

Cervical Cancer and HIV Diseases Co-dynamics with Optimal Control and Cost Effectiveness

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Abstract: The deterministic model for co-infection of cervical cancer and HIV (Human Immunodeficiency Virus) diseases is formulated and rigorously analyzed. The optimal control theory is employed to the model to study the level of effort is needed to control the transmission of co-infection of cervical cancer and HIV diseases using three controls; prevention, screening and treatment control strategies. Numerical solutions show a remarkable decrease of infected individuals with HPV (Human Papilloma Virus) infection, cervical cancer, cervical cancer and HIV, cervical cancer and AIDS (Acquire Immunodeficiency Syndrome), HIV infection and AIDS after applying the combination of the optimal prevention, screening and treatment control strategies. However, Incremental Cost-Effective Ratio (ICER) shows that the best control strategy of minimizing cervical cancer among HIV-infected individuals with low cost is to use the combination of prevention and treatment control strategies.

Keywords: HPV Infection, HIV Infection, Cervical Cancer, Optimal Control, Cost-Effectiveness

1. Introduction

Cervical cancer is a major cause of morbidity and mortality among women in sub-Saharan countries and about 70% of cervical cancers are caused by Human Papillomavirus (HPV) types 16 and 18 which are transmitted sexually through body contact. Some studies have shown that HIV-infected women after being infected with HPV infection have a high risk to progress to HPV-related cervical diseases and invasive cervical cancer than women without having HIV infection [1, 2, 3].

The aim of this work is to study the effect of incorporating three optimal control strategies to the co-infection model of cervical cancer and HIV diseases. In [15] formulated co-infection model of cervical cancer and HIV diseases but the findings of this paper differ from the work presented in [15]

because the co-infection model incorporates three optimal control strategies; prevention, screening, and treatment.

2. Optimal Control Analysis

Here, we introduce optimal control strategies to the co-infection model of cervical cancer and HIV disease as presented in [15]. The co-infection model in [15] is developed as follows:

The total population of individuals at any time t , denoted as N is categorized into ten compartments according to the individual's status of infection as follows: Susceptible individuals (S), HIV-infected individuals no HPV infection (I_h), AIDS individuals no HPV infection (D_{ht}), Unscreened HPV infected individuals no HIV infection (I_{pu}), Screened

infectious individuals showing the impact of HPV infection without HIV infection (I_{ps}), Individuals with cervical cancer no HIV infection, Unscreened HPV infected individuals with HIV infection (I_{hpu}), Screened infectious individuals

showing the impact of HPV infection with HIV infection (I_{hps}), HIV-infected individuals with cervical cancer (I_{hc}) and AIDS individuals with cervical cancer (D_{hlc}). Thus,

$$N(t) = S(t) + I_h(t) + I_{hpu}(t) + I_{hps}(t) + I_{pu}(t) + I_{ps}(t) + I_{hc}(t) + I_c(t) + D_{hl}(t) + D_{hlc}(t)$$

The rates of transferring between different compartments are as described in Table 1.

Table 1. Description of parameters and their values for the model of co-infection HIV and cervical cancer diseases.

Parameter	Description	Value	Reference
μ	Natural mortality rate	0.01584yr ⁻¹	[11]
ω_1	Natural recovered rate for HIV-infected individuals with HPV infection	0.7yr ⁻¹	[12]
ω_2	Natural recovered rate for HPV unscreened infected individuals	0.366yr ⁻¹	Estimated
σ_2	Treatment rate for HPV screened infected individuals with only HPV infection.	0.2000yr ⁻¹	Estimated
σ_1	Treatment rate for HPV screened infected individuals with HPV and HIV infections.	0.2200yr ⁻¹	Estimated
α_1	Progression rate from HPV unscreened infected individuals with HIV infection to HPV screened infected individuals with HIV infection.	0.1000yr ⁻¹	Estimated
α_2	Progression rate from HPV screened infected individuals with HIV infection to cervical cancer individuals with HIV infection.	0.1286yr ⁻¹	Estimated
α_3	Progression rate from cervical cancer individuals with HIV infection to AIDS individuals with cervical cancer.	0.1640yr ⁻¹	Estimated
α_4	Progression rate from HPV unscreened infected individuals to HPV screened infected individuals.	0.1100yr ⁻¹	Estimated
α_5	Progression rate from HPV screened infected individuals to cervical cancer individuals.	0.127100yr ⁻¹	[12]
α_6	Progression rate from HPV unscreened infected individuals with HIV infection to cervical cancer individuals with HIV infection.	0.1300yr ⁻¹	Estimated
α_7	Progression rate from HIV infected individuals to AIDS individuals.	0.1160yr ⁻¹	[4]
	Progression rate from HPV unscreened infected individuals to cervical cancer individuals.	0.1200yr ⁻¹	Estimated
d_{pu}	The death rate due to HPV infection for HPV unscreened infected individuals.	Close to zero	[12]
d_{ps}	The death rate due to impact of HPV infection for HPV screened infected individuals.	0.0002	Estimated
d_c	Death rate due to cervical cancer	0.037yr ⁻¹	[13]
d_{hpu}	The death rate due to HIV and impact of HPV infection for HPV unscreened infected individuals with HIV infection.	0.0003yr ⁻¹	Estimated
d_{hps}	The death rate due to HIV and impact of HPV infection for HPV screened infected individuals with HIV infection.	0.0005yr ⁻¹	Estimated
d_{hc}	Death rate due to cervical cancer and HIV	0.0493yr ⁻¹	Estimated
d_{hlc}	Death rate due to cervical cancer and AIDS	0.1848yr ⁻¹	Estimated
d_h	Death rate due to HIV	0.0070yr ⁻¹	Estimated
d_{hl}	Death rate due to AIDS	0.1584yr ⁻¹	[14]
η_1	Infectivity rate of HIV infection	1.0000	Estimated
η_2	Infectivity rate of AIDS	1.0029	Estimated
η_3	Infectivity rate for HPV unscreened infected individuals with HIV infection.	1.0054	Estimated
η_4	Infectivity rate for HPV screened infected individuals with HIV infection.	1.0040	Estimated
η_5	Infectivity rate for cervical cancer individuals with HIV infection	1.1152	Estimated
η_6	Infectivity rate for cervical cancer individuals with AIDS	1.1240	Estimated
η_7	Infectivity rate for HPV unscreened infected individuals	1.016	Estimated
η_8	Infectivity rate for HPV screened infected individuals	1.0130	Estimated
η_9	Infectivity rate for cervical cancer individuals	1.0510	Estimated
β_H	Probability of transmission HIV infection		
β_{HC}	Probability of transmission both HIV and HPV infections	$0 < \beta_{HC} < 1$	
β_C	Probability of transmission HPV infection	$0 < \beta_C < 1$	
q	Mean number of contacts	1-3	Estimated

The mathematical model is defined by the following system of ordinary differential equations:

$$\begin{aligned}
 \frac{dS}{dt} &= \pi + \omega_2 I_{pu} + \sigma_2 I_{ps} - (\mu + \lambda_H + \lambda_{HC} + \lambda_C) S \\
 \frac{dI_h}{dt} &= \lambda_H S + \omega_1 I_{hpu} + \sigma_1 I_{hps} - (\mu + d_h + \alpha_7 + \lambda_C) I_h \\
 \frac{dI_{hpu}}{dt} &= \lambda_{HC} S + \lambda_C I_h + \lambda_H I_{pu} - (\alpha_1 + \alpha_6 + \omega_1 + \mu + d_{hpu}) I_{hpu} \\
 \frac{dI_{pu}}{dt} &= \lambda_C S - \lambda_H I_{pu} - (\omega_2 + \mu + d_{pu} + \alpha_4 + \alpha_8) I_{pu} \\
 \frac{dI_{ps}}{dt} &= \alpha_4 I_{pu} - (\lambda_H + \sigma_2 + \alpha_5 + \mu + d_{ps}) I_{ps} \quad (1) \\
 \frac{dI_{hps}}{dt} &= \alpha_1 I_{hpu} + \lambda_H I_{ps} - (\mu + d_{hps} + \alpha_2 + \sigma_1) I_{hps} \\
 \frac{dI_{hc}}{dt} &= \alpha_2 I_{hps} + \alpha_6 I_{hpu} - (\mu + d_{hc} + \alpha_3) I_{hc} \\
 \frac{dI_c}{dt} &= \alpha_8 I_{pu} + \alpha_5 I_{ps} - (\mu + d_c) I_c \\
 \frac{dD_{hl}}{dt} &= \alpha_7 I_h - (\mu + d_{hl}) D_{hl} \\
 \frac{dD_{hlc}}{dt} &= \alpha_3 I_{hc} - (\mu + d_{hlc}) D_{hlc}
 \end{aligned}$$

where

$$\begin{aligned}
 \lambda_H &= \frac{\beta_H q}{N} (\eta_1 I_h + \eta_2 D_{hl}) \quad \text{with } \eta_2 > \eta_1 \\
 \lambda_{HC} &= \frac{\beta_{HC} q}{N} (\eta_3 I_{hpu} + \eta_4 I_{hps} + \eta_5 I_{hc} + \eta_6 D_{hlc}) \quad \text{with } \eta_6 > \eta_5 > \eta_3 > \eta_4 \\
 \lambda_C &= \frac{\beta_C q}{N} (\eta_7 I_{pu} + \eta_8 I_{ps} + \eta_9 I_c) \quad \text{with } \eta_9 > \eta_7 > \eta_8.
 \end{aligned}$$

Hence, the system (1) is modified by introducing time-dependent control; $u_1(t)$ represents prevention control strategy (Education campaign and health hygiene practice), $u_2(t)$ represents the treatment of early stages of cervical cancer and $u_3(t)$ represents screening individuals showing an impact of HPV infection leads to cervical cancer. The following system of equations is obtained

$$\begin{aligned}
 \frac{dS}{dt} &= \pi + (u_2 + \sigma_2) I_{ps} + \omega_2 I_{pu} - (1 - u_1) (\lambda_H + \lambda_{HC} + \lambda_C) S - \mu S \\
 \frac{dI_h}{dt} &= (1 - u_1) (\lambda_H S - \lambda_C I_h) + (u_2 + \sigma_1) I_{hps} + \omega_1 I_{hpu} - (\alpha_7 + d_h + \mu) I_h \\
 \frac{dI_{hpu}}{dt} &= (1 - u_1) (\lambda_{HC} S + \lambda_H I_{pu} + \lambda_C I_h) - (u_3 + \alpha_1) I_{hpu} - (\alpha_6 + d_{hpu} + \omega_1 + \mu) I_{hpu}
 \end{aligned}$$

$$\begin{aligned}
\frac{dI_{pu}}{dt} &= (1-u_1)(\lambda_C S - \lambda_H I_{hpu}) - (u_3 + \alpha_4) I_{hpu} - (\alpha_8 + d_{pu} + \omega_2 + \mu) I_{hpu} \\
\frac{dI_{hps}}{dt} &= (u_3 + \alpha_1) I_{hpu} + (1-u_1) \lambda_H I_{ps} - (u_2 + \sigma_1) I_{hps} - (\alpha_2 + d_{hps} + \mu) I_{hps} \\
\frac{dI_{ps}}{dt} &= (u_3 + \alpha_4) I_{pu} - (1-u_1) \lambda_H I_{ps} - (u_2 + \sigma_2) I_{ps} - (\alpha_5 + d_{ps} + \mu) I_{ps} \\
\frac{dI_{hc}}{dt} &= \alpha_2 I_{hps} + \alpha_6 I_{hpu} - (\mu + d_{hc} + \alpha_3) I_{hc} \\
\frac{dI_c}{dt} &= \alpha_5 I_{ps} + \alpha_8 I_{pu} - (\mu + d_c) I_c \\
\frac{dD_{hl}}{dt} &= \alpha_7 I_h - (\mu + d_{hl}) D_{hl} \\
\frac{dD_{hlc}}{dt} &= \alpha_3 I_{hc} - (\mu + d_{hlc}) D_{hlc}
\end{aligned} \tag{2}$$

The objective functional is defined as follows

$$J(u_1, u_2, u_3) = \lim_{u_1, u_2, u_3} \int_0^{t_f} \left(A_1 I_{hpu} + A_2 I_{pu} + A_3 I_{hps} + A_4 I_{ps} + B_1 \frac{u_1^2}{2} + B_2 \frac{u_2^2}{2} + B_3 \frac{u_3^2}{2} \right) dt \tag{3}$$

where A_i and B_j for $i=1,2,3,4$ and $j=1,2,3$ 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 screening individuals with or without HIV infection having HPV infection and $\frac{B_3 u_3^2}{2}$ represents the cost of control effort on treating individuals having cervical cancer with or without HIV infection. The main goal of introducing time-dependent controls in the co-infection model is to prevent women not to acquire HPV infection which leads to cervical cancer and to minimize infected women showing the impact of HPV infection lead to cervical cancer while minimizing the cost of

controls $u_1(t)$, $u_2(t)$ and $u_3(t)$ as in [5, 6, 7]. The goal is to seek an optimal control u_1^* , u_2^* and u_3^* numerically such that

$$J(u_1^*, u_2^*, u_3^*) = \min \{ J(u_1, u_2, u_3) \mid u_1, u_2, u_3 \in \Omega \} \tag{4}$$

where $\Omega = \{(u_1, u_2, u_3) \text{ such that } u_1, u_2, u_3 \text{ measurable with } 0 \leq u_1 \leq 1, 0 \leq u_2 \leq 1 \text{ and } 0 \leq u_3 \leq 1 \text{ for } t \in [0, t_f]\}$ is the control set. The necessary conditions that an optimal must satisfy come from the Pontryagin's maximum principle [8]. This principle converts (2) and (3) into the problem of minimizing point-wise Hamiltonian, H , with respect to u_1 , u_2 and u_3 .

$$\begin{aligned}
H &= A_1 I_{hpu} + A_2 I_{pu} + A_3 I_{hps} + A_4 I_{ps} + B_1 \frac{u_1^2}{2} + B_2 \frac{u_2^2}{2} + B_3 \frac{u_3^2}{2} \\
&+ M_S (\pi + (u_2 + \sigma_2) I_{ps} + \omega_2 I_{pu} - (1-u_1)(\lambda_H + \lambda_{HC} + \lambda_C) S - \mu S) \\
&+ M_{I_h} ((1-u_1)(\lambda_H S - \lambda_C I_h) + (u_2 + \sigma_1) I_{hps} + \omega_1 I_{hpu} - (\alpha_7 + d_h + \mu) I_h) \\
&+ M_{I_{hpu}} ((1-u_1)(\lambda_{HC} S + \lambda_H I_{pu} + \lambda_C I_h) - (u_3 + \alpha_1) I_{hpu} - (\alpha_6 + d_{hpu} + \omega_1 + \mu) I_{hpu}) \\
&+ M_{I_{pu}} ((1-u_1)(\lambda_C S - \lambda_H I_{hpu}) - (u_3 + \alpha_4) I_{hpu} - (\alpha_8 + d_{pu} + \omega_2 + \mu) I_{hpu})
\end{aligned}$$

$$\begin{aligned}
& +M_{I_{hps}} \left((u_3 + \alpha_1) I_{hpu} + (1-u_1) \lambda_H I_{ps} - (u_2 + \sigma_1) I_{hps} - (\alpha_2 + d_{hps} + \mu) I_{hps} \right) \\
& +M_{I_{ps}} \left((u_3 + \alpha_4) I_{pu} - (1-u_1) \lambda_H I_{ps} - (u_2 + \sigma_2) I_{ps} - (\alpha_5 + d_{ps} + \mu) I_{ps} \right) \\
& +M_{I_{hc}} \left(\alpha_2 I_{hps} + \alpha_6 I_{hpu} - (\mu + d_{ch} + \alpha_3) I_{hc} \right) \\
& +M_{I_c} \left(\alpha_5 I_{ps} + \alpha_8 I_{pu} - (\mu + d_c) I_c \right) \\
& +M_{D_{hl}} \left(\alpha_7 I_h - (\mu + d_{hl}) D_{hl} \right) \\
& +M_{D_{hlc}} \left(\alpha_3 I_{hc} - (\mu + d_{hlc}) D_{hlc} \right)
\end{aligned} \tag{5}$$

where, $M_S, M_{I_h}, M_{I_{hpu}}, M_{I_{pu}}, M_{I_{hps}}, M_{I_{ps}}, M_{I_{hc}}, M_{I_c}, M_{D_{hl}}$ and $M_{D_{hlc}}$ are the co-state variables or the adjoint variables.

Theorem: For the optimal control triples u_1^*, u_2^* and u_3^* that minimize $J(u_1, u_2, u_3)$ over Ω , there exist adjoint variables $M_S, M_{I_h}, M_{I_{hpu}}, M_{I_{pu}}, M_{I_{hps}}, M_{I_{ps}}, M_{I_{hc}}, M_{I_c}, M_{D_{hl}}$ and $M_{D_{hlc}}$ satisfying

$$\frac{-dM_j}{dt} = \frac{\partial H}{\partial j} \tag{6}$$

where $j = S, I_h, I_{hpu}, I_{pu}, I_{hps}, I_{hc}, I_c, D_{hl}, D_{hlc}$ and with transversality condition $M_S(t) = M_{I_h}(t) = M_{I_{hpu}}(t) = M_{I_{pu}}(t) = M_{I_{hps}}(t) = M_{I_{ps}}(t) = M_{I_{hc}}(t) = M_{I_c}(t) = M_{D_{hl}}(t_f) = M_{D_{hlc}}(t_f) = 0$ and,

$$u_1^* = \max \left\{ 0, \min \left[1, \frac{1}{B_1} \left(I_{ps} \lambda_H (M_{I_{hps}} - M_{I_{ps}}) + S \lambda_H (M_{I_h} - M_S) + I_{pu} \lambda_H (M_{I_{hpu}} - M_{I_{pu}}) \right) \right. \right. \\ \left. \left. + S \lambda_{HC} (M_{I_{hpu}} - M_S) + S \lambda_C (M_{I_{pu}} - M_S) + \lambda_C I_H (M_{I_{hpu}} - M_{I_h}) \right] \right\} \tag{7}$$

$$u_2^* = \max \left\{ 0, \min \left[1, \frac{1}{B_2} \left(I_{hps} (M_{I_{hps}} - M_{I_h}) + I_{ps} (M_{I_{ps}} - M_S) \right) \right] \right\} \tag{8}$$

$$u_3^* = \max \left\{ 0, \min \left[1, \frac{1}{B_3} \left(I_{hpu} (M_{I_{hpu}} - M_{I_{hps}}) + I_{pu} (M_{I_{pu}} - M_{I_{ps}}) \right) \right] \right\} \tag{9}$$

Proof. Corollary 4.1 of Fleming and Riches [9] gives the existence of an optimal control due to the convexity of the integrand J with respect to u_1, u_2 and u_3 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;

$$\begin{aligned}
-\frac{dM_S}{dt} &= M_S \mu + \frac{I_{ps} \lambda_H (1-u_1) (M_{I_{hps}} - M_{I_{ps}})}{N} + \frac{I_{pu} \lambda_H (1-u_1) (M_{I_{hpu}} - M_{I_{pu}})}{N} \\
&+ \lambda_{HC} (1-u_1) (M_S - M_{I_{hpu}}) + \frac{I_h \lambda_C (1-u_1) (M_{I_{hpu}} - M_{I_h})}{N} + \lambda_H (1-u_1) (M_S - M_{I_h})
\end{aligned}$$

$$\begin{aligned}
& +\lambda_C(1-u_1)(M_S-M_{I_{hps}})+\frac{S(1-u_1)\lambda_H(M_{I_h}-M_S)}{N}+\frac{S(1-u_1)\lambda_{HC}(M_{I_{hpu}}-M_S)}{N}. \\
-\frac{dM_{I_h}}{dt} & =\alpha_7 M_{D_{hl}}+M_{I_h}(\mu+d_h)+\frac{I_{ps}q(1-u_1)\beta_H\eta_1(M_{I_{ps}}-M_{I_{hps}})}{N}+\frac{I_{ps}\lambda_H(1-u_1)(M_{I_{hps}}-M_{I_{ps}})}{N} \\
& +\frac{S\beta_Hq\eta_1(1-u_1)(M_S-M_{I_{ps}})}{N}+\frac{I_{pu}\beta_Hq\eta_1(1-u_1)(M_{I_{pu}}-M_{I_{hpu}})}{N}+\frac{S(1-u_1)\lambda_{HC}(M_{I_{hpu}}-M_S)}{N} \\
& +\frac{I_{pu}\lambda_H(1-u_1)(M_{I_{hpu}}-M_{I_{hps}})}{N}+\frac{I_h\lambda_C(1-u_1)(M_{I_{hpu}}-M_{I_h})}{N}+\frac{S\lambda_H(1-u_1)(M_{I_h}-M_S)}{N} \\
& +\lambda_C(1-u_1)(M_{I_h}-M_{I_{hpu}})+\frac{S\lambda_C(1-u_1)(M_{I_{pu}}-M_S)}{N} \\
-\frac{dM_{I_{hpu}}}{dt} & =-A_1+\alpha_6(M_{I_{hpu}}-M_{I_{hc}})+M_{I_{hpu}}(\mu+d_{hpu})+(u_3+\alpha_1)(M_{I_{hpu}}-M_{I_{hps}})+\omega_1(M_{I_{hpu}}-M_{I_h}) \\
& +\frac{I_{ps}(1-u_1)\lambda_H(M_{I_{hps}}-M_{I_{ps}})}{N}+\frac{S\lambda_H(1-u_1)(M_{I_h}-M_S)}{N}+\frac{Sq(1-u_1)\beta_{HC}\eta_3(M_S-M_{I_{hpu}})}{N} \\
& +\frac{I_{pu}(1-u_1)\lambda_H(M_{I_{hpu}}-M_{I_{pu}})}{N}+\frac{\lambda_C I_h(1-u_1)(M_{I_{hpu}}-M_{I_h})}{N}+\frac{S\lambda_{HC}(1-u_1)(M_{I_{hpu}}-M_S)}{N} \\
& +\frac{S\lambda_C(1-u_1)(M_{I_{pu}}-M_S)}{N}. \\
-\frac{dM_{I_{pu}}}{dt} & =-A_2+\alpha_8(M_{I_{pu}}-M_{I_c})+\frac{I_{ps}\lambda_H(1-u_1)(M_{I_{hps}}-M_{I_{ps}})}{N}+\frac{I_{pu}\lambda_H(1-u_1)(M_{I_{hpu}}-M_{I_{pu}})}{N} \\
& +\frac{I_h(1-u_1)q\beta_C\eta_7(M_{I_h}-M_{I_{hpu}})}{N}+M_{I_{pu}}(\mu+d_{pu})+\lambda_H(1-u_1)(M_{I_{pu}}-M_{I_{hpu}})+\omega_2(M_{I_{pu}}-M_S) \\
& +\frac{I_h\lambda_C(1-u_1)(M_{I_{hpu}}-M_{I_h})}{N}+(u_3+\alpha_4)(M_{I_{pu}}-M_{I_{ps}})+\frac{S(1-u_1)\lambda_{HC}(M_{I_{hpu}}-M_S)}{N} \\
& +\frac{S(1-u_1)\lambda_C(M_{I_{pu}}-M_S)}{N}+\frac{S(1-u_1)\lambda_H(M_{I_h}-M_S)}{N}+\frac{Sq(1-u_1)\beta_C\eta_7(M_S-M_{I_{pu}})}{N} \\
-\frac{dM_{I_{hps}}}{dt} & =-A_3+\alpha_2(M_{I_{hps}}-M_{I_{hc}})+\frac{I_{ps}(1-u_1)\lambda_H(M_{I_{ps}}-M_{I_h})}{N}+\frac{S\lambda_h(1-u_1)(M_{I_h}-M_S)}{N} \\
& +\frac{I_h(1-u_1)\lambda_C(M_{I_{hpu}}-M_{I_h})}{N}+(u_3+\sigma_1)(M_{I_{hps}}-M_{I_h})+M_{I_{hps}}(\mu+d_{hps})+\frac{I_{pu}\lambda_H(1-u_1)(M_{I_{hpu}}-M_{I_{pu}})}{N}
\end{aligned}$$

$$\begin{aligned}
& + \frac{Sq(1-u_1)\beta_{HC}\eta_4(M_S - M_{I_{hpu}})}{N} + \frac{S\lambda_C(1-u_1)(M_{I_{pu}} - M_S)}{N} + \frac{S(1-u_1)\lambda_{HC}(M_{I_{hpu}} - M_S)}{N} \\
& - \frac{dM_{I_{ps}}}{N} = -A_4 + \alpha_5(M_{I_{ps}} - M_{I_{hc}}) + M_{I_{ps}}(\mu + d_{ps}) + (u_2 + \sigma_1)(M_{I_{ps}} - M_S) \\
& + \frac{I_{ps}\lambda_H(1-u_1)(M_{I_{hps}} - M_{I_{ps}})}{N} + (1-u_1)\lambda_H(M_{I_{ps}} - M_{I_{hps}}) + (1-u_1)I_{pu}\lambda_H(M_{I_{hpu}} - M_{I_{pu}}) \\
& + \frac{S(1-u_1)\beta_C\eta_8q(M_S - M_{I_{pu}})}{N} + \frac{S\lambda_C(1-u_1)(M_{I_{pu}} - M_S)}{N} + \frac{I_h\lambda_C(1-u_1)(M_{I_{hpu}} - M_{I_h})}{N} \\
& + \frac{I_h(1-u_1)\beta_C\eta_8q(M_{I_h} - M_{I_{hpu}})}{N} + \frac{S(1-u_1)\lambda_H(M_{I_h} - M_S)}{N} + \frac{S(1-u_1)\lambda_{HC}(M_{I_{hpu}} - M_S)}{N} \\
& - \frac{dM_{I_{hc}}}{dt} = M_{I_{hc}}(\mu + d_{ch}) + \alpha_3(M_{I_{hc}} - M_{D_{hlc}}) + \frac{I_{ps}\lambda_H(1-u_1)(M_{I_{hps}} - M_{I_{ps}})}{N} + \frac{S\lambda_H(1-u_1)(M_{I_h} - M_S)}{N} \\
& + \frac{Sq\beta_{HC}\eta_5(M_S - M_{I_{hpu}})}{N} + \frac{S\lambda_{HC}(1-u_1)(M_{I_{hpu}} - M_S)}{N} + \frac{S\lambda_C(1-u_1)(M_{I_{hpu}} - M_S)}{N} \\
& + \frac{I_{pu}\lambda_H(1-u_1)(M_{I_{hpu}} - M_{I_{pu}})}{N} + \frac{I_h\lambda_C(1-u_1)(M_{I_{hpu}} - M_{I_h})}{N} \\
& - \frac{dM_{I_c}}{dt} = M_{I_c}(\mu + d_c) + \frac{I_{ps}\lambda_H(M_{I_{hps}} - M_{I_{ps}})}{N} + \frac{S\lambda_H(1-u_1)(M_{I_h} - M_S)}{N} + \frac{S\lambda_{HC}(1-u_1)(M_{I_{hpu}} - M_S)}{N} \\
& + \frac{S\beta_Cq\eta_9(1-u_1)(M_S - M_{I_{pu}})}{N} + \frac{I_{pu}\lambda_H(1-u_1)(M_{I_{hpu}} - M_{I_{pu}})}{N} + \frac{S\lambda_C(1-u_1)(M_{I_{pu}} - M_S)}{N} \\
& + \frac{I_h\beta_Cq\eta_9(1-u_1)(M_{I_h} - M_{I_{hpu}})}{N} + \frac{I_h\lambda_C(1-u_1)(M_{I_{hpu}} - M_{I_h})}{N} \\
& - \frac{dM_{D_{hl}}}{dt} = (\mu + d_{hl})M_{D_{hl}} + \frac{I_{ps}\beta_hq\eta_2(1-u_1)(M_{I_{ps}} - M_{I_{hps}})}{N} + \frac{I_{ps}(1-u_1)\lambda_H(M_{I_{hps}} - M_{I_{ps}})}{N} \\
& + \frac{S\beta_H\eta_2q(1-u_1)(M_S - M_{I_h})}{N} + \frac{S\lambda_H(1-u_1)(M_{I_h} - M_S)}{N} + \frac{S\lambda_{HC}(1-u_1)(M_{I_{hpu}} - M_S)}{N} \\
& + \frac{I_h\lambda_C(1-u_1)(M_{I_{hpu}} - M_{I_h})}{N} + \frac{I_{pu}\lambda_H(1-u_1)(M_{I_{hpu}} - M_{I_{pu}})}{N} + \frac{I_{pu}\beta_H\eta_2q(1-u_1)(M_{I_{pu}} - M_{I_{hpu}})}{N} + \frac{S\lambda_C(1-u_1)(M_{I_{pu}} - M_S)}{N} \\
& - \frac{dM_{D_{hlc}}}{dt} = (\mu + d_{hlc})M_{D_{hlc}} + \frac{(1-u_1)I_{ps}\lambda_H(M_{I_{hps}} - M_{I_{ps}})}{N} + \frac{S(1-u_1)\lambda_H(M_{I_h} - M_S)}{N}
\end{aligned} \tag{10}$$

Optimality equations (7)-(9) are obtained by computing partial derivative of the Hamiltonian equation (5) with

respect to each control variables as follows

$$0 = \frac{\partial H}{\partial u_i} \text{ for } i = 1, 2, 3$$

Solving for u_1^* , u_2^* and u_3^* , subject to the constraints, provides the characterization equations (7)-(9). In the next part, the numerical solutions of optimality system are discussed.

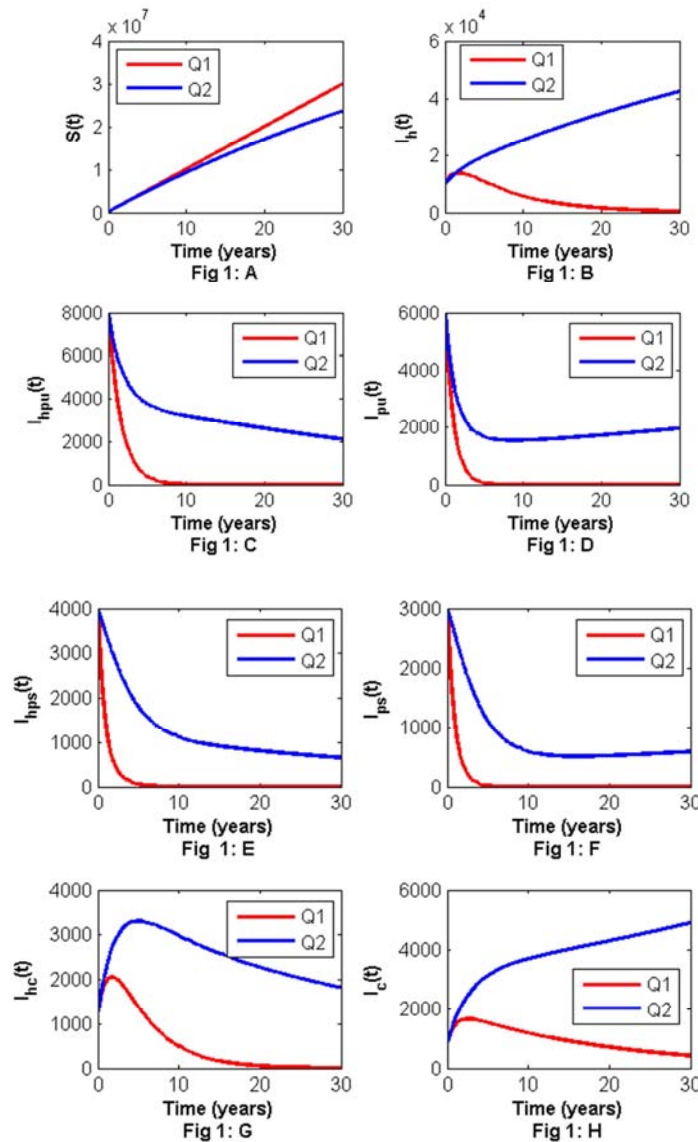
3. Numerical Solutions

In order to obtain optimal control solutions, the optimality system which consists of two systems namely; the state system and the adjoint system is solved. In solving state equations using forward fourth order Runge-Kutta, an initial guess of all controls over time are made and the initial value of state variables are introduced. Having the solution of state functions and the value of optimal controls, the adjoint equations are solved using backward fourth order Runge-

Kutta by using transversality condition. In this simulation, the weights are chosen be $A_1 = 80$, $A_2 = 75$, $A_3 = 50$, $A_4 = 45$, $B_1 = 100$, $B_2 = 110$ and $B_3 = 120$. Other parameter descriptions and values used in getting numerical results of the co-infection model of cervical cancer and HIV diseases are presented in Table 1. Control strategies are formed and studied numerically as follows

3.1. Strategy I: Combination of Prevention and Treatment Control Strategies

The combination of prevention control strategy u_1 and treatment control u_2 are used to optimize objective functional while setting screening control u_3 equal to zero. The results show that applying optimal prevention and treatment control strategies; the population of susceptible individuals increases whereas the population of all infected compartments decreases as illustrated in Figure1: A and Figure1: B-J respectively.



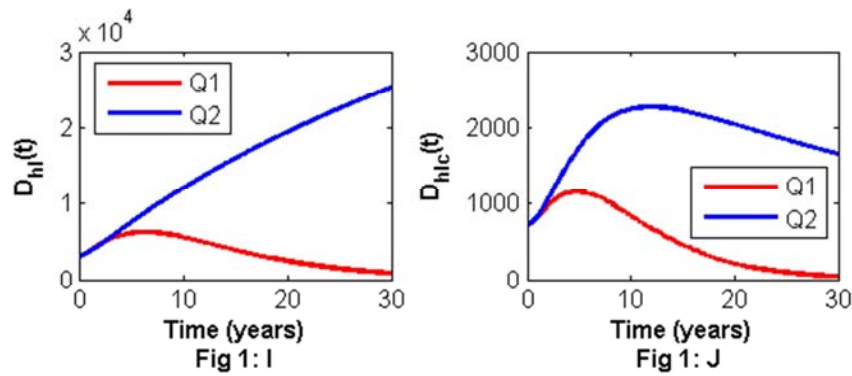
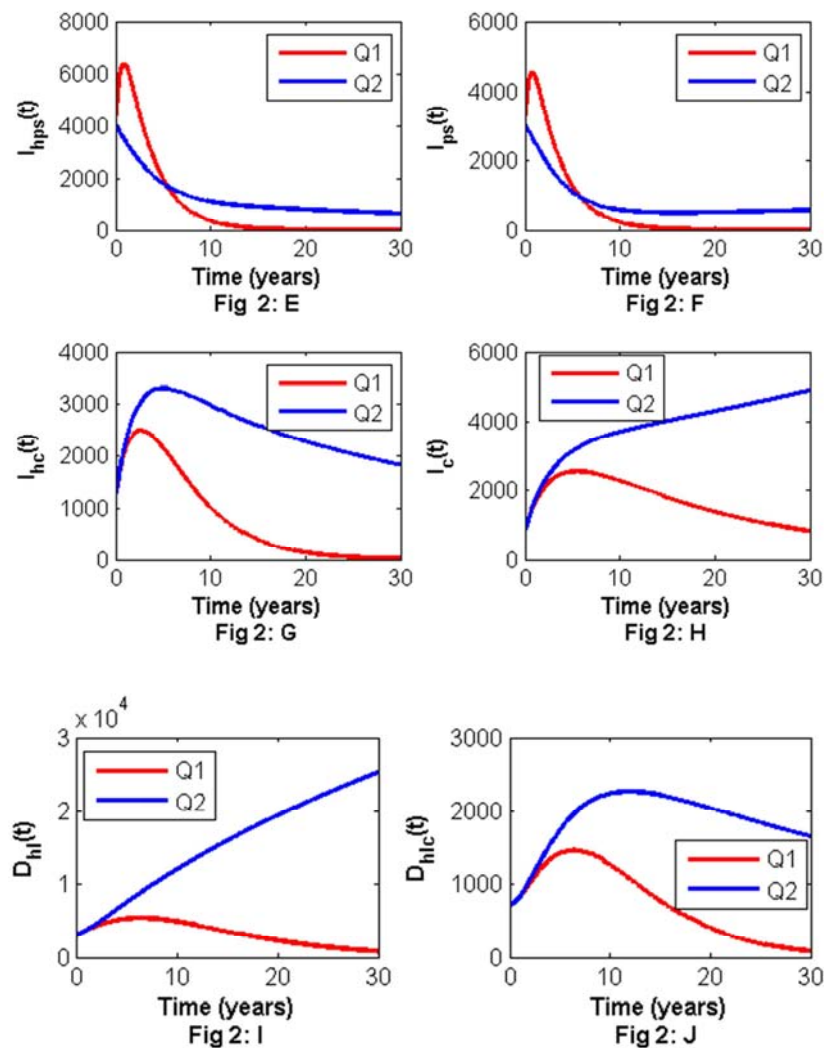


Figure 1. The use of prevention and treatment control strategies. Figure 1: A - J are time series plot of different population where $Q_1 = u_1 \neq 0, u_2 \neq 0, u_3 = 0$ with control and $Q_2 = (u_1 = 0, u_2 = 0, u_3 = 0)$ without control.

3.2. Strategy II: Combination of Prevention Control Strategy and Screening Strategy

The combination of prevention control strategy, u_1 , and screening control strategy, u_3 , are used to optimize objective

functional while setting treatment control strategy, u_2 , equal to zero. Results illustrate that the population of susceptible individuals increases (see Figure 2: A) while the population of infected individuals decreases (see Figure 2: B-J).



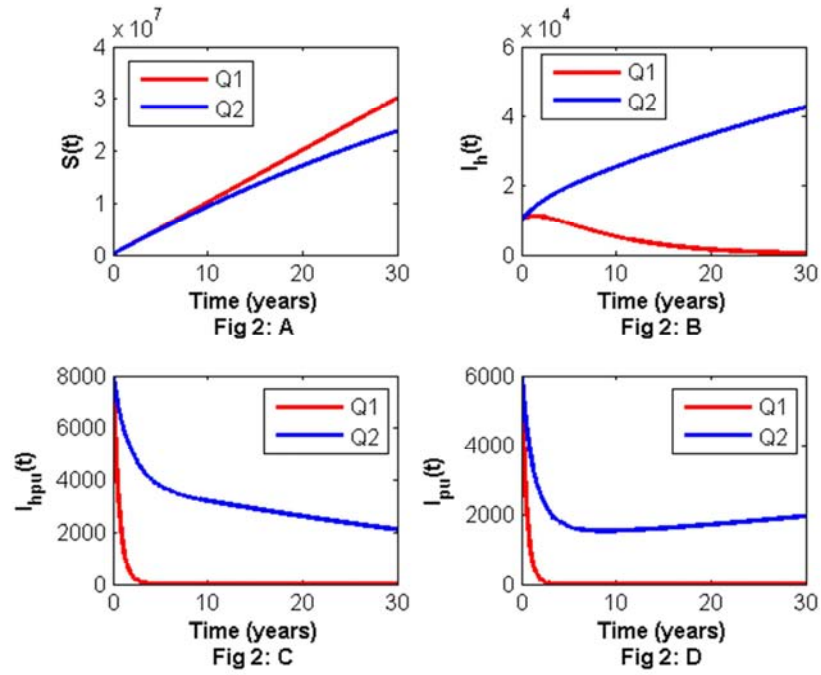
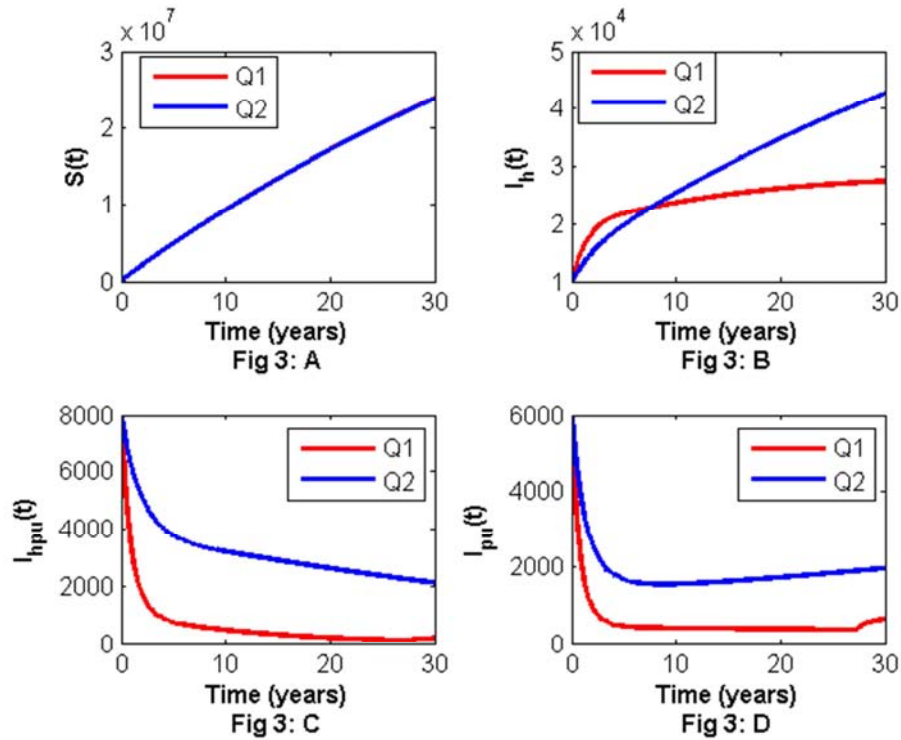


Figure 2. The use prevention and screening control strategies. Figure 2: A - J are time series plot of different population where $Q_1 = u_1 \neq 0, u_2 = 0, u_3 \neq 0$ with control and $Q_2 = (u_1 = 0, u_2 = 0, u_3 = 0)$ without control.

3.3. Strategy III: Combination of Screening and Treatment Control Strategies

The combination of treatment control u_2 and screening control u_3 are used to optimize objective functional while

setting vaccination control u_1 to zero. Results indicate that there is unremarkable increase of susceptible individuals and the population of infected individuals declines not much compared with other combination control strategies as illustrated in Figure 3: A and Figure 3: B - J respectively.



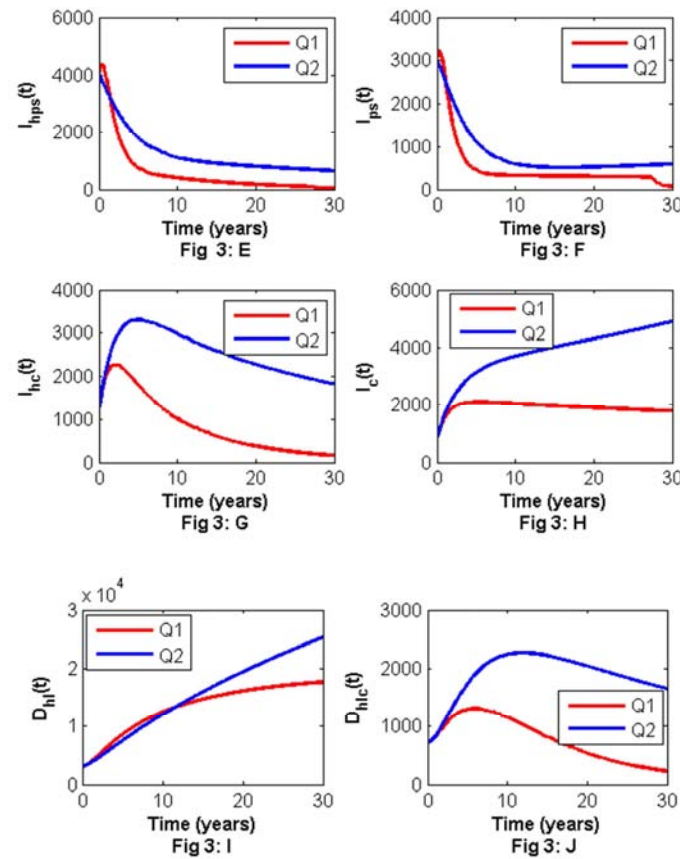
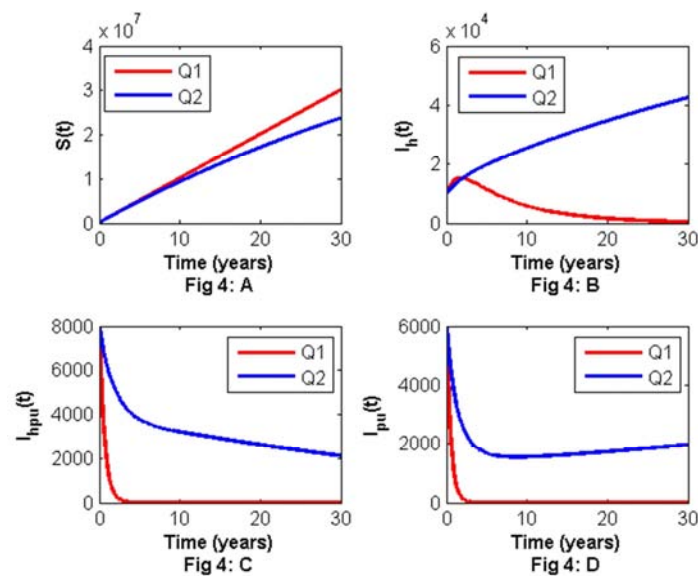


Figure 3. The use of screening and treatment control strategies. Figure 3: A - J are time series plot of different population where $Q_1 = u_1 = 0, u_2 \neq 0, u_3 \neq 0$ with control and $Q_2 = (u_1 = 0, u_2 = 0, u_3 = 0)$ without control.

3.4. Strategy IV: Combination of Prevention, Treatment and Screening Control Strategies

The combination of prevention control strategy, treatment control strategy u_2 , and screening control strategy u_3 are used to optimize objective functional. Results illustrates that

the population of susceptible individuals increases as shown in Figure 4: A while the population of infected individuals decrease compared with other combination of control strategies as shown in Figure 4: B - J.



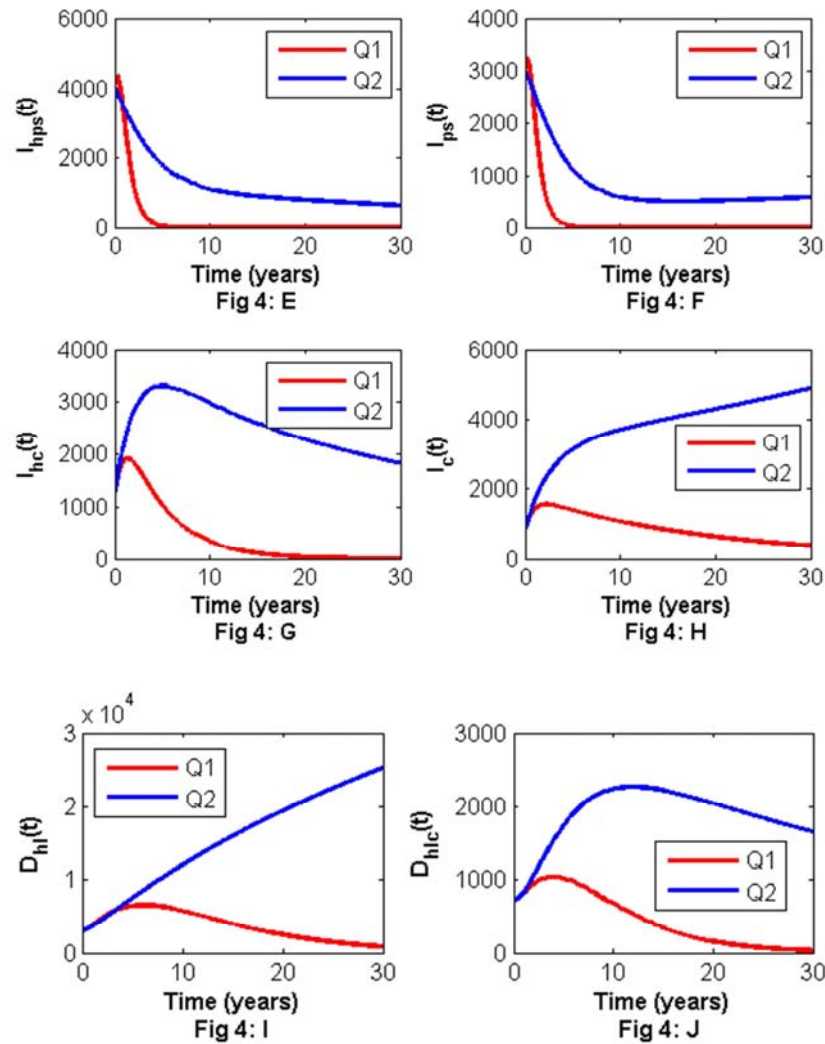


Figure 4. Showing impact of using all control strategies. Figure 4: A - J are time series plot of different population where $Q_1 = u_1 \neq 0, u_2 \neq 0, u_3 \neq 0$ with control and $Q_2 = (u_1 = 0, u_2 = 0, u_3 = 0)$ without control.

4. Cost-effectiveness Analysis

Here, Incremental Cost Effectiveness Ratio (ICER) is used to quantify the cost-effectiveness of different strategies. This approach is useful to understand which strategy saves a lot of averted species while spending low cost. This technique is needed to compare more than one competing interventions strategies incrementally, one intervention should be compared with the next less effective alternative [10]. The ICER formula is given by

$$\text{ICER} = \frac{\text{Difference in intervention cost}}{\text{Difference in the total number of infection averted}}$$

The total number of infection averted is obtained by calculating the difference between the total number of new cases of individuals having HPV infection without control and the total number of new cases of individuals having HPV infection with control.

Table 2. Calculation of ICER after arranging the number of total infections averted in ascending order.

Strategy	Total Cost (\$)	Total infections Averted	ICER
Strategy III	\$2,480.00	64,637.00	0.0384
Strategy II	\$2,770.20	75,510.00	0.0266
Strategy I	\$3,090.00	91,109.00	0.0205
Strategy IV	\$4,383.30	93,870.00	0.4684

$$\text{ICER}(\text{Strategy III}) = \frac{2,480.50}{64,637.00} = 0.0384,$$

$$\text{ICER}(\text{Strategy II}) = \frac{2,770.20 - 2,480.50}{75,510.00 - 64,637.00} = 0.0266,$$

$$\text{ICER}(\text{Strategy I}) = \frac{3,090.00 - 2,770.20}{91,109.00 - 75,510.00} = 0.0205 \text{ and}$$

$$\text{ICER}(\text{Strategy IV}) = \frac{4,383.30 - 3,090.00}{93,870.00 - 91,109.00} = 0.4684.$$

Comparing strategy III and strategy II, ICER of strategy II

is less than ICER of strategy III. Hence strategy III is more costly and less effective than strategy II. Thus, strategy III is omitted and ICER is recalculated.

Table 3. Computation of ICER after dropping strategy III.

Strategy	Total Cost(\$)	Total Infections Averted	ICER
Strategy II	\$2,770.20	75,510.00	0.0367
Strategy I	\$ 3,090.00	91,109.00	0.0205
Strategy IV	\$4,383.30	93,870.00	0.4684

Comparing strategy II and strategy I, ICER of strategy I is less than ICER of strategy II. Thus, strategy II is omitted and the ICER is recalculated.

Table 4. Computation of ICER after dropping strategy II.

Strategy	Total Cost(\$)	Total Infections Averted	ICER
Strategy I	\$ 3,090.00	91,109.00	0.0339
Strategy IV	\$4,383.30	93,870.00	0.4684

By comparing strategy I and strategy IV, ICER of strategy I is less than ICER of strategy IV. Therefore, strategy IV is dropped and strategy I is considered.

Thus, according to Incremental Cost Effectiveness Ratio analysis, the combination of optimal prevention and treatment control strategies is the best way of minimizing cervical cancer among women with or without HIV infection in our community following the combination of all control strategies.

5. Conclusion

This paper designed and analyzed a deterministic model for co-infection of cervical cancer and HIV diseases. The optimal control theory was employed to the main model and analyzed using Potrayagin's Maximum Principle. The different combination of three optimal control strategies; prevention, screening, and treatment were studied numerically. Also, cost-effectiveness analysis was performed and the following results were obtained

- The combination of optimal screening and treatment strategies is not much powerful way of controlling HPV infection and cervical cancer in the community compared with other combination of optimal control strategies as shown in Figure 3. Also, applying the combination of all control strategies (prevention, screening, and treatment) is the best way of minimizing co-infection of cervical cancer and HIV diseases in a community as shown in Figure 4.
- In the case of Incremental Cost Effectiveness Ratio analysis, the combination of optimal prevention and treatment strategies is the most cost-effective control to minimize cervical cancer among women with or without HIV infection. The second is the combination of all optimal control strategies; prevention, screening, and treatment. The third is the combination of optimal prevention and screening control strategies.

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