment (R_s), HPV recovered (R_p), HSV-II recovered (R_h) and HPV-HSV-II co-infectious recovered is also considered.

The whole population is susceptible to both HPV and HSV-II with the recruitment rate Π. It is assumed that individuals enter to the susceptible sub-class through birth at a rate Π and the number of susceptible increases by those individuals that lost their temporary immunity from sub-class of HPV recovered (R_p), HSV-II recovered (R_h) and HPV-HSV-II recovered (R_{ph}) with a rate ω_1, ω_2 and ω_3 respectively. Any susceptible individuals become infected with HPV at the force of infection $\lambda_p = \left[\beta(I_p + \gamma_4 I_{ph})\right]/[N]$ and join HPV infectious sub-class (I_p) or HSV-II with force of infection $\lambda_h = \frac{[\beta(I_h+\gamma_5 I_{ph})]}{[N]}$ and move to HSV-II infectious sub-class (I_h).

An individual in the sub-class (I_p) is infected with HSV-II and individuals in the sub-class (I_h) infected with HPV at the rate of modification parameters φ_1 and φ_2 respectively, progressing to the individuals with HPV and HSV-II co-infection (I_{ph}) sub-class. The infectious sub-class of HPV (I_p) also can get drug therapy with γ_1 rate and move to drug resistance sub-class (R_s) or dies due to disease causing death rate d_1. Similarly the infectious sub-class of HSV-II (I_h) also can get drug therapy with rate of γ_2 and join drug resistance sub-class (R_s) or dies from disease causing death with a rate of d_2. The HPV-HSV-II co-infectious (I_{sp}) sub-class can get drug therapy with a rate of γ_3 and join drug resistance sub-class (R_s) or dies either HPV or HSV-II causing death with rate of HPV or HSV-II only infected individuals [10].

After eight months, HPV infections sub-class (I_p) progress to cervical cancer sub-class with probability q. An individual with cervical cancer can acquire HSV-II infectious at the rate of modification parameter φ_3 and proceeds into the sub-class with co-infectious of cervical cancer and HSV-II (I_{hc}). Similarly, individuals with co-infectious of HPV-HSV-II progress to co-infectious of

cervical cancer and HSV-II (I_{hc}) with rate of α. Infectious sub-classes of HPV (I_p), HSV-II (I_h) and HPV-HSV-II co-infectious (I_{ph}) move to the recovered sub-classes of HPV (R_p), HSV-II (R_h) and HPV-HSV-II (R_{ph}) with rate ψ_1, ψ_2 and ψ_3 respectively with helps of natural immunity. An individual in the drug resistance compartment join recovered sub-class of HPV-HSV-II (R_{ph}) at a rate of η by drug therapy, with therapy efficacy of ρ proportion of individuals join the recovered sub-class (R_{ph}) or move to the HPV-HSV-II co-infectious (I_{ph}) sub-class with $(1-\rho)$ proportion by adopting the drug therapy. All individuals are subject to a natural death at the rate μ [10].

Based on the basic assumptions and as given in [10], the model equations are as follows in *Eq. (1)*.

$$\begin{aligned}
dS/dt &= \Pi + \omega_1 R_p + \omega_2 R_h + \omega_3 R_{ph} - (\lambda_p + \lambda_h + \mu)S,\\
dI_p/dt &= \lambda_p S - (\varphi_1\lambda_h + \gamma_1 + \psi_1 + \mu + d_1)I_p,\\
dI_h/dt &= \lambda_h S - (\varphi_2\lambda_p + \gamma_2 + \psi_2 + \mu + d_2)I_h,\\
dI_{ph}/dt &= \varphi_1\lambda_h I_p + \varphi_2\lambda_p I_h - (\alpha + \gamma_3 + \psi_3 + \mu + d_1 + d_2)I_{ph},\\
dC/dt &= (1-q)\gamma_1 I_p - (\varphi_3\lambda_h + \mu)C,\\
dI_{hc}/dt &= \varphi_3\lambda_h C + \alpha I_{ph} + (1-\rho)\eta R_s - (\mu + d_2)I_{hc},\\
dR_s/dt &= q\gamma_1 I_p + \gamma_3 I_{ph} + \gamma_2 I_h - (\eta + \mu)R_s,\\
dR_p/dt &= \psi_1 I_p - (\omega_1 + \mu)R_p,\\
dR_h/dt &= \psi_2 I_h - (\omega_2 + \mu)R_h,\\
dR_{ph}/dt &= \psi_3 I_{ph} + \eta\rho R_s - (\omega_3 + \mu)R_{ph}.
\end{aligned} \tag{1}$$

With initial condition $S(0) > 0$, $I_h(0) \geq 0$, $I_p(0) \geq 0$, $I_{ph}(0) \geq 0$, $I_{hc}(0) \geq 0$, $R_s(0) \geq 0, R_p(0) \geq 0$, $R_h(0) \geq 0$, $R_p(0) \geq 0$, $R_{ph}(0) \geq 0$.

3 | Optimal Control Analysis of the Model

In the model *Eq. (1)*, we introduce four control strategy; $u_1(t)$ represents prevention effort that helps to reduce contact rate of HPV, $u_2(t)$ represents prevention effort that help to reduce contact rate of HSV-II, $u_3(t)$ represents treatment effort that increases recovery rate of HPV infection and $u_4(t)$ represents treatment effort that increases recovery rate of HSV-II infection. Time is specified and is relatively short and is given by $t \in [0, T]$, T is the terminal time.

After incorporating control functions $u_1(t), u_2(t), u_3(t)$ and $u_4(t)$ in HPV-HSV-II coinfection model [10], we obtain the following state system for model *Eq. (1)*.

$$dS/dt = \Pi + \omega_1 R_p + \omega_2 R_h + \omega_3 R_{ph} - \Big((1-u_1)\lambda_p + (1-u_2)\lambda_h + \mu\Big)S,$$

$$dI_p/dt = (1-u_1)\lambda_p S - (1-u_2)\varphi_1\lambda_h I_p - (u_3 + \gamma_1 + \psi_1 + \mu + d_1)I_p,$$

$$dI_h/dt = (1-u_2)\lambda_h S - (1-u_1)\varphi_2\lambda_p I_p - (u_4 + \gamma_2 + \psi_2 + \mu + d_2)I_h,$$

$$dI_{ph}/dt = (1-u_2)\varphi_1\lambda_h I_p + (1-u_1)\varphi_2\lambda_p I_h - (u_3 + u_4 + \alpha + \gamma_3 + \psi_3 + \mu + d_1 + d_2)I_h,$$

$$dC/dt = (1-q)\gamma_1 I_p - (1-u_2)\varphi_3\lambda_h C - \mu C, \qquad (2)$$

$$dI_{hc}/dt = (1-u_2)\varphi_3\lambda_h C + \alpha I_{ph} + (1-\rho)\eta R_s - (\mu + d_2)I_{hc},$$

$$dR_s/dt = q\gamma_1 I_p + \gamma_3 I_{ph} + \gamma_2 I_h - (\eta + \mu)R_s,$$

$$dR_p/dt = (u_3 + \psi_1)I_p - (\omega_1 + \mu)R_p,$$

$$dR_h/dt = (u_4 + \psi_2)I_h - (\omega_2 + \mu)R_h,$$

$$dR_{ph}/dt = (u_3 + u_4 + \psi_3)I_{ph} + \eta\rho R_s - (\omega_3 + \mu)R_{ph}.$$

With initial condition $S(0) > 0$, $I_h(0) \geq 0$, $I_p(0) \geq 0$, $I_{ph}(0) \geq 0$, $I_{hc}(0) \geq 0$, $R_s(0) \geq 0, R_p(0) \geq 0$, $R_h(0) \geq 0$, $R_p(0) \geq 0$, $R_{ph}(0) \geq 0$ and a bounded Lebesgue measurable control set is given as

$$\Omega = \left\{\big(u_1(t), u_2(t), u_3(t), u_4(t)\big) \in \big(L^\infty(0,T)\big)^4 : 0 \leq u_i(t) \leq 1-\epsilon, \forall_t \in [0,T]\right\}. \qquad (3)$$

The controls are bounded between 0 and 1. When the controls vanish, it means that no extra measures are implemented for the reduction of the disease. When the controls take the maximum value 1, it means that the intervention is 100% perfectly implemented which is not time in reality and thus we assume $u_i \leq 1-\epsilon$, $i = 1,2,3,4$, where $\epsilon \ll 1$ denotes a positive real number.

The optimal control problem in *Eq. (2)* is to minimize the objective functional defined as

$$J(u) = \int_0^T \left[M_1 I_p(t) + M_2 I_h(t) + M_3 I_{ph}(t) + \frac{1}{2}\sum_{i=1}^4 B_i u_i^2\right]dt \rightarrow \min. \qquad (4)$$

Where constants M_j and B_i for $j = 1,2,3$ and $i = 1,2,3,4$ are positive weights. The term $\frac{B_1 u_1^2}{2}$ represents the cost of control effort on prevention strategy against HPV infection, $\frac{B_2 u_2^2}{2}$ represents the cost of control effort on prevention strategy against HSV-II infection, $\frac{B_3 u_3^2}{2}$ represents the cost of control effort on treatment of HPV infection and $\frac{B_4 u_4^2}{2}$ represents the cost of control effort on treatment of HSV-II infection. Additionally, the functional J corresponds the total cost due to HPV and HSV-II outbreak and its control strategies. Further, the integrand function.

$$L(\varnothing, u) = M_1 I_p(t) + M_2 I_h(t) + M_3 I_{ph}(t) + \frac{1}{2}\sum_{i=1}^{4} B_i u_i^2. \quad (5)$$

Measures the current cost at time t. Finally, the fixed constant T denotes the terminal innervations time. The goal is to find an optimal control value $u^* = (u_1^*, u_2^*, u_3^*, u_4^*)$ of the controls $u = (u_1, u_2, u_3, u_4)$ such that the optimal control problem can be defined as

$$J(u_1^*, u_2^*, u_3^*, u_4^*) = \min_{\Omega} J\big(u_1(t), u_2(t), u_3(t), u_4(t)\big). \quad (6)$$

Satisfying model *Eq. (2)*.

3.1 | Existence of Optimal Controls

In this subsection, we prove the existence of such optimal control functions which minimize the cost function in the finite intervention period. The following result guarantees the existence of optimal control functions. A detail and similar analysis on existence of optimal control can be obtained in [11], [12].

Theorem 1. There exists an optimal control $u^* = (u_1^*, u_2^*, u_3^*, u_4^*)$ in Ω and a corresponding solution vector $\overline{X} = (\overline{S}, \overline{I_p}, \overline{I_h}, \overline{I_{ph}}, \overline{C}, \overline{I_{hc}}, \overline{R_s}, \overline{R_p}, \overline{R_h}, \overline{R_{ph}})$ to the initial *Value Problem (2)* such that

$$J(u_1^*, u_2^*, u_3^*, u_4^*) = \min_{\Omega} J\big(u_1(t), u_2(t), u_3(t), u_4(t)\big).$$

Proof. The entire state variables involved in the model are continuously differentiable. Therefore, we need to verify the following four conditions as given in [11], [13]:

I. The set of solutions to the *System (2)* with control variables are non empty.
II. The set Ω is convex and closed.
III. The state system can be written as linear function of control variables with coefficients depending on time and state variables.
IV. The integrand L of *Eq. (5)* is convex on Ω and $L(\varnothing, u) \geq g(u)$, where g is continuous and $\|u\|^{-1} g(u) \to +\infty$ as $\|u\| \to \infty$.

Since the total population in *Eq. (2)* is defined as

$$N(t) = S(t) + I_p(t) + I_h(t) + I_{ph}(t) + C(t) + I_{hc}(t) + R_s(t) + R_p(t) + R_h(t) + R_{Ph}(t).$$

From governing *System (2)* it follows that $dN/dt = \Pi - \mu N$.

It follows that the solutions of the state system are continuous and bounded for each admissible control functions in Ω. Further, the right hand side functions of the model *Eqs. (2)* satisfy the Lipschitz condition with respect to state variables. Therefore, the initial *Value Problem (2)* has a unique solution corresponding to each admissible control function $u \in \Omega$. Thus, condition (i) is proved.

To prove (ii), consider $\Omega = \{u \in \mathbb{R}^4 : \|u\| \leq 1 - \epsilon\}$.

Let $u_1, u_2 \in \Omega$ such that $\|u_1\| \leq 1 - \epsilon$ and $\|u_2\| \leq 1 - \epsilon$. Then for any $\lambda \in [0,1]$, $\|\lambda u_1 + (1-\lambda)u_2\| \leq \lambda\|u_1\| + (1-\lambda)\|u_2\| \leq 1 - \epsilon$.

This implies that Ω is convex and closed. The state *System (2)* is linear in control variables u_1, u_2, u_3 and u_4 with coefficients depending on state variables. With this condition (iii) is satisfied. The integrand of the cost functional is the sum of convex function and hence convex with respect to control variables. Furthermore,

$$L(\varnothing, u) = M_1 I_p(t) + M_2 I_h(t) + M_3 I_{ph}(t) + \frac{1}{2}\sum_{i=1}^{4} B_i u_i^2. \tag{7}$$

Let $\chi = min\left(\frac{1}{2}\sum_{i=1}^{4} B_i u_i^2\right) > 0$ and define a continuous function $g(u) = \chi\|u\|^{-1}$. Then from *Eq. (7)* we have $L(\varnothing, u) \geq g(u)$. Clearly, $\|u\|^{-1} g(u) \to +\infty$ as $\|u\| \to \infty$. Thus, condition (iv) is achieved. Therefore, the existence of an optimal control pair $(\overline{X}, u^*)$ is satisfying *Eq. (2)* and *Eq. (5)* is assured by results given in [11]. Hence the proof.

3.2 | Characterization of Optimal Control

The necessary conditions that an optimal must satisfy come from the Pontryagin's Maximum Principle [14]. If $u^*(t) \in \Omega$ is optimal for *Problems (2)* and *(5)* with fixed final time T, then there exists a non trivial absolutely continuous mapping $\lambda: [0, T] \to \mathbb{R}^{10}$, $\lambda = (\lambda_1(t), \lambda_2(t), \lambda_3(t), \lambda_4(t), \lambda_5(t), \lambda_6(t), \lambda_7(t), \lambda_8(t), \lambda_9(t), \lambda_{10}(t))$ called the adjoint variables or co-state variables, such that

I. The Hamiltonian function is defined as

$$H = M_1 I_p(t) + M_2 I_h(t) + M_3 I_{ph}(t) + \frac{1}{2}\sum_{i=1}^{4} B_i u_i^2 + \sum_{i=1}^{10} \lambda_i(t) g_i(t, \varnothing, u). \tag{8}$$

Where g_i stands for the right hands of the *Constraints (2)* for $i = 1, \ldots, 10$.

II. The control system

$$S' = \frac{\partial H}{\partial \lambda_1}, I_p' = \frac{\partial H}{\partial \lambda_2}, I_h' = \frac{\partial H}{\partial \lambda_3}, I_{ph}' = \frac{\partial H}{\partial \lambda_4}, C' = \frac{\partial H}{\partial \lambda_5}, I_{hc}' = \frac{\partial H}{\partial \lambda_6}, R_s' = \frac{\partial H}{\partial \lambda_7}, R_p' = \frac{\partial H}{\partial \lambda_8}, R_h' = \frac{\partial H}{\partial \lambda_9}, R_{ph}' = \frac{\partial H}{\partial \lambda_{10}}. \tag{9}$$

III. The adjoint system

$$\lambda_1' = -\frac{\partial H}{\partial S}, \lambda_2' = -\frac{\partial H}{\partial I_p}, \lambda_3' = -\frac{\partial H}{\partial I_h}, \lambda_4' = -\frac{\partial H}{\partial I_{ph}}, \lambda_5' = -\frac{\partial H}{\partial C}, \lambda_6' = -\frac{\partial H}{\partial I_{hc}}, \lambda_7' = -\frac{\partial H}{\partial R_s}, \lambda_8' = -\frac{\partial H}{\partial R_p}, \lambda_9' = -\frac{\partial H}{\partial R_h}, \lambda_{10}' = -\frac{\partial H}{\partial R_{ph}}. \tag{10}$$

IV. The optimality condition

$$H\left(\varnothing^*(t), u^*(t), \lambda^*(t)\right) = \min_{u \in \Omega} H\left(\varnothing^*(t), u^*(t), \lambda^*(t)\right). \tag{11}$$

V. Moreover, the transversality condition

$$\lambda_i(T) = 0, \quad i = 1, \ldots, 10. \tag{12}$$

Holds for almost all $t \in [0, T]$.

In the next result, we discuss characterization of optimal controls and adjoint variables.

Theorem 2. For the optimal controls $u^* = (u_1^*,\ u_2^*,\ u_3^*,\ u_4^*)$ that minimize $J(u_1(t), u_2(t), u_3(t), u_4(t))$ over Ω, there exists adjoint variables $\lambda_1(t)$, $\lambda_2(t)$, $\lambda_3(t)$, $\lambda_4(t)$, $\lambda_5(t)$, $\lambda_6(t)$, $\lambda_7(t)$, $\lambda_8(t)$, $\lambda_9(t)$ and $\lambda_{10}(t)$ satisfying

$$\frac{d\lambda_i}{dt} = -\frac{\partial H}{\partial u_i}. \tag{13}$$

Where $i = 1, \dots, 10$, $j = S,\ I_p,\ I_h,\ I_{ph},\ C,\ I_{hc},\ R_s,\ R_p,\ R_h,\ R_{Ph}$ and with transiversality conditions $\lambda_i^*(T) = 0,\ i = 1, \dots, 10$. Moreover, the corresponding optimal controls $u_1^*,\ u_2^*,\ u_3^*$ and u_4^* are given by

$$\begin{aligned} u_1^*(t) &= \min\{\max\{0, \Phi_1\}, 1-\epsilon\}, \\ u_2^*(t) &= \min\{\max\{0, \Phi_2\}, 1-\epsilon\}, \\ u_3^*(t) &= \min\{\max\{0, \Phi_3\}, 1-\epsilon\}, \\ u_4^*(t) &= \min\{\max\{0, \Phi_4\}, 1-\epsilon\}, \end{aligned} \tag{14}$$

where

$$\Phi_1 = \frac{(\lambda_2 - \lambda_1)\lambda_p S + (\lambda_4 - \lambda_3)\varphi_2\lambda_p I_h}{B_1},$$

$$\Phi_2 = \frac{(\lambda_3 - \lambda_1)\lambda_h S + (\lambda_4 - \lambda_2)\varphi_1\lambda_h I_p + (\lambda_6 - \lambda_5)\varphi_3\lambda_h C}{B_2},$$

$$\Phi_3 = \frac{(\lambda_2 - \lambda_8)I_p + (\lambda_4 - \lambda_{10})I_{ph}}{B_3},$$

$$\Phi_4 = \frac{(\lambda_3 - \lambda_9)I_h + (\lambda_4 - \lambda_{10})I_{ph}}{B_4}.$$

Proof. Corollary 4.1 of Fleming and Rishel [11] gives the existence of an optimal control due to the convexity of the integrand J with respect to u_1, u_2, u_3 and u_4 a priori boundedness of the state solutions and the Lipchitz property of the state system with respect to the state variables. Differentiating Hamiltonian functions with respect to state variables gives differential equations governing the adjoint variables as follows:

$$\frac{d\lambda_1}{dt} = \lambda_1\left[(1-u_1)\lambda_p + (1-u_2)\lambda_h + \mu\right] - \lambda_2(1-u_1)\lambda_p - \lambda_3(1-u_2)\lambda_h,$$

$$\frac{d\lambda_2}{dt} = -M_1 + \lambda_1\left[(1-u_1)\frac{\beta S}{N}\right] + \lambda_2\left[(1-u_2)\varphi_1\lambda_h + (u_3 + \psi_1 + \gamma_1 + \mu + d_1) - (1-u_1)\frac{\beta S}{N}\right] - \lambda_4(1-u_2)\varphi_1\lambda_h - \lambda_5\varphi_2\lambda_p - \lambda_7\gamma_2 - \lambda_9(u_4 + \psi_2),$$

$$\frac{d\lambda_4}{dt} = -M_3 + \lambda_1\left[(1-u_1)\frac{\beta\gamma_4 S}{N} + (1-u_2)\frac{\beta\gamma_5 S}{N}\right] - \lambda_2\left[(1-u_1)\frac{\beta\gamma_4 S}{N} - (1-u_2)\varphi_1\frac{\beta\gamma_5 S}{N}\right] - \lambda_3\left[(1-u_2)\frac{\beta\gamma_5 S}{N} - (1-u_1)\varphi_2\frac{\beta\gamma_4 S}{N}\right] - \lambda_4\left[(1-u_2)\varphi_1\frac{\beta\gamma_5 S}{N} + (1-u_2)\varphi_2\frac{\beta\gamma_4 S}{N} - (u_3 + u_4 + \psi_3 + \alpha + \gamma_3 + \mu + d_1 + d_2)\right] + \lambda_5\left[(1-u_2)\varphi_3\frac{\beta\gamma_5 C}{N}\right] - \lambda_6\left[(1-u_2)\varphi_3\frac{\beta\gamma_5 C}{N} + \alpha\right] - \lambda_7\gamma_3 - \lambda_{10}(u_3 + u_4 + \varphi_3),$$

$$\frac{d\lambda_5}{dt} = \lambda_5\left[(1-u_2)\varphi_3\lambda_h + \mu\right] - \lambda_6[(1-u_2)\varphi_3\lambda_h],$$

$$\frac{d\lambda_6}{dt} = \lambda_6(\mu + d_2),$$

$$\frac{d\lambda_7}{dt} = \lambda_7(\eta + \mu) - \lambda_{10}(\eta\rho) - \lambda_6(1-p)\eta,$$

$$\frac{d\lambda_8}{dt} = \lambda_8(\omega_1 + \mu) - \lambda_1\omega_1,$$

$$\frac{d\lambda_9}{dt} = \lambda_9(\omega_2 + \mu) - \lambda_1\omega_2,$$

$$\frac{d\lambda_{10}}{dt} = \lambda_{10}(\omega_3 + \mu) - \lambda_1\omega_3.$$

Optimality *Eq. (14)* are obtained by computing partial derivative of the Hamiltonian *Eq. (8)* with respect to each control variables as follows: $\frac{\partial H}{\partial u_i} = 0$, for $= 1, 2, 3, 4$.

Solving for u_1^*, u_2^*, u_3^* and u_4^* subject to the constraints, provides the characterization *Eqs. (14)*.

3.3 | 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 $i = 1,2,3,4,5,6, \ldots, 10$ with bounded coefficients. Thus, there exists a $M > 0$ such that $|\lambda_i(t)| < M$ for $i = 1,2,3,4,5,6, \ldots, 10$ on $[0, T]$.

Theorem 3. ([15]). For T sufficiently small the solution to the optimality system is unique.

4 | Numerical Simulation

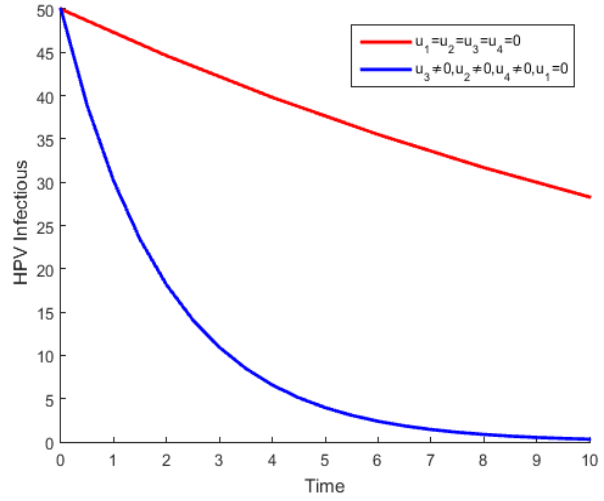
In this section, the numerical solutions of optimality system are discussed. Using the initial conditions $S(0) = 300$, $I_p(0) = 50$, $I_h(0) = 120$, $I_{ph}(0) = 100$, $I_{hch}(0) = 90$, $C(0) = 70$, $R_{sh}(0) = 140$, $R_{ph}(0) = 30$, $R_{hh}(0) = 80$, $R_{phh}(0) = 100$ and also coefficients of the state and controls that we used are $M1 = 20, M2 = 15, M3 = 10, B1 = 5$, $B2 = 5, B3 = 5, B4 = 5$ a simulation study is conducted. Finally, an optimal control strategy is designed and discussed using different control strategies. To solve the optimal controls and states, we use the Runge-Kutta numerical method using MATLAB program. It needs to solve ten-state equations and ten adjoint equations. For that, first we solve *System (2)* with a guess for the controls forward in time and then using the transversality conditions as initial values and the adjoint system is solved backward in time using the current iteration solution of the state system.

Table 1. Parameter values used in simulations.

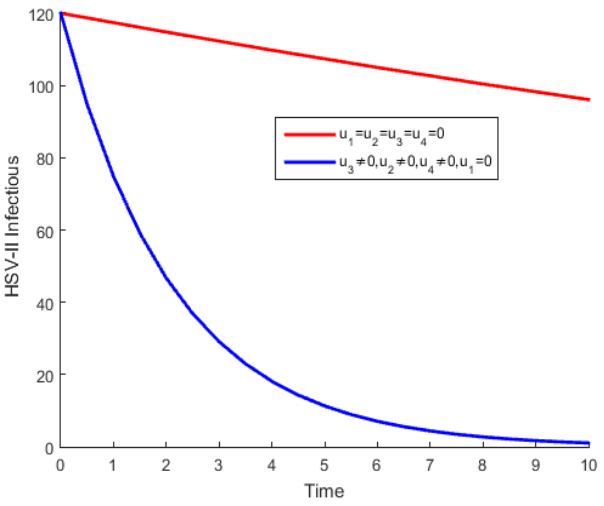
Parameter	Value	Source	Parameter	Value	Source
Π	0.0087	[10]	φ_1	0.054	[10]
γ_4	0.025	[10]	φ_2	0.055	[10]
γ_5	0.054	[10]	φ_3	0.15	[10]
μ	0.02	[10]	γ_1	0.03	[10]
ω_1	0.0021	[10]	γ_2	0.0023	[10]
ω_2	0.0031	[10]	γ_3	0.023	[10]
ω_3	0.0041	[10]	ψ_1	0.03	[10]
ρ	0.11	[10]	ψ_2	0.02	[10]
q	0.012	[10]	ψ_3	0.04	[10]
α	0.03	[10]	d_1	0.034	[10]
η	0.8	[10]	d_2	0.0023	[10]
β	0.068	[10]			

Intervention I. Optimal use of HSV-II prevention, HPV treatment and HSV-II treatment.

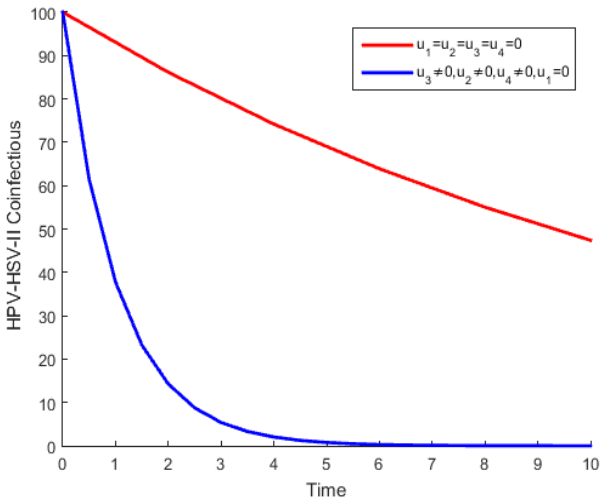
This intervention strategy combines prevention effort for HSV-II and both treatment effort for HPV and HSV-II are used to optimize objective functional while setting prevention effort for HPV equal to zero. As shown in *Fig. 1*, the magnitudes of infectious population reduce more when controls are in use than the case without controls.



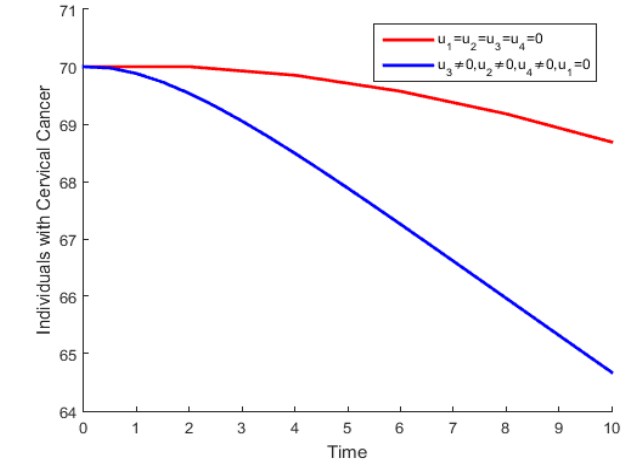
a.



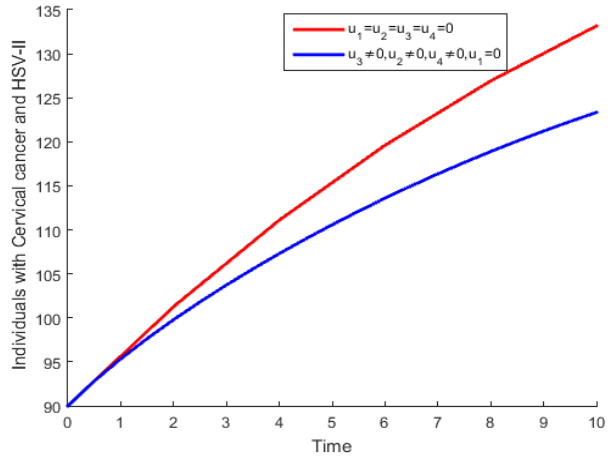
b.



c.



d.

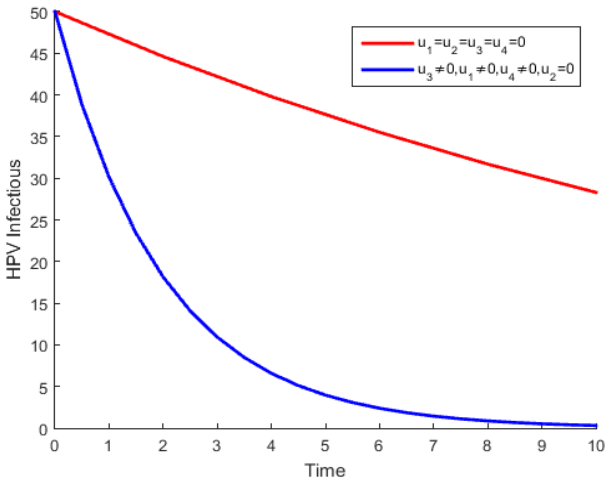


e.

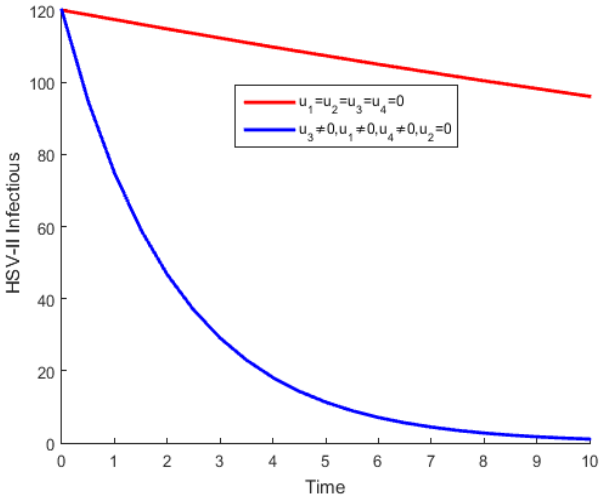
Fig. 1. Simulations showing optimal use of HSV-II prevention, HPV treatment and HSV-II treatment.

Intervention II. Optimal use of HPV prevention, HPV treatment and HSV-II treatment.

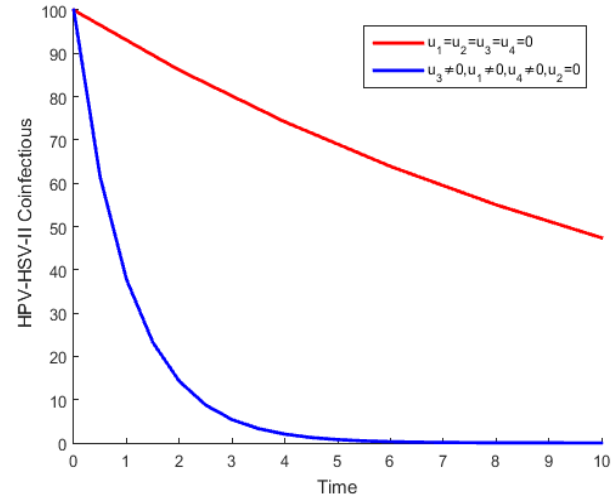
This intervention combines prevention effort for HPV and both treatment effort for HPV and HSV-II are used to optimize objective functional while setting prevention effort for HSV-II equal to zero. Results illustrate that the size of infectious population reduce sharply with controls more than the case without controls as shown in *Fig. 2*.



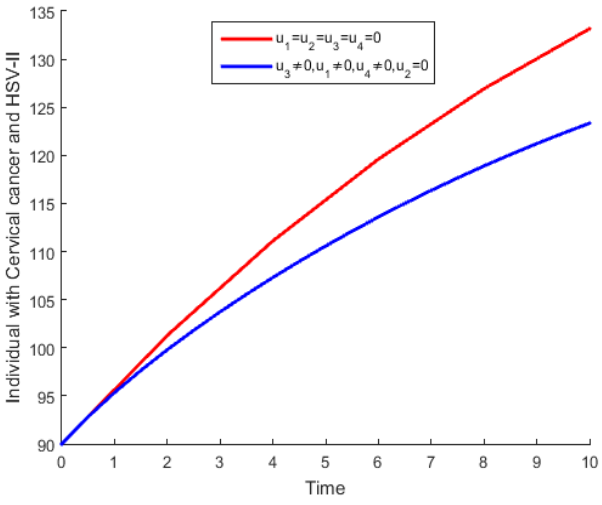
a.


HSV-II Infectious
Time
$u_1=u_2=u_3=u_4=0$
$u_3\neq0,u_1\neq0,u_4\neq0,u_2=0$

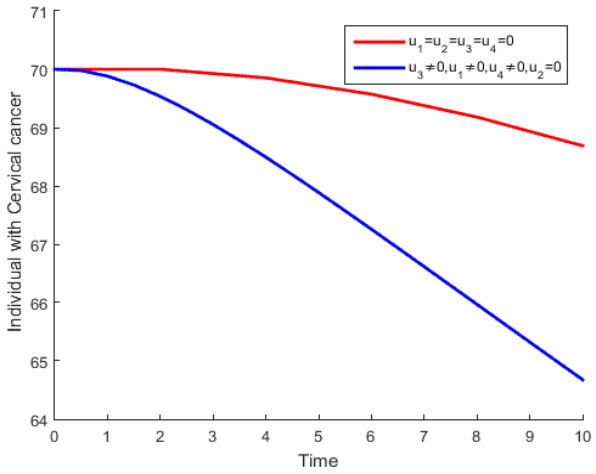
b.


HPV-HSV-II Coinfectious
Time
$u_1=u_2=u_3=u_4=0$
$u_3\neq0,u_1\neq0,u_4\neq0,u_2=0$

c.


Individual with Cervical cancer and HSV-II
Time
$u_1=u_2=u_3=u_4=0$
$u_3\neq0,u_1\neq0,u_4\neq0,u_2=0$

d.

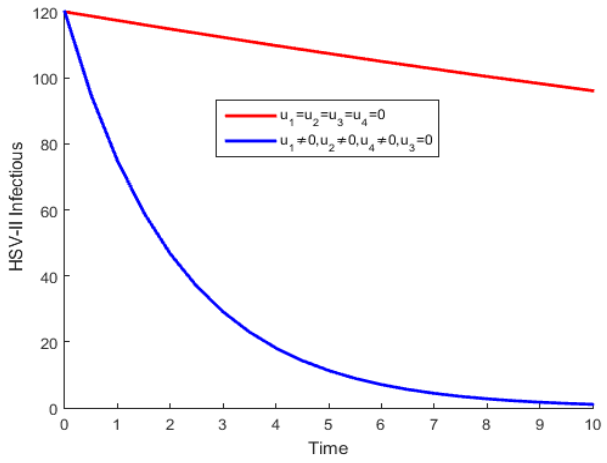


e.

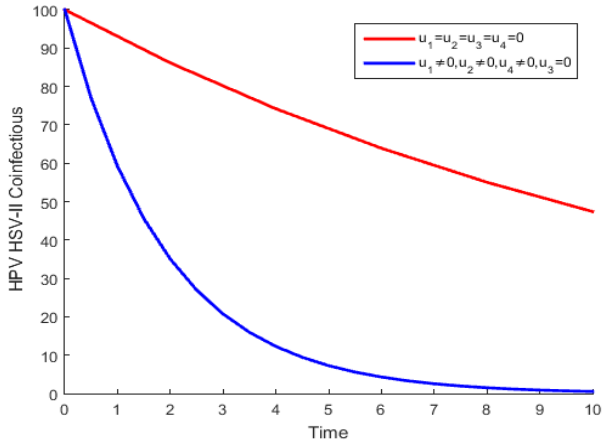
Fig. 2. Simulations showing optimal use of HPV prevention, HPV treatment and HSV-II treatment.

Intervention III. Optimal use of HPV prevention, HSV-II prevention and HSV-II treatment.

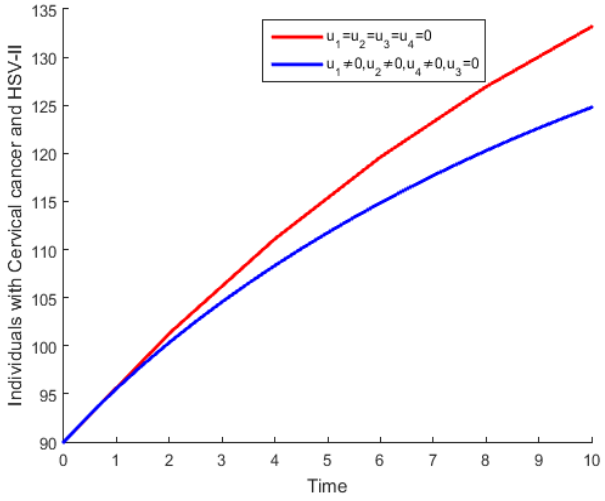
This strategy illustrates effect of prevention effort for both HPV and HSV-II and treatment effort for HSV-II are used to optimize objective functional while setting treatment effort for HPV equal to zero. As expected, the number of infectious population diminishes more rapidly with controls than the case without controls as illustrated in *Fig. 3*.



a.



b.

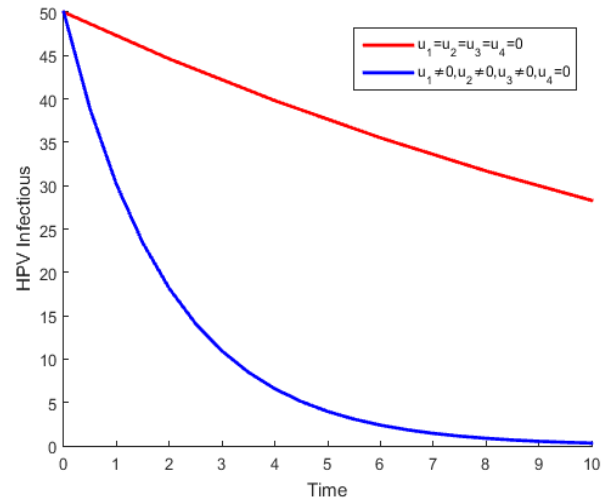


c.

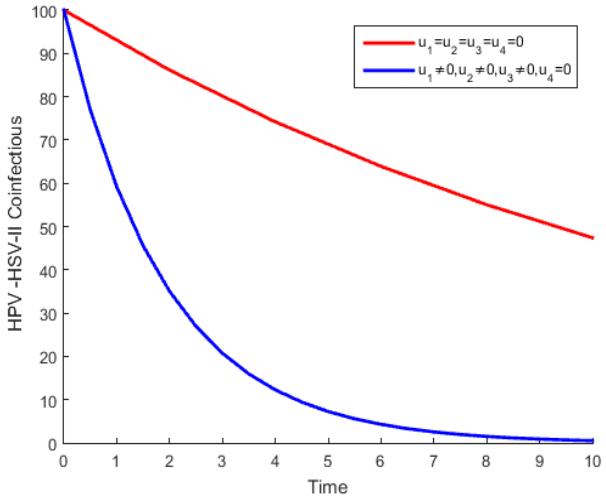
Fig. 3. Simulations showing optimal use of HPV prevention, HSV-II prevention and HSV-II treatment.

Intervention IV. Optimal use of HPV prevention, HSV-II prevention and HPV treatment.

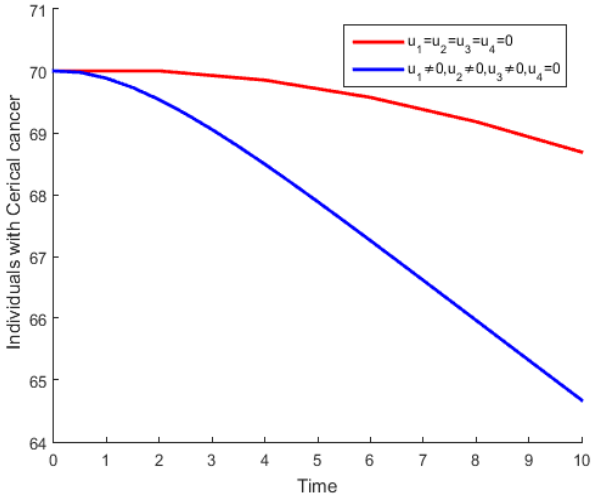
This strategy shows effect of prevention effort for both HPV and HSV-II and treatment effort for HPV are used to optimize objective functional while setting treatment effort for HSV-II equal to zero. Results describe that, the number of infectious population decreases more rapidly with controls than the case without controls as illustrated in *Fig. 4*.



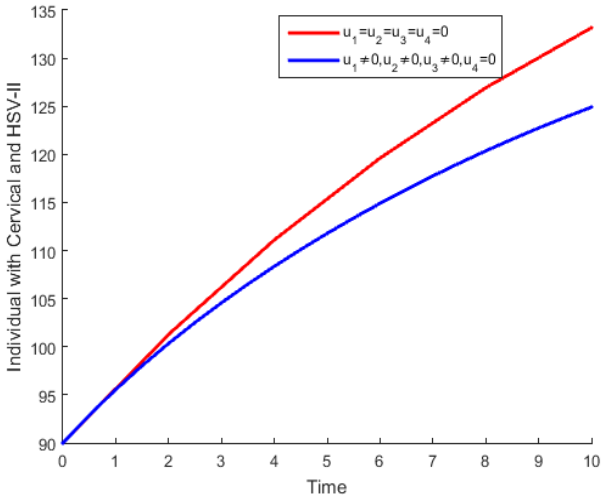
a.



b.



c.

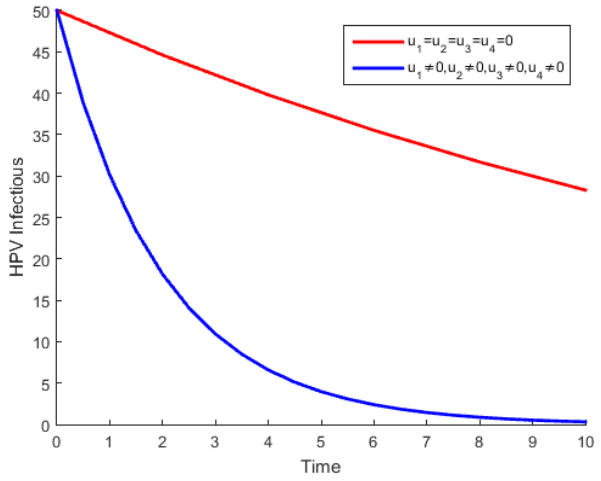


e.

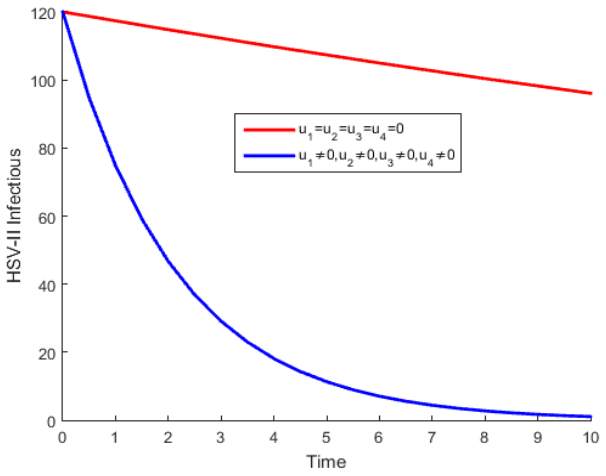
Fig. 4. Simulations showing optimal use of HPV prevention, HSV-II prevention and HPV treatment.

Intervention V. Optimal use of both prevention and treatment.

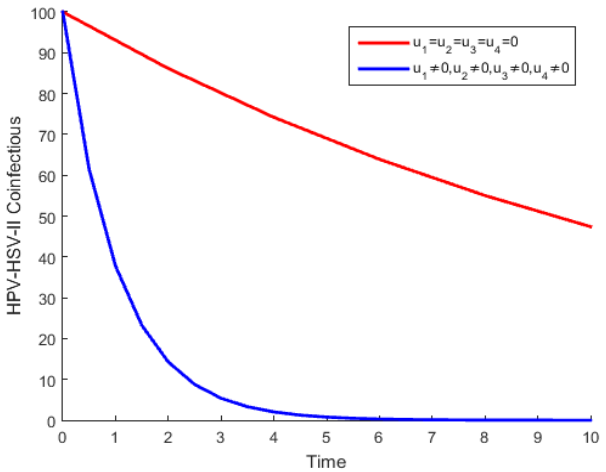
This intervention strategy uses both prevention effort and both treatment efforts are used to optimize objective functional. The size of infectious population decreases more sharply when controls are in use than the case when controls are not used as described in *Fig. 5*.



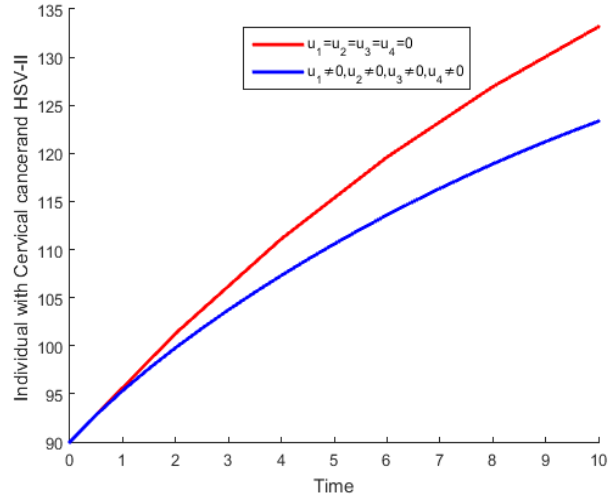
a.



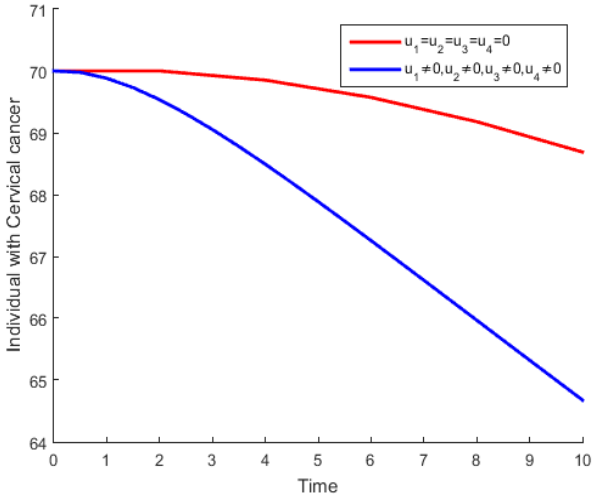
b.



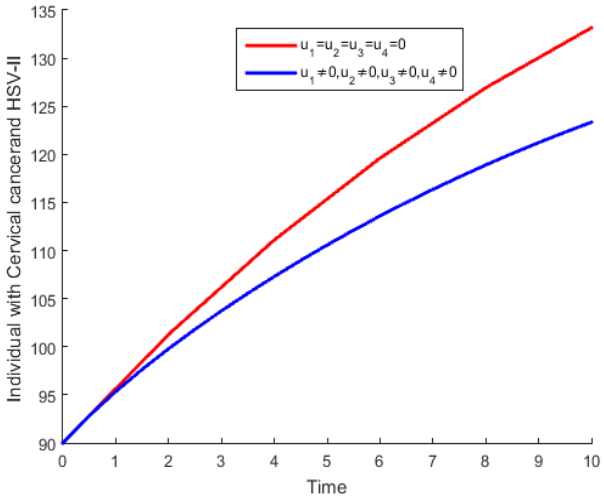
c.



d.



e.



f.

Fig. 5. Simulations showing optimal use of both prevention and treatment.

5 | Conclusion

In this paper, an optimal control problem was formulated to study the effects of combining different control strategies on HPV-HSV-II coinfection model in [11]. In this study, we formulated an optimal control strategy that minimizes the cost for implementation of the controls while also minimizing the infectious individuals over the intervention interval. The existence of optimal controls and characterization was done using Pontryagin's Maximum Principle. The size of infectious population decrease more sharply when controls are in use than the case when controls are not used. Also, the result shows that the sizes of infectious population are minimized by using different control strategies.

HPV-HSV-II coinfection remain a challenge especially in developing countries, but from results of this study we recommend that, the government should introduce education programmers on the importance of voluntary and routinely screening on HPV-HSV-II coinfection. In future work, we plan to extend the study by incorporating protected and treatment class to HPV-HSV-II transmission dynamics.

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