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Optimal Control Strategy on the Transmission Dynamics of Human Papillomavirus (HPV) and Human Immunodeficiency Viruses (HIV) Coinfection

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Abstract

In this paper, optimal control theory is applied to Human Papillomavirus (HPV) and Human immunodeficiency viruses (HIV) coinfection model given by using a system of ordinary differential equations. Optimal control strategy was employed to study the effect of combining various intervention strategies on the transmission dynamics of HPV-HIV coinfection diseases. The necessary conditions for the existence of the optimal controls were established using Pontryagin's Maximum Principle. Optimal control system was performed with help of Runge-Kutta forward-backward sweep numerical approximation method. Finally, numerical simulation illustrated that a combination of prevention, screening and treatment is the most effective strategy to minimize the disease from the community.

Keywords: Coinfection, Mathematical model, Stability, Optimal control, Simulation.

1 | Introduction

Human Papillomavirus infection is an infection caused by Human Papillomavirus (HPV), a DNA virus from the Papillomaviridae family [1]. According to the Centers for Disease Control and Prevention (CDC), HPV is the most common Sexually Transmitted Infection (STI) and about 90% eliminated on their own within two years [2]-[3]. In the 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].

Human Immunodeficiency Viruses (HIV) are an RNA retrovirus. HIV translates its RNA to DNA with a viral enzyme called reverse transcriptase [6]. The target cell of HIV is CD4 T cells. A healthy human body has about 1000/mm3 of CD4 T cells. When the CD4 T cells of a patient decline to 200/mm3 or below, then that person is classified as having AIDS [7]. In the world, new HIV infections among young women aged 15–24 years were reduced by 25% between 2010 and 2018.

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The annual number of deaths from AIDS-related illness among people living with HIV globally has fallen from a peak of 1.7 million in 2004 to 770 000 in 2018. The global decline in deaths has largely been driven by progress in eastern and southern Africa, which is home to 54% of the world's people living with HIV. AIDS-related mortality in the region declined by 44% from 2010 to 2018. The annual number of new infections since 2010 has declined from 2.1 million to 1.7 million in 2018 [8].

Co-infection is more than one disease co-existing within a single host. HPV and HIV/AIDS are among the diseases that contaminate a large number of individuals worldwide. HPV-HIV is the co-infection of two diseases responsible for loss of many lives. People with a weakened immune system such as those with HIV/AIDS are susceptible to diseases such as HPV. The patient with the co-infection is observed to have some of the symptoms including dry cough, weakness and difficulty in breathing [9]. If the body immune system is strong, HPV infection can be fought off. For HIV/AIDS victims, the sexually transmitted diseases are the ones causing very serious sickness and if not treated they cause death as well [10]. When an individual is co-infected with HPV and HIV at acute and clinical latency stages is called the initial stage. The final stage of the co-infection of HIV and HPV involves AIDS and Cervical cancer.

The aim of this work is to study the effect of incorporating optimal control strategies to the mathematical model of HIV/AIDS and HPV co-infection in [11].

2 | Model Assumption

The total sexually active population at time t, denoted by $N(t)$ is sub-divided into thirteen mutually-exclusive compartments, namely susceptible individuals, which are capable of becoming infected $S(t)$, individuals who are exposed to HIV $E_h(t)$, individuals who are exposed to HPV $E_p(t)$, individuals who are exposed to both HIV and HPV $E_{hp}(t)$, asymptomatic to HIV but show no symptoms of the disease $A_h(t)$, asymptomatic to HPV but show no symptoms of the disease $A_p(t)$, asymptomatic to both HI-V and HPV but show no symptoms of the disease $A_{hp}(t)$, infected individuals with clinical symptoms of HIV $I_h(t)$, infected individuals with clinical symptoms of HPV $I_p(t)$, infected individuals with clinical symptoms of both HIV and HPV $I_{hp}(t)$, individuals having AIDS $A(t)$, individuals having Cervical cancer $C(t)$, individuals having both AIDS and Cervical cancer $AC(t)$ [11]. The total population at time t is given by

$$\begin{aligned} N(t) = S(t) + E_h(t) + E_p(t) + E_{hp}(t) + A_h(t) + A_p(t) + A_{hP}(t) + I_h(t) \\ + I_p(t) + I_{hp}(t) + A(t) + C(t) + AC(t). \end{aligned} \tag{1}$$

The susceptible population is increased by the recruitment of individuals (assumed susceptible) into the population at a rate Π. Susceptible individuals acquire HIV infection with infection force of $\lambda_h = [\beta_h q_h(\gamma_1 A_h + \gamma_2 I_h)]/[N]$. Here β_h is a transmission rate of HIV infection, q_h is a mean number of contacts and infectivity rates of HIV infection are γ_1 and γ_2 with $\gamma_2 > \gamma_1$. Similarly, susceptible individuals acquire HPV infection with infection force of $\lambda_p = [\beta_p q_p(\gamma_3 A_p + \gamma_4 I_p)]/[N]$. Here β_p is a transmission rate of HPV infection, q_p is a mean number of contacts and infectivity rates of HPV infection are γ_3 and γ_4 with $\gamma_4 > \gamma_3$. Finally susceptible individuals acquire both HIV and HPV infection with infection force of $\lambda_{hp} = [\beta_{hp} q_{hp}(\gamma_5 A_{hp} + \gamma_6 I_{hp})]/[N]$. Here β_{hp} is a transmission rate of HIV and HPV infection, q_{hp} is a mean number of contacts and infectivity rates of multiple infections are γ_5 and γ_6 with $\gamma_6 > \gamma_5$. Individuals in class E_h, E_p and E_{hp} progress to the symptomatic individuals I_h, I_p and I_{hp} with probability p, q and e respectively. Individuals in class E_h, E_p and E_{hp} progress to the asymptomatic individuals A_h, A_p and A_{hp} with probability $(1-p)$, $(1-q)$ and $(1-e)$ respectively. Individuals in E_h and E_p compartments move to E_{hp} with rate θ_1 and θ_2 respectively. Individuals in class A_h and A_p may asymptomatic to both infection A_{hp} with a rate θ_3 and θ_4 respectively. Individuals in class I_h and I_p may symptomatic to both infection I_{hp} with a rate θ_5 and θ_6 respectively. Individuals in class A_h, A_p and A_{hp} after having a symptom of HIV,

HPV, and HIV-HPV move to class A, C and AC with rate ω_1, ω_2 and ω_3 respectively. Individuals in class I_h, I_p and I_{hp} compartments may develop AIDS, Cervical cancer and co-infection of AIDS and cervical cancer with the progression rates α_1, α_2 and α_3 respectively. Finally, individuals in A and C may develop co-infection of HIV-HPV (AC) with rates ε_1 and ε_2 respectively. All individuals have natural mortality rate μ [11].

Based on the model assumptions, the model equations are given as follows:

$$
\begin{aligned}
dS/dt &= \Pi - \left(\lambda_h + \lambda_p + \lambda_{hp}\right)S - \mu S,\\
dE_p/dt &= \lambda_p S - (\eta + \theta_2 + \mu)E_p,\\
dE_h/dt &= \lambda_h S - (\eta + \theta_1 + \mu)E_h,\\
dE_{hp}/dt &= \lambda_{hp} S + \theta_1 E_h + \theta_2 E_p - (\eta + \mu)E_{hp},\\
dA_p/dt &= (1-q)\eta E_p - (\omega_3 + \theta_4 + \mu)A_p,\\
dA_h/dt &= (1-p)\eta E_h - (\omega_1 + \theta_3 + \mu)A_h,\\
dA_{hp}/dt &= (1-e)\eta E_{hp} + \theta_3 A_h + \theta_4 A_p - (\omega_2 + \mu)A_{hp},\\
dI_p/dt &= q\eta E_p - (\alpha_3 + \theta_6 + \mu)I_p,\\
dI_h/dt &= p\eta E_h - (\alpha_1 + \theta_5 + \mu)I_h,\\
dI_{hp}/dt &= e\eta E_{hp} + \theta_5 I_h + \theta_6 I_p - (\alpha_2 + \mu)I_{hp},\\
dC/dt &= \alpha_3 I_p + \omega_3 A_p - (\varepsilon_2 + \mu)C,\\
dA/dt &= \alpha_1 I_h + \omega_1 A_h - (\varepsilon_1 + \mu)A,\\
dAC/dt &= \alpha_2 I_{hp} + \omega_2 A_{hp} + \varepsilon_1 A + \varepsilon_2 C - \mu AC,\\
\text{Here, } \lambda_h &= [\beta_h q_h(\gamma_1 A_h + \gamma_2 I_h)]/[N],\\
\lambda_p &= \left[\beta_p q_p(\gamma_3 A_p + \gamma_4 I_p)\right]/[N],\\
\lambda_{hp} &= \left[\beta_{hp} q_{hp}(\gamma_5 A_{hp} + \gamma_6 I_{hp})\right]/[N].
\end{aligned}
\tag{2}
$$

With initial condition

$$
\begin{aligned}
&S(0) > S_0, \quad E_h(0) \geq E_{h0}, \quad E_p(0) \geq E_{p0},\\
&E_{hp}(0) \geq E_{hp0}, \quad A_h(0) \geq A_{h0}, \quad A_p(0) \geq A_{p0}, \quad A_{hp}(0)\\
&\geq A_{hp0}, \quad I_h(0) \geq I_{h0}, \quad I_p(0) \geq I_{p0}, \quad I_{hp}(0) \geq I_{hp0}, \quad A(0) \geq A_0,\\
&C(0) \geq C_0, \quad AC(0) \geq AC_0.
\end{aligned}
\tag{3}
$$

3 | Optimal Control Analysis of the Model

In this section, we introduce optimal control strategies to the HPV-HIV coinfection model in [11]. The model *Eq. (2)* is modified by introducing control function; $u_1(t)$ represents HPV prevention effort, $u_2(t)$

represents HIV prevention effort, $u_3(t)$ represents HPV screening effort, $u_4(t)$ represents HIV screening effort, $u_5(t)$ represents HPV infection treating effort and $u_6(t)$ represents HIV infection treating effort. Time is specified and is relatively short and is given by $t \in [0, T]$, T is the terminal time. Thus, the corresponding state system for the model *Eq. (1)* is given as follows:

$$
\begin{aligned}
dS/dt &= \Pi - \left((1-u_1)\lambda_p + (1-u_2)\lambda_h + (1-u_1)(1-u_2)\lambda_{hp} + \mu\right)S,\\
dE_p/dt &= (1-u_1)\lambda_p S - (1-u_3)\eta E_p - (\theta_2 + \mu)E_p,\\
dE_h/dt &= (1-u_2)\lambda_h S - (1-u_4)\eta E_h - (\theta_1 + \mu)E_h,\\
dE_{hp}/dt &= (1-u_1)(1-u_2)\lambda_{hp} S + \theta_1 E_h + \theta_2 E_p - (1-u_1)(1-u_2)\eta E_{hp} - \mu E_{hp},\\
dA_p/dt &= (1-u_3)(1-q)\eta E_p - (u_5 + \omega_3 + \theta_4 + \mu)A_p,\\
dA_h/dt &= (1-u_4)(1-p)\eta E_h - (u_6 + \omega_1 + \theta_3 + \mu)A_h,\\
dA_{hp}/dt &= (1-u_3)(1-u_4)(1-e)\eta E_{hp} + \theta_3 A_h + \theta_4 A_p - (u_5 + u_6 + \omega_2 + \mu)A_{hp},\\
dI_p/dt &= (1-u_3)q\eta E_p - (u_5 + \alpha_3 + \theta_6 + \mu)I_p,\\
dI_h/dt &= (1-u_4)p\eta E_h - (u_6 + \alpha_1 + \theta_5 + \mu)I_h,\\
dI_{hp}/dt &= (1-u_3)(1-u_4)e\eta E_{hp} + \theta_5 I_h + \theta_6 I_p - (u_5 + u_6 + \alpha_2 + \mu)I_{hp},\\
dC/dt &= (u_5 + \alpha_3)I_p + (u_5 + \omega_3)A_p - (\varepsilon_2 + \mu)C,\\
dA/dt &= (u_6 + \alpha_1)I_h + (u_6 + \omega_1)A_h - (\varepsilon_1 + \mu)A,\\
dAC/dt &= (u_5 + u_6 + \alpha_2)I_{hp} + (u_5 + u_6 + \omega_2)A_{hp} + \varepsilon_1 A + \varepsilon_2 C - \mu AC.
\end{aligned}
\tag{4}
$$

The main objective is to determine the optimal control values $u^* = (u_1^*, u_2^*, u_3^*, u_4^*, u_5^*, u_6^*)$ of the controls $u = (u_1, u_2, u_3, u_4, u_5, u_6)$ such that the associated state trajectories $\bar{S}$, $\bar{E_p}$, $\bar{E_h}, \bar{E_{ph}}, \bar{A_h}, \bar{A_p}$, $\bar{A_{ph}}$, $\bar{I_h}$, $\bar{I_p}$, $\bar{I_{ph}}, \bar{C}$, $\bar{A}, \overline{CA}$ are solution of the system *Eq. (4)* in the intervention time interval [0, T] with initial condition in *Eq. (3)* and minimize the objective functional. The controls are bounded between 0 and 1. When the controls vanish, it means 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 assumed $u_i \leq 1 - \epsilon$, $i = 1,2,3,4,5,6$, where $\epsilon \ll 1$ denotes a positive real number. Our cost functional considers the number of exposed individuals E_h, E_p, E_{ph}, the number of asymptomatic individuals A_h, A_p, A_{ph}, the number of symptomatic individuals I_h, I_p, I_{ph} and the implementation cost of strategies related to the controls $u_i, i = 1,2,3,4,5,6$. Thus, the objective functional is given by

$$
\begin{aligned}
J(u) = \int_0^T [&M_1 E_p(t) + M_2 E_h(t) + M_3 E_{ph}(t) + M_4 A_p(t) + M_5 A_h(t) + M_6 A_{ph}(t) +\\
&M_7 I_p(t) + M_8 I_h(t) + M_9 I_{ph}(t) + \frac{1}{2}\sum_{i=1}^{6} B_i u_i^2]dt \rightarrow \min.
\end{aligned}
\tag{5}
$$

Where constants M_i and B_i are positive. The weight constants B_1, B_2, B_3, B_4, B_5 and B_6 are the measure of relative costs of interventions associated with the controls u_1, u_2, u_3, u_4, u_5 and u_6, respectively, and also balances the units of integrand. Additionally, the functional J corresponds the total cost due to cervical cancer and AIDS outbreak and its control strategies. Further, the integrand function

$$L(\varnothing, u) = M_1E_p(t) + M_2E_h(t) + M_3E_{ph}(t) + M_4A_p(t) + M_5A_h(t) + M_6A_{ph}(t) + M_7I_p(t) + M_8I_h(t) + M_9I_{ph}(t) + \frac{1}{2}\sum_{i=1}^{6} B_i u_i^2,$$

measures the current cost at time t. Finally, the fixed constant T denotes the terminal innervations time. The set of admissible control functions is defined by

$$\Omega = \left\{ \left(u_1(.), u_2(.), u_3(.), u_4(.), u_5(.), u_6(.)\right) \in \left(L^{\infty}(0,T)\right)^6 : 0 \le u_i(t) \le 1 - \epsilon, \forall_t \in [0,T] \right\}. \quad (6)$$

Then we consider the optimal control problem of obtaining $(\bar{S}(.), \bar{E}_p(.), \bar{E}_h(.), \overline{E_{ph}}(.), \overline{A_h}(.), \overline{A_p}(.), \overline{A_{ph}}(.), \bar{I}_h(.), \bar{I}_p(.), \overline{I_{ph}}(.), \bar{C}(.), \bar{A}(.), \overline{CA}(.))$ associated with admissible controls $\left(u_1(.), u_2(.), u_3(.), u_4(.), u_5(.), u_6(.)\right) \in \Omega$ on the intervention time interval $[0, T]$, subject to the state system *Eq. (4)* in $\mathbb{R}^{13}$ with initial condition given in *Eq. (3)* and minimizing the cost functional *Eq. (5)*. Thus, the optimal control problem can be defined as

$$J(u_1^*, u_2^*, u_3^*, u_4^*, u_5^*, u_6^*) = \min_{\Omega} J\left(u_1(.), u_2(.), u_3(.), u_4(.), u_5(.), u_6(.)\right). \quad (7)$$

Satisfying *Eq. (4)* and *Eq. (3)*.

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 [12]-[13].

Theorem 1. There exists an optimal control $u^* = (u_1^*, u_2^*, u_3^*, u_4^*, u_5^*, u_6^*)$ in Ω and a corresponding solution vector $\bar{X} = (\bar{S}, \bar{E}_p, \bar{E}_h, \overline{E_{ph}}, \overline{A_h}, \overline{A_p}, \overline{A_{ph}}, \bar{I}_h, \bar{I}_p, \overline{I_{ph}}, \bar{C}, \bar{A}, \overline{CA})$ to the initial value problem *Eq. (3)* and *Eq. (4)* such that

$$J(u_1^*, u_2^*, u_3^*, u_4^*, u_5^*, u_6^*) = \min_{\Omega} J\left(u_1(.), u_2(.), u_3(.), u_4(.), u_5(.), u_6(.)\right).$$

Proof. The entire state variables involved in the model are continuously differentiable. Therefore, we need to verify the following four conditions as given in [12]

I. The set of solutions to the system *Eq. (4)* 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 $L(\varnothing, u) \ge g(u)$, where g continuous and $\|u\|^{-1}g(u) \to +\infty$ as $\|u\| \to \infty$.

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

$$N(t) = S(t) + E_h(t) + E_p(t) + E_{hp}(t) + A_h(t) + A_p(t) + A_{hP}(t) + I_h(t) + I_p(t) + I_{hp}(t) + A(t) + C(t) + AC(t).$$

From governing system *Eq. (4)* 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 *Eq. (4)* satisfy the Lipschitz condition

with respect to state variables. Therefore, the initial value problem *Eq. (4)* and *Eq. (3)* has a unique solution corresponding to each admissible control function $u \in \Omega$. Thus, *Condition (1)* is proved.

To prove *Condition (2)*, consider

$$\Omega = \left\{u \in \mathbb{R}^6 : \|u\| \leq 1 - \epsilon\right\}.$$

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 *Eq. (4)* is linear in control variables u_1, u_2, u_3, u_4, u_5 and u_6 with coefficients depending on state variables. With this *Condition (3)* is satisfied. The integrand of the cost functional is the sum of convex function and hence convex with respect to control variables. Furthermore,

$$\begin{aligned} L(\varnothing, u) = {} & M_1 E_p(t) + M_2 E_h(t) + M_3 E_{ph}(t) + M_4 A_p(t) + M_5 A_h(t) + M_6 A_{ph}(t) + \\ & M_7 I_p(t) + M_8 I_h(t) + M_9 I_{ph}(t) + \frac{1}{2}\sum_{i=1}^{6} B_i u_i^2 \geq \frac{1}{2}\sum_{i=1}^{6} B_i u_i^2. \end{aligned} \tag{8}$$

Let $\chi = min\left(\frac{1}{2}\sum_{i=1}^{6} B_i u_i^2\right) > 0$ and define a continuous function $g(u) = \chi\|u\|^{-1}$. Then from *Eq. (8)* we have $L(\varnothing, u) \geq g(u)$. Clearly, $\|u\|^{-1} g(u) \to +\infty$ as $\|u\| \to \infty$. Thus, condition (4) is achieved. Therefore, the existence of an optimal control pair $(\overline{X}, u^*)$ is satisfying *Eq. (4)* and *Eq. (7)* is assured by results given in [12]. Hence the proof.

3.2 | Characterization of Optimal Control

In this section, we determine optimality conditions for the optimal control problem defined above and its detail properties. According to Pontryagin's Maximum Principle [14] if $u^*(.) \in \Omega$ is optimal for problem *Eq. (4)* and *Eq. (7)* with fixed final time T, then there exists a non trivial absolutely continuous mapping $\lambda : [0, T] \to \mathbb{R}^{13}$, $\lambda = (\lambda_1(t), \lambda_2(t), \lambda_3(t), \lambda_4(t), \lambda_5(t), \lambda_6(t), \lambda_7(t), \lambda_8(t), \lambda_9(t), \lambda_{10}(t), \lambda_{11}(t), \lambda_{12}(t), \lambda_{13}(t))$ called the adjoint vector, such that

I. The Hamiltonian function is defined as

$$\begin{aligned} H = {} & M_1 E_p(t) + M_2 E_h(t) + M_3 E_{ph}(t) + M_4 A_p(t) + M_5 A_h(t) + M_6 A_{ph}(t) + \\ & M_7 I_p(t) + M_8 I_h(t) + M_9 I_{ph}(t) + \frac{1}{2}\sum_{i=1}^{6} B_i u_i^2 + \sum_{i=1}^{13} \lambda_i(t) g_i(t, \varnothing, u). \end{aligned} \tag{9}$$

Where g_i stands for the right hands of the *Constraints (4)* for $i = 1, \ldots, 13$.

II. The control system

$$\begin{aligned} & S' = \frac{\partial H}{\partial \lambda_1}, E_p' = \frac{\partial H}{\partial \lambda_2}, E_h' = \frac{\partial H}{\partial \lambda_3}, E_{ph}' = \frac{\partial H}{\partial \lambda_4}, A_p' = \frac{\partial H}{\partial \lambda_5}, A_h' = \frac{\partial H}{\partial \lambda_6}, A_{ph}' = \frac{\partial H}{\partial \lambda_7}, I_p' = \\ & \frac{\partial H}{\partial \lambda_8}, I_h' = \frac{\partial H}{\partial \lambda_9}, I_{ph}' = \frac{\partial H}{\partial \lambda_{10}}, C = \frac{\partial H}{\partial \lambda_{11}}, A = \frac{\partial H}{\partial \lambda_{12}}, CA = \frac{\partial H}{\partial \lambda_{13}}. \end{aligned} \tag{10}$$

III. The adjoint system

$$\begin{aligned} & \lambda_1' = -\frac{\partial H}{\partial S}, \lambda_2' = -\frac{\partial H}{\partial E_p}, \lambda_3' = -\frac{\partial H}{\partial E_h}, \lambda_4' = -\frac{\partial H}{\partial E_{ph}}, \lambda_5' = -\frac{\partial H}{\partial A_p}, \lambda_6' = -\frac{\partial H}{\partial A_h}, \lambda_7' = \\ & -\frac{\partial H}{\partial A_{ph}}, \lambda_8' = -\frac{\partial H}{\partial I_p}, \lambda_9' = -\frac{\partial H}{\partial I_h}, \lambda_{10}' = -\frac{\partial H}{\partial I_{ph}}, \lambda_{11}' = -\frac{\partial H}{\partial C}, \lambda_{12}' = -\frac{\partial H}{\partial A}, \lambda_{13}' = -\frac{\partial H}{\partial CA}. \end{aligned} \tag{11}$$

IV. The optimality conditions

$$H\left(\varnothing^*(t), u^*(t), \lambda^*(t)\right) = \min_{u \in \Omega} H\left(\varnothing^*(t), u^*(t), \lambda^*(t)\right). \tag{12}$$

V. Moreover, the transversality condition

$$\lambda_i(T) = 0, \quad i = 1, \dots, 13. \tag{13}$$

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

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

Theorem 2. Let $u^* = (u_1^*, u_2^*, u_3^*, u_4^*, u_5^*, u_6^*)$ be the optimal control and $(\bar{S}(.), \overline{E_p}(.), \overline{E_h}(.), \overline{E_{ph}}(.), \overline{A_h}(.), \overline{A_p}(.), \overline{A_{ph}}(.), \overline{I_h}(.), \overline{I_p}(.), \overline{I_{ph}}(.), \overline{C}(.), \overline{A}(.), \overline{CA}(.))$ be associated unique optimal solutions of the optimal control problem *Eq. (4)* and *Eqs. (6)-(7)* with fixed final time T. Then there exists adjoint function $\lambda_i^*(.), \ i = 1, \dots, 13$ satisfying the following canonical equations

$$\begin{aligned}
\frac{d\lambda_1}{dt} &= \lambda_1[(1-u_1)\lambda_p + (1-u_2)\lambda_h + (1-u_1)(1-u_2)\lambda_{ph} + \mu] - \lambda_2(1-u_1)\lambda_p \\
&\quad - \lambda_3(1-u_2)\lambda_h - \lambda_4(1-u_1)(1-u_2)\lambda_{ph}], \\
\frac{d\lambda_2}{dt} &= -M_1 + \lambda_2[(1-u_3)\eta + (\theta_2 + \mu)] - \lambda_4\theta_2 - \lambda_5(1-u_3)(1-q)\eta - \lambda_8(1-u_3)q\eta, \\
\frac{d\lambda_3}{dt} &= -M_2 + \lambda_3[(1-u_4)\eta + (\theta_1 + \mu)] - \lambda_4\theta_1 - \lambda_6(1-u_4)(1-p)\eta - \lambda_9(1-u_4)p\eta, \\
\frac{d\lambda_3}{dt} &= -M_2 + \lambda_3[(1-u_4)\eta + (\theta_1 + \mu)] - \lambda_4\theta_1 - \lambda_6(1-u_4)(1-p)\eta - \lambda_9(1-u_4)p\eta, \\
\frac{d\lambda_4}{dt} &= -M_3 + \lambda_4[(1-u_3)(1-u_4)\eta + \mu] - \lambda_7(1-u_3)(1-u_4)(1-e)\eta - \lambda_{10}(1-u_3)(1-u_4)e\eta, \\
\frac{d\lambda_5}{dt} &= -M_4 + \lambda_1\left[(1-u_1)\frac{\beta_p q_p \gamma_3 S}{N}\right] - \lambda_2\left[(1-u_1)\frac{\beta_p q_p \gamma_3 S}{N}\right] + \lambda_5(u_5 + \omega_3 + \theta_4 + \mu) - \lambda_7\theta_4 - \lambda_{11}(u_5 + \omega_3), \\
\frac{d\lambda_6}{dt} &= -M_5 + \lambda_1\left[(1-u_2)\frac{\beta_h q_h \gamma_1 S}{N}\right] - \lambda_3\left[(1-u_2)\frac{\beta_h q_h \gamma_1 S}{N}\right] + \lambda_6(u_6 + \omega_1 + \theta_3 + \mu) - \lambda_7\theta_3 - \lambda_{12}(u_6 + \omega_1), \\
\frac{d\lambda_7}{dt} &= -M_6 + \lambda_1\left[(1-u_1)(1-u_2)\frac{\beta_{ph} q_{ph} \gamma_5 S}{N}\right] - \lambda_4\left[(1-u_1)(1-u_2)\frac{\beta_{ph} q_{ph} \gamma_5 S}{N}\right] + \\
&\quad \lambda_7(u_5 + +u_6 + \omega_2 + \mu) - \lambda_{13}(u_5 + u_6 + \omega_2), \\
\frac{d\lambda_8}{dt} &= -M_7 + \lambda_1\left[(1-u_1)\frac{\beta_p q_p \gamma_4 S}{N}\right] - \lambda_2\left[(1-u_1)\frac{\beta_p q_p \gamma_4 S}{N}\right] + \lambda_8(u_5 + \alpha_3 + \theta_6 + \mu) - \lambda_{10}\theta_6 - \lambda_{11}(u_5 + \alpha_3), \\
\frac{d\lambda_9}{dt} &= -M_8 + \lambda_1\left[(1-u_2)\frac{\beta_h q_h \gamma_2 S}{N}\right] - \lambda_3\left[(1-u_2)\frac{\beta_h q_h \gamma_2 S}{N}\right] + \lambda_9(u_6 + \alpha_1 + \theta_5 + \mu) - \\
&\quad \lambda_{10}\theta_5 - \lambda_{12}(u_6 + \alpha_1), \\
\frac{d\lambda_{10}}{dt} &= -M_9 + \lambda_1\left[(1-u_1)(1-u_2)\frac{\beta_{ph} q_{ph} \gamma_6 S}{N}\right] - \lambda_4\left[(1-u_1)(1-u_2)\frac{\beta_{ph} q_{ph} \gamma_6 S}{N}\right] + \\
&\quad \lambda_{10}(u_5 + u_6 + \alpha_2 + \mu) - \lambda_{13}(u_5 + u_6 + \alpha_2), \\
\frac{d\lambda_{11}}{dt} &= \lambda_{11}(\xi_2 + \mu) - \lambda_{13}\xi_2, \\
\frac{d\lambda_{12}}{dt} &= \lambda_{12}(\xi_1 + \mu) - \lambda_{13}\xi_1, \frac{d\lambda_{13}}{dt} = \lambda_{13}\mu.
\end{aligned} \tag{14}$$

With transiversality conditions

$$\lambda_i^*(T) = 0, \quad i = 1, \dots, 13. \tag{15}$$

Moreover, the corresponding optimal controls u_1^*, u_2^*, u_3^*, u_4^*, u_5^* and u_6^* are given by

$$\begin{aligned} u_1^*(t) &= \min\{\max\{0, \Phi_1\}, 1-\epsilon\}, \quad u_4^*(t) = \min\{\max\{0, \Phi_4\}, 1-\epsilon\}, \\ u_2^*(t) &= \min\{\max\{0, \Phi_2\}, 1-\epsilon\}, \quad u_5^*(t) = \min\{\max\{0, \Phi_5\}, 1-\epsilon\}, \\ u_3^*(t) &= \min\{\max\{0, \Phi_3\}, 1-\epsilon\}, \quad u_6^*(t) = \min\{\max\{0, \Phi_6\}, 1-\epsilon\}. \end{aligned} \tag{16}$$

Where

$$\Phi_1 = \frac{\lambda_p S(\lambda_2 - \lambda_1) + (1-u_2)\lambda_{ph} S(\lambda_4 - \lambda_1)}{B_1},$$

$$\Phi_2 = \frac{\lambda_h S(\lambda_3 - \lambda_1) + (1-u_1)\lambda_{ph} S(\lambda_4 - \lambda_1)}{B_2},$$

$$\Phi_3 = \frac{\lambda_5(1-q)\eta E_p + \lambda_7(1-u_4)(1-e)\eta E_{ph} + \lambda_8 q\eta E_p + \lambda_{10}(1-u_4)e\eta E_{ph} - \lambda_4(1-u_4)\eta E_{ph} - \lambda_2\eta E_p}{B_3},$$

$$\Phi_4 = \frac{\lambda_6(1-p)\eta E_h + \lambda_7(1-u_3)(1-e)\eta E_{ph} + \lambda_9 p\eta E_h + \lambda_{10}(1-u_3)e\eta E_{ph} - \lambda_4(1-u_3)\eta E_{ph} - \lambda_3\eta E_h}{B_4},$$

$$\Phi_5 = \frac{\lambda_5 A_p + \lambda_7 A_{ph} + \lambda_8 I_p + \lambda_{10} I_{ph} - \lambda_{11}(A_p + I_p) - \lambda_{13}(A_{ph} + I_{ph})}{B_5},$$

$$\Phi_6 = \frac{\lambda_6 A_h + \lambda_7 A_{ph} + \lambda_9 I_h + \lambda_{10} I_{ph} - \lambda_{12}(A_h + I_h) - \lambda_{13}(A_{ph} + I_{ph})}{B_6}.$$

Proof: The adjoint system, transversality conditions and optimality conditions are standard results from Pontryagin's Maximum Principle [12], [15]. Thus, system *Eq. (14)* is directly derived from *Eq. (11)* and the transversality conditions *Eq. (15)* follow from *Eq. (12)*. Further, using the optimality condition it follows that

$$\frac{\partial H}{\partial u_i} = 0, \text{ for } \quad i = 1, 2, 3, 4, 5, 6. \tag{17}$$

Consequently, the optimality controls *Eq. (16)* can be directly solved from *Eq. (17)* by taking into account the boundedness condition given in *Eq. (6)*.

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 $i = 1,2,3,4,5,6, \dots, 13$ with bounded coefficients. Thus, there exists a $M > 0$ such that $|\lambda_i(t)| < M$ for $i = 1,2,3,4,5,6, \dots, 13$ on $[0, T]$.

Theorem 3. For T sufficiently small the solution to the optimality system is unique [16].

4 | Numerical Simulation

In this section, we discuss the numerical simulation of the optimality system. Using the initial conditions $S(0) = 2500$, $E_h(0) = 700, E_p(0) = 600$, $E_{hp}(0) = 500, A_h(0) = 800$, $A_p(0) = 750, A_{hp}(0) = 700, I_h(0) = 500$, $I_p(0) = 400$, $I_{hp}(0) = 200$, $A(0) = 600$, $C(0) = 500$, $AC(0) = 400$ and also coefficients of the state and controls that we used are $M1 = 80, M2 = 75, M3 = 50, M4 = 80, M5 = 75, M6 = 50, M7 = 80, M8 = 75, M9 = 50, B1 = 100$, $B2 = 110, B3 = 120, B4 = 130, B5 = 125, B6 = 135$ 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 thirteen-state equations and thirteen 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
Π	0.004	[1]
λ_h	0.00197	assumed
λ_p	0.002	assumed
λ_{hp}	0.0018	assumed
μ	0.02	[11]
α_1	0.016	[11]
α_2	0.017	[11]
α_3	0.011	[11]
p	0.067	[11]
q	0.067	[11]
e	0.067	[11]
θ_1	0.003	[11]
θ_2	0.003	[11]
θ_3	0.003	[11]
θ_4	0.003	[11]
θ_5	0.003	[11]
θ_6	0.003	[11]
ω_1	0.054	[11]
ω_2	0.064	[11]
ω_3	0.039	[11]
ε_1	0.001	[11]
ε_2	0.001	[11]
η	0.0024	[11]

Intervention I. Optimal use of u_2, u_3, u_4, u_5 and u_6: This intervention strategy combines prevention effort for HIV u_2 ,screening effort $(u_3 \& u_4)$ and treatment effort $(u_5 \& u_6)$ are used to optimize objective functional while setting prevention effort for HPV u_1 equal to zero. As shown in *Fig. 1*, the magnitudes of exposed and infectious population reduce more when controls are in use than the case without controls.

Intervention II. Optimal use of u_1, u_3, u_4, u_5 and u_6: This intervention combines prevention effort for HPV u_1, screening effort $(u_3 \& u_4)$ and treatment effort $(u_5 \& u_6)$ are used to optimize objective functional while setting prevention effort for HIV u_2 equal to zero. Results illustrate that the size of exposed and infectious population reduce sharply with controls more than the case without controls as shown in *Fig. 2*.

Intervention III. Optimal use of u_1, u_2, u_3, u_4 and u_5: This strategy illustrates effect of prevention effort ($u_1 \& u_2$), screening effort $(u_3 \& u_4)$ and treatment effort for HPV u_5 are used to optimize objective functional while setting treatment effort for HIV u_6 equal to zero. As expected, the number of exposed and infectious population diminishes more rapidly with controls than the case without controls as illustrated in *Fig. 3*.

Intervention IV. Optimal use of all controls u_1, u_2, u_3, u_4, u_5 and u_6: This intervention strategy uses prevention effort $(u_1 \& u_2)$, screening effort $(u_3 \& u_4)$ and treatment effort ($u_5 \& u_6$) are used to optimize objective functional. The size of exposed and infectious population decreases more sharply when controls are in use than the case when controls are not used as described in *Fig. 4*.

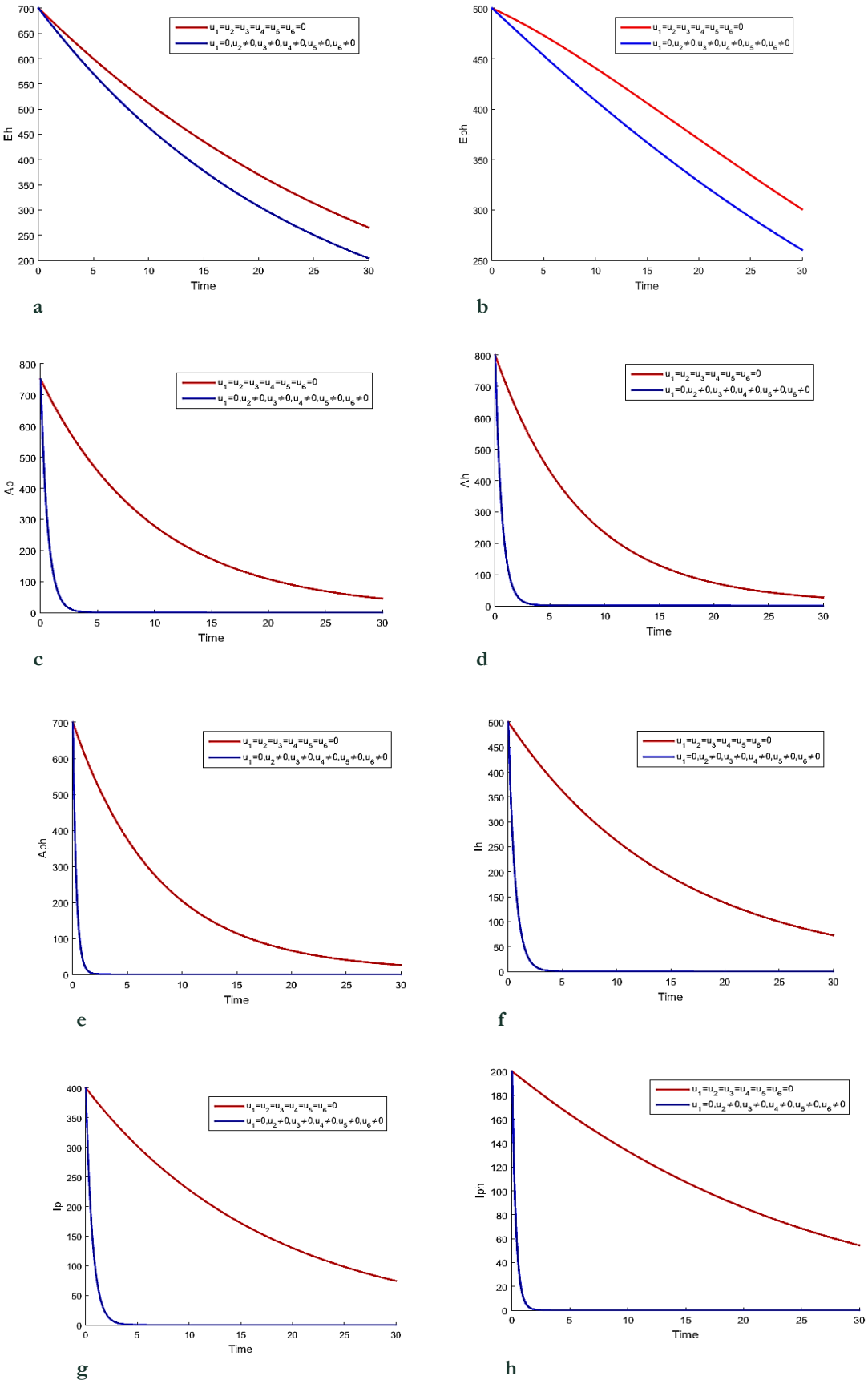
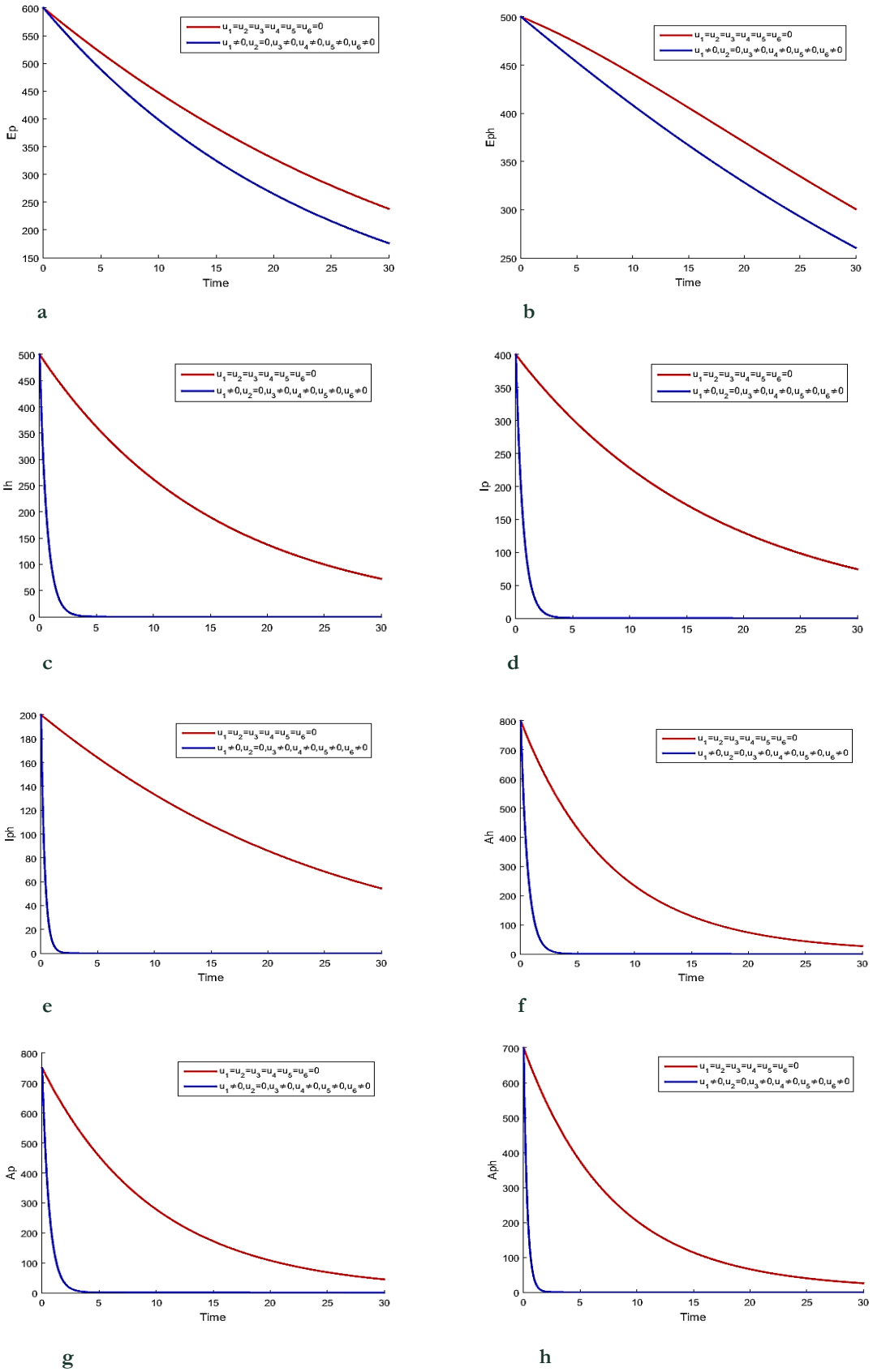


Fig 1. Simulations showing optimal use of u_2, u_3, u_4, u_5 and u_6.



a b c d e f g h

Fig. 2. Simulations showing optimal use of u_1, u_3, u_4, u_5 and u_6.

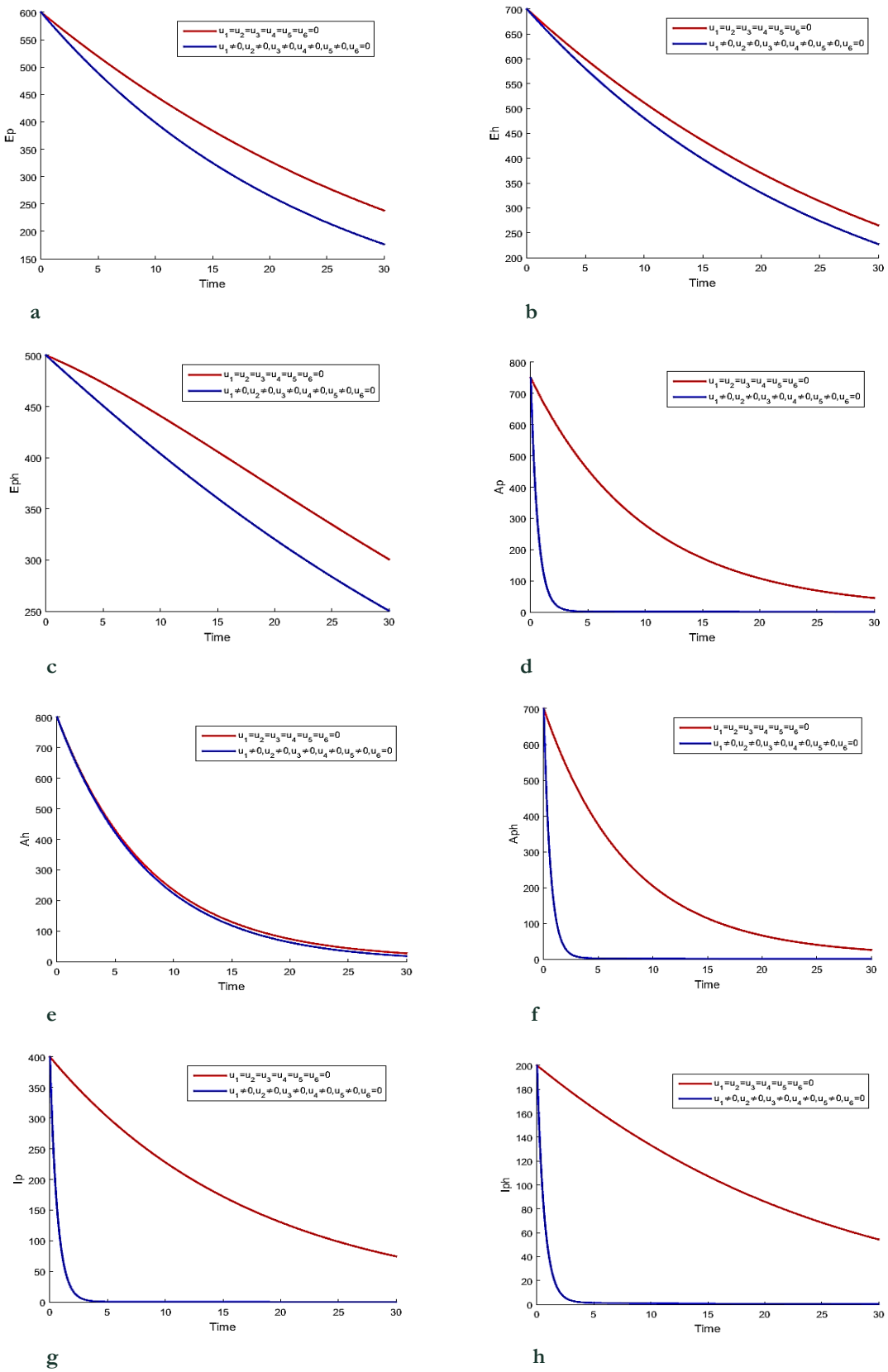


Fig 3. Simulations showing optimal use of u_1, u_2, u_3, u_4 and u_5.

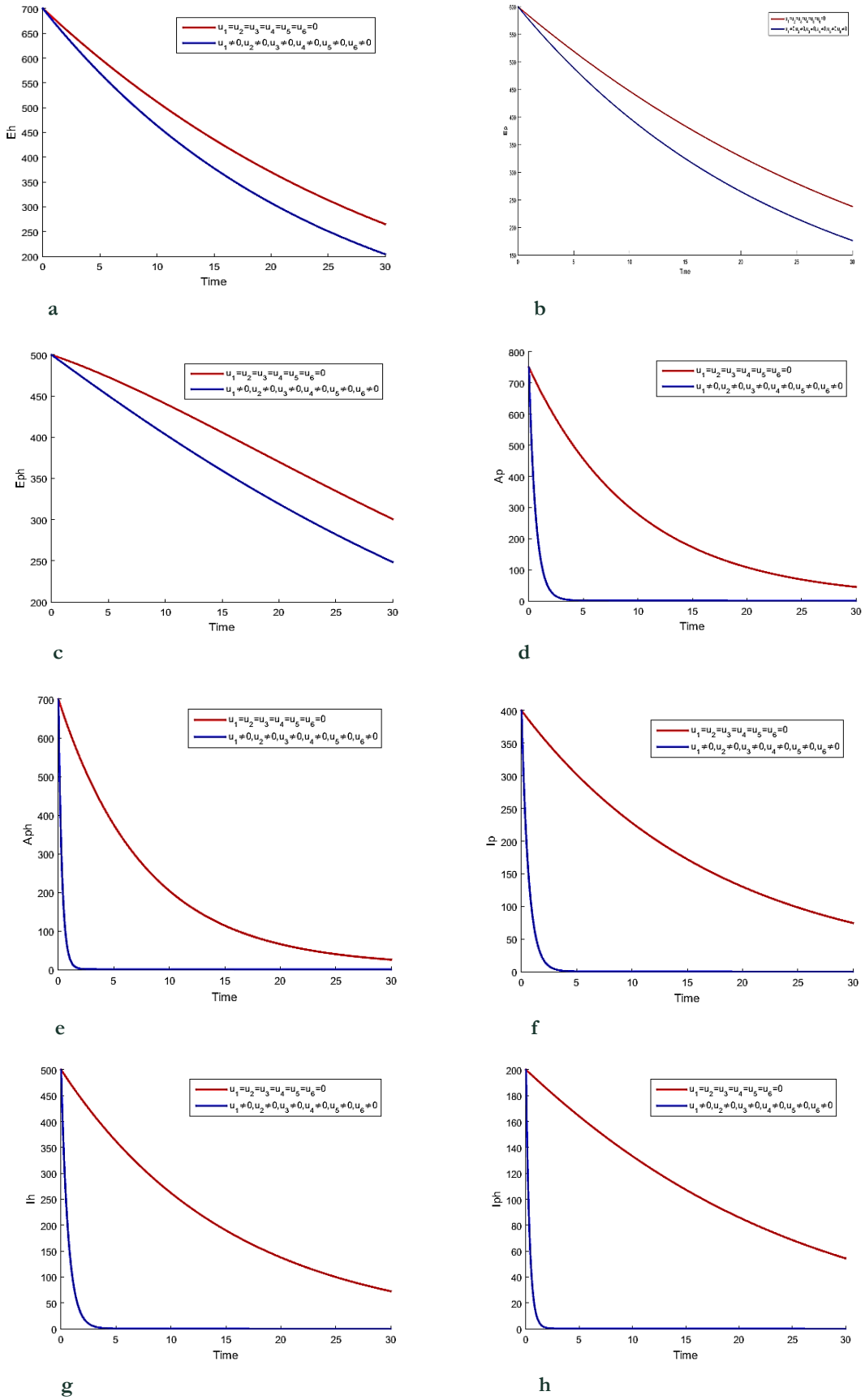


Fig 4. Simulations showing optimal use of u_1, u_2, u_3, u_4, u_5 and u_6.

5 | Conclusion

In this paper, an optimal control problem was formulated and analysed to study the effects of combining at least five control strategies on the transmission dynamics of HPV-HIV coinfection [11]. In this study, we have designed an optimal control problem that minimizes the cost for implementation of the controls while also minimizing the total exposed and infectious individuals over the intervention interval. The existence of optimal controls and characterization was established using Pontryagin's Maximum Principle. The results reveal that the size of exposed and infectious population is eradicated from the population by combining different intervention rather than using one intervention strategy.

HPV-HIV 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-HIV coinfection. In future work, we plan to extend the study by incorporating protected and treatment class to HPV- HIV transmission dynamics.

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