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ON MODELLING THE IN-HOST DYNAMICS OF HIV/HPV CO-INFECTION IN THE HUMAN POPULATION

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Abstract. Mathematical modelling of in-host dynamics has proven to be useful in the control of infectious diseases. An in-host model for the transmission dynamics of the human papillomavirus (HPV) among women living with the human immunodeficiency virus (HIV), incorporating HIV treatment and HPV vaccination is presented. The developed model considers latency and adaptive immune response through cytotoxic T-lymphocytes (CTLs) on the co-infection dynamics. The positivity and boundedness of solutions is proven and the disease-free equilibrium as well as the endemic equilibrium points are computed. The stability of equilibrium points is also proven. The model exhibits three significant reproduction numbers, that is, the basic reproduction number, \mathcal{R}_0 , the effective reproduction number, \mathcal{R}_c and the immune response reproduction number, \mathcal{R}_K . The conditions for stability based on the reproduction numbers are stated and numerical simulations performed. The simulations established that although the adaptive immune response is effective in the reduction of HPV, it is not adequate, especially among HIV-positive women. Therefore, HPV vaccination before the onset of sexual activity or among HIV-infected women in addition to proper adherence to HIV treatment is beneficial in reducing HPV in-host.

Keywords: human papillomavirus; immune response; cytotoxic T-Lymphocytes; vaccination.

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1. INTRODUCTION

The human papillomavirus, (HPV), is a small DNA virus that accounts for most cervical cancer cases. It is a sexually transmitted infection prevalent among sexually active adults. On average, it is estimated that about 75% of sexually active adults are infected with HPV at some point in their lifetime. However, not all HPV infections lead to cervical cancer or other related cancers, some of the infections are cleared naturally by the host immune system. The triggering of the immune system is not always spontaneous since the virus will try as much as possible to evade detection. The development of antibodies for a specific HPV type does not necessarily guarantee that there will be no re-infection with another HPV type and therefore the reduction of sexual partners and proper use of condoms is recommended.

Due to immunodeficiency, the human immunodeficiency virus (HIV) alters the natural history of HPV and therefore promoting a faster progression of high-grade lesions of cervical cancer. In relation to modelling the dynamics of HIV/HPV co-infection not much work has been presented in literature due to the complexity of the co-infection dynamics. HIV-positive women tend to be more susceptible to HPV infection due to immune suppression that is caused by HIV infection. Verma *et al.* [1] developed a within-host HIV/HPV co-infection model with immune response. Their work outlined the effect of HIV *tat* protein on the proliferation of HPV within the body. HIV *tat* protein promotes/enhances the production of HPV oncoproteins *E6, E7*, responsible for HPV cell proliferation [2, 3, 4, 1]. These proteins also promote the persistence of HPV and consequently the occurrence of cervical lesions in the long run. The model presented by Verma *et al.* [1] did not consider the contribution of latently infected HPV cells in the persistence of HPV infection among women living with HIV. We, therefore, add latency to the model and analyse the dynamics.

McClymont *et al.* [5] presented a clinical trial study that modelled the impact of vaccination on the dynamics of HPV among women and girls living with HIV [5]. In their study, eligible participants were given either a dose, two doses or three doses of the Gardasil vaccine. The results from the trial indicated that participants who already had high-risk HPV at enrolment had more breakthrough HPV infections as compared to those without HPV. In addition to this breakthrough, infections were found to be considerably lower among those who had been given

three doses of the vaccine as compared to those who had been given only a dose of the vaccine. Also, vaccine failure was found to be higher among HIV-positive participants as compared to HIV-negative participants. Other follow-up trials on the subject matter can be obtained from [6, 5, 7].

The other key issue that clinical trials have tried to address is the effect of adherence to HIV treatment. A clinical trial by Minkoff *et al.* [8] outlined that strict adherence to combined Antiretroviral Therapy (cART) may reduce the HPV burden among HIV-positive women and girls [8]. Verma *et al.* [1] proceeded to validate the results in their mechanistic model and showed that effective adherence to HIV treatment is advantageous in reducing the transmission of HPV within cells provided other prevention measures such as condom use and reduction of sexual partners are also implemented. See the following paper for analyses of mathematical models of co-infection [9, 10] and so on. The present work also explores the effect of adherence considering that the model incorporates latently infected cells and immune response. We envisage that the results produced by the current study will help answer the question of whether latent infections matter in reducing the persistence of HPV infection among HIV-positive women and girls. We also hope that the current study will lobby more for cheaper yet effective vaccination options to be offered early to women and girls, especially in areas where HIV is prevalent.

The rest of the paper is organised as follows; in Section 2, we present the model formulation followed by rigorous mathematical analysis in Sections 3 and 4. In Section 5 we propose and calculate the effective basic reproduction number for the model with treatment. Finally, the numerical simulations are presented in Section 6 and a conclusion discussing the results is presented in Section 7.

2. MODEL FORMULATION

The model presented is an extension of the work by [11, 1]. The new model incorporates; latently infected cells for both HIV and HPV dynamics, HPV vaccination against high-risk types HPV (16/18) and HIV treatment. The co-infection model is comprised of ten classes namely; HIV classes given by, healthy target cells, T_H , latently infected cells, L_H , actively infected cells, I_H and HIV-free virus, V_H . The HPV classes are given by, healthy epithelial cells, T_s , latently infected cells, L , actively infected cells that are not self-proliferating, I_1 , actively infected cells

that are self-proliferating, I_2 , the HPV virions, V , and the CTL cells, K . Recruitment rates for healthy target cells, T_H , and healthy epithelial cells, T_s are considered to be s , $\Lambda(1 + \eta V_H)$ respectively where η is the effect of HIV *tat* protein [1]. The model assumes that, $0 \leq \eta \leq 1$, where, the case $\eta = 0$ means *tat* protein has no effect on the dynamics and the case $\eta = 1$ indicates otherwise [1]. Due to HIV *tat* protein, there is a disruption of the epithelial tight junctions and therefore there is a faster proliferation of actively infected cells [1]. Transmission of HIV infection is considered to occur at a rate, κ . The model includes latency in the HIV class as outlined in the work by [12, 13, 14]. A fraction, ρ of the transmission can lead to latent HIV infections, while the $(1 - \rho)$ of the transmission leads to active HIV infections. Latent HPV cells are further assumed to mature into actively infected cells at a rate, ζ . The model assumes the burst size of actively infected HIV cells to be N_1 and the HIV-free virus decays at a rate, c , while the cells (T_H, L_H, I_H) are assumed to die at rate d_1, d_2, d_3 respectively. In modelling the dynamics of HPV within-host we adopt the within-host model by Chazuka *et al.* [11]. Transmission of HPV occurs at a contact rate, β and the force of infection is a saturated incidence function adopted from Verma *et al.* [1, 15], and given by

$$\frac{\beta V}{\gamma + T_s}.$$

Latently infected cells are assumed to mature into actively infected cells, I_1 at a rate, ψ . Due to oncogene expression at a rate, ε , I_1 cells can proliferate and become I_2 cells. The self-proliferation of I_2 cells occurs at a rate $r\varepsilon$, where r , represents the transit-amplifying rate as indicated by [1, 15]. By the unusual presence of these I_2 cells, the adaptive immune response (Cytotoxic T-cells (CTLs)) are triggered and this occurs at a rate, σ . The model assumes that only I_2 cells trigger immune responses due to unusual cell growth. Upon activation of the immune response, the CTLs will dock onto the infected cells I_1, I_2 and kill these infected cells at a rate, θ . CTLs are assumed to decay at a rate of, ν . The burst size of the HPV virions is given by N_2 and it decays at a rate, δ . Below is the schematic representation of the model and the model equations governed by differential equations.

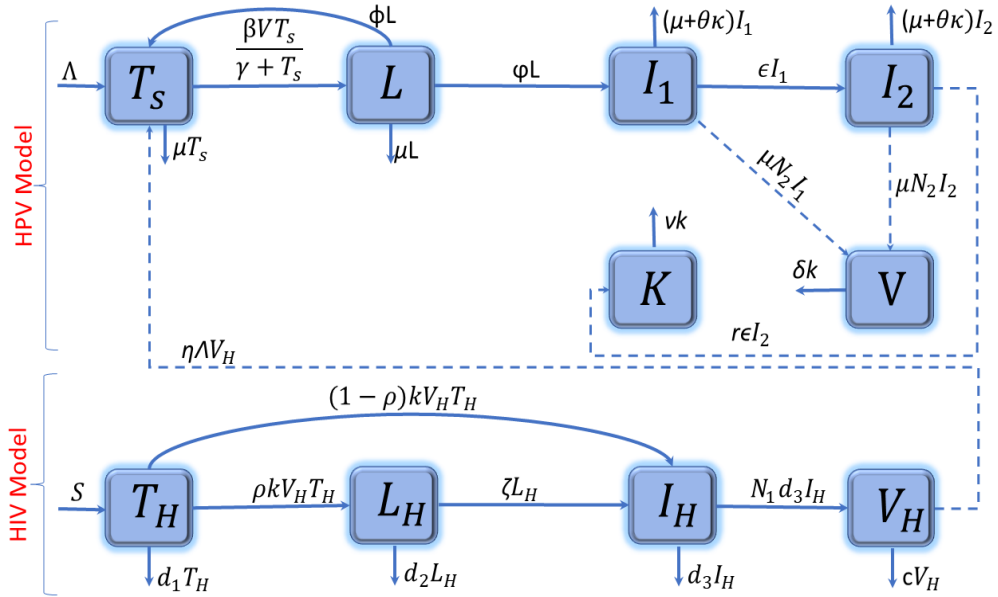


FIGURE 1. Flow diagram for within-host HIV/HPV co-infection in the presence of immune response.

$$(1) \quad \left\{ \begin{array}{l} \dot{T}_H = s - \kappa V_H T_H - d_1 T_H, \\ \dot{L}_H = \rho \kappa V_H T_H - d_2 L_H - \zeta L_H, \\ \dot{I}_H = (1 - \rho) \kappa V_H T_H + \zeta L_H - d_3 I_H, \\ \dot{V}_H = N_1 d_3 I_H - c V_H, \\ \dot{T}_s = \Lambda (1 + \eta V_H) + \phi L - \frac{\beta V T_s}{(\gamma + T_s)} - \mu T_s, \\ \dot{L} = \frac{\beta V T_s}{(\gamma + T_s)} - \mu L - \psi L - \phi L, \\ \dot{I}_1 = \psi L - \epsilon I_1 - \mu I_1 - \theta K I_1, \\ \dot{I}_2 = \epsilon I_1 + r \epsilon I_2 - \mu I_2 - \theta K I_2, \\ \dot{V} = N_2 \mu (I_1 + I_2) - \delta V, \\ \dot{K} = \sigma I_2 K - v K, \end{array} \right.$$

with initial conditions;

$$T_H(0) > 0, L_H(0) \geq 0, I_H(0) \geq 0, V_H(0) \geq 0, T_s(0) > 0, L(0) \geq 0, I_1(0) \geq 0, I_2(0) \geq 0, \\ V(0) \geq 0, K(0) \geq 0.$$

3. MODEL ANALYSIS

3.1. Positivity and boundedness of solutions.

This sub-section explores the existence of non-negative solutions for model (1).

Theorem 1. *For any initial conditions $T_{H0} > 0, L_{H0} \geq 0, I_{H0} \geq 0, V_{H0} \geq 0, T_{s0} > 0, L_0 \geq 0, I_{10} \geq 0, I_{20} \geq 0, V_0 \geq 0, K_0 \geq 0$, model system (1) has a unique solution and this solution is non-negative and bounded for all $t \geq 0$.*

Proof. Using the classical differential equations theory [16], it follows that there is a unique local solution to model system (1) in $[0, t)$. Therefore,

$$(2) \quad \left\{ \begin{array}{l} \dot{T}_H(t)|_{T_H=0} = s \geq 0, \\ \dot{L}_H(t)|_{L_H=0} = \rho \kappa V_H T_H \geq 0, \text{ for } V_H \geq 0, T_H > 0, \\ \dot{I}_H(t)|_{I_H=0} = (1 - \rho) \kappa V_H T_H + \zeta L_H \geq 0, \text{ for } V_H, L_h \geq 0 \text{ and } T_H > 0, \\ \dot{V}_H(t)|_{V_H=0} = N_1 d_3 I_H \geq 0, \text{ for } I_H \geq 0, \\ \dot{T}_s(t)|_{T_s=0} = \Lambda(\eta V_H + 1) + \phi L \geq 0, \text{ for } V_H, L \geq 0, \\ \dot{L}(t)|_{L=0} = \frac{\beta V T_s}{(\gamma + T_s)} \geq 0, \text{ for } V \geq 0 \text{ and } T_s > 0, \\ \dot{I}_1(t)|_{I_1=0} = \psi L \geq 0, \text{ for } L \geq 0, \\ \dot{I}_2(t)|_{I_2=0} = \varepsilon I_1 \geq 0, \text{ for } I_1 \geq 0, \\ \dot{V}(t)|_{V=0} = N_2 \mu (I_1 + I_2) \geq 0, \text{ for } I_1, I_2 \geq 0, \\ \dot{K}(t)|_{K=0} = 0 \geq 0, \end{array} \right.$$

hence this proves the positivity of all solutions of system (1) for all $t \geq 0$. To prove boundedness, for the HIV model we can already see that from the first equation of model system (1),

$$\dot{T}_H(t) \leq s - d_1 T_H.$$

Thus it follows that $\limsup_{t \rightarrow \infty} T_H(t) \leq \frac{s}{d_1}$. Hence, $T_H(t)$ is ultimately bounded. To show that the infected cells $L_H(t), I_H(t)$ are also bounded we state the following Lyapunov function

$$\mathcal{H}(t) = T_H + L_H + I_H$$

and hence

$$\dot{\mathcal{H}}(t) = \dot{T}_H + \dot{L}_H + \dot{I}_H$$

$$\begin{aligned}
&= s - (d_1 T_H + d_2 L_H + d_3 I_H) \\
(3) \quad &\leq s - m \mathcal{H}(t),
\end{aligned}$$

where $m = \min\{d_1, d_2, d_3\}$. Hence, $\limsup_{t \rightarrow \infty} \mathcal{H}(t) \leq \frac{s}{m}$. Thus, $\mathcal{H}(t)$ is ultimately bounded, implying that L_H and I_H which we now denote by B_1 and B_2 respectively are also bounded. Now to show the boundedness of $V_H(t)$ we have

$$\dot{V}_H(t) \leq N_1 d_3 B_1 - c V_H$$

and thus, $\limsup_{t \rightarrow \infty} V_H(t) \leq \frac{N_1 d_3 I_H B_1}{c}$. Therefore, $V_H(t)$ is also ultimately bounded. Now for the HPV model it is observed from the fifth equation of model system(1) that

$$\dot{T}_s(t) \leq \Lambda - \mu T_s$$

and therefore, $\limsup_{t \rightarrow \infty} T_s(t) \leq \frac{\Lambda}{\mu}$, hence, $T_s(t)$ is ultimately bounded. To establish the boundedness of classes, $L(t), I_1(t), I_2(t)$ and $K(t)$ we state the following Lyapunov function

$$(4) \quad \mathcal{D}(t) = T_s(t) + L(t) + I_1(t) + I_2(t) + \frac{\theta}{\sigma} K$$

and so,

$$\begin{aligned}
\dot{\mathcal{D}}(t) &= \dot{T}_s + \dot{L} + \dot{I}_1 + \dot{I}_2 + \frac{\theta}{\sigma} \dot{K}(t) \\
&= \Lambda + \eta \Lambda V_H + r \epsilon I_2 - \mu(T_s + L + I_1 + I_2) - \theta K I_1 - \frac{\theta \nu}{\sigma} K \\
&\leq \Lambda - \mu(T_s + L + I_1 + I_2) - \frac{\theta \nu}{\sigma} K \\
&\leq \Lambda - p \mathcal{D}(t),
\end{aligned}$$

where $p = \min\{\mu, \nu\}$. Thus, $\limsup_{t \rightarrow \infty} \mathcal{D}(t) \leq \frac{\Lambda}{p}$, such that $\mathcal{D}(t)$ is ultimately bounded. This implies that classes, $L(t), I_1(t), I_2(t)$ and $K(t)$ now denoted as B_3, B_4, B_5 and B_6 respectively are also bounded. Now, to show the boundedness of $V(t)$ we have

$$\dot{V}(t) \leq N_2 \mu (B_4 + B_5) - \delta V$$

and thus, $\limsup_{t \rightarrow \infty} \dot{V}(t) \leq \frac{N_2 \mu (B_4 + B_5)}{\delta}$. Hence it also follows that $V(t)$ is ultimately bounded. This proves that all the solutions $T_H(t), L_H(t), I_H(t), V_H(t), T_s(t), L(t), I_1(t), I_2(t)$ and $K(t)$ are all bounded. Therefore every local solution can be prolonged up to any time $t_a > 0$, meaning that the solution exists globally. This completes the proof. \square

4. EQUILIBRIUM POINTS AND THE CO-INFECTION REPRODUCTION NUMBER

4.1. The infection-free equilibrium. The model exhibits three equilibrium points of interest, that is; the infection-free equilibrium, (E_0) ; the first endemic equilibrium point also known as the CTL-free equilibrium, (E_1) and the second endemic equilibrium point also known as the CTL-active equilibrium, (E_2) . The model considers that HIV-positive women and girls develop HPV hence we use the initial concentrations of the HIV equilibrium denoted by, $\bar{E}_H = [\bar{T}_H, \bar{L}_H, \bar{I}_H, \bar{V}_H]$, (refer to [1, 7]). This leads to the simplification of model (1) to;

$$(5) \quad \begin{cases} \dot{T}_s = \Lambda(\eta V_H + 1) + \phi L - \frac{\beta V T_s}{(\gamma + T_s)} - \mu T_s, \\ \dot{L} = \frac{\beta V T_s}{(\gamma + T_s)} - \mu L - \psi L - \phi L, \\ \dot{I}_1 = \psi L - \varepsilon I_1 - \mu I_1 - \theta K I_1, \quad \dot{I}_2 = \varepsilon I_1 + r \varepsilon I_2 - \mu I_2 - \theta K I_2, \\ \dot{V} = N_2 \mu (I_1 + I_2) - \delta V, \\ \dot{K} = \sigma I_2 K - \nu K, \end{cases}$$

and therefore E_0 , is given by

$$(6) \quad E_0 = \left(\frac{\Lambda[1 + \eta \bar{V}_H]}{\mu}, 0, 0, 0, 0, 0 \right).$$

4.2. Computation of the basic reproduction number. The model basic reproduction number, \mathcal{R}_0 , for system (5) is found using the next-generation approach by [17] as follows:

$$\mathcal{F} = \begin{bmatrix} 0 & 0 & 0 & \frac{\beta \Lambda (\eta \bar{V}_H + 1)}{(\gamma \mu + \Lambda (\eta \bar{V}_H + 1))} \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{bmatrix}, \mathcal{V} = \begin{bmatrix} (\psi + \phi + \mu) & 0 & 0 & 0 \\ -\psi & (\varepsilon + \mu) & 0 & 0 \\ 0 & -\varepsilon & (\mu - r\varepsilon) & 0 \\ 0 & -N_2 \mu & -N_2 \mu & \delta \end{bmatrix}$$

and the inverse of \mathcal{V} is given by

$$\mathcal{V}^{-1} = \begin{bmatrix} \frac{1}{(\psi + \phi + \mu)} & 0 & 0 & 0 \\ \frac{\psi}{(\varepsilon + \mu)(\mu + \psi + \phi)} & \frac{1}{(\varepsilon + \mu)} & 0 & 0 \\ p_1 & \frac{\varepsilon}{(\mu - r\varepsilon)(\varepsilon + \mu)} & \frac{1}{\mu - r\varepsilon} & 0 \\ p_2 & p_3 & \frac{N_2\mu}{\delta(\mu - r\varepsilon)} & \frac{1}{\delta} \end{bmatrix}$$

where $p_1 = \frac{\varepsilon\mu}{(\varepsilon + \mu)(\mu - r\varepsilon)(\mu + \psi + \phi)}$, $p_2 = \frac{N_2\mu\psi(\mu + \varepsilon - r\varepsilon)}{\delta(\mu - r\varepsilon)(\varepsilon + \mu)(\mu + \psi + \phi)}$ and $p_3 = \frac{N_2\mu(\mu + \varepsilon - r\varepsilon)}{\delta(\mu - r\varepsilon)(\varepsilon + \mu)}$. Therefore,

$$\mathcal{F}\mathcal{V}^{-1} = \begin{bmatrix} \frac{\beta\Lambda(\eta\bar{V}_H + 1)p_2}{w_1} & \frac{\beta\Lambda(\eta\bar{V}_H + 1)p_3}{w_1} & \frac{N_2\mu\beta\Lambda(\eta\bar{V}_H + 1)}{\delta(\mu - r\varepsilon)w_1} & \frac{\beta\Lambda(\eta\bar{V}_H + 1)}{\delta w_1} \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{bmatrix}$$

with $w_1 = (\gamma\mu + \Lambda(\eta\bar{V}_H + 1))$. Hence,

$$(7) \quad \mathcal{R}_0 = \rho \mathcal{F}\mathcal{V}^{-1} = \frac{\beta N_2 \mu \psi \Lambda (\eta \bar{V}_H + 1) (\mu + \varepsilon - r\varepsilon)}{\delta (\mu - r\varepsilon) (\mu + \varepsilon) (\mu + \psi + \phi) [\Lambda (\eta \bar{V}_H + 1) + \gamma \mu]}.$$

Expression (7) is positive since $\mu > r\varepsilon$ as indicated in [11] and the effects of *tat* protein are assumed to vary from person to person, therefore, affecting the dynamics of HPV in-host as indicated by [1].

4.3. The endemic equilibrium. The first and second endemic equilibrium points for the model are given as follows; the first endemic equilibrium point (CTL-free equilibrium);

$$(8) \quad T_s^e = \frac{\Lambda}{\mu} - \frac{\Lambda(1 + \eta\bar{V}_H)(\mathcal{R}_0 - 1)[\gamma\mu + \Lambda(\eta\bar{V}_H + 1)]}{\mu\mathcal{A}_1}, L^e = \frac{\Lambda(1 + \eta\bar{V}_H)(\mathcal{R}_0 - 1)(\gamma\mu + \Lambda(1 + \eta\bar{V}_H))}{(\mu + \psi)\mathcal{A}_1},$$

$$I_1^e = \frac{\Lambda(1 + \eta\bar{V}_H)\psi(\mathcal{R}_0 - 1)[\gamma\mu + \Lambda(1 + \eta\bar{V}_H)]}{(\mu + \psi)(\varepsilon + \mu)\mathcal{A}_1}, I_2^e = \frac{\Lambda(1 + \eta\bar{V}_H)\psi\varepsilon(\mathcal{R}_0 - 1)[\gamma\mu + \Lambda(1 + \eta\bar{V}_H)]}{(\mu + \psi)(\mu - r\varepsilon)(\varepsilon + \mu)\mathcal{A}_1},$$

$$V^e = \frac{N_2\mu\psi\Lambda(1 + \eta\bar{V}_H)(\mu + \varepsilon - r\varepsilon)[\Lambda(1 + \eta\bar{V}_H) + \gamma\mu][1 - \mathcal{R}_0]}{\delta(\mu - r\varepsilon)(\mu + \varepsilon)(\mu + \psi)\mathcal{A}_1}, \quad K^e = 0,$$

where $\mathcal{A}_1 = [\mathcal{R}_0\gamma\mu + \Lambda(1 + \eta\bar{V}_h)(\mathcal{R}_0 - 1)]$,

and the second endemic equilibrium point, E_2 , (CTL-active) is given by;

$$T_s^* = \frac{\Lambda\sigma\varepsilon\psi - v\Psi_0(\Psi_1 + \theta K^*)(\Psi_2 + \theta K^*)}{\sigma\varepsilon\psi\mu}, \quad L^* = \frac{v(\Psi_1 + \theta K^*)(\Psi_2 + \theta K^*)}{\sigma\varepsilon\psi},$$

$$(9) \quad I_1^* = \frac{v(\Psi_2 + \theta K^*)}{\sigma\varepsilon}, \quad I_2^* = \frac{v}{\sigma}, \quad V^* = \frac{N_2v\mu(\Psi_4 + \theta K^*)}{\delta\sigma\varepsilon}, \quad K = K^*.$$

Now K^* is found by solving the quartic polynomial given by

$$(10) \quad f(K) = a_0K^4 + a_1K^3 + a_2K^2 + a_3K + a_4,$$

with

$$a_0 = \theta^4\delta\Psi_0\Psi_3v^2 > 0,$$

$$a_1 = \theta^3 [2\delta v^2\Psi_0\Psi_3(\Psi_1 + \Psi_2) - \delta\Psi_0\beta N_2\mu v^2],$$

$$a_2 = \theta^2 \left[\delta\Psi_0v^2\Psi_3(\Psi_1^2 + 4\Psi_1\Psi_2 + \Psi_2^2) - \beta\mu v^2 N_2\Psi_0(\Psi_1 + \Psi_2 + \Psi_4), \right. \\ \left. - v\psi\Psi_3(\delta\varepsilon\sigma\Lambda + \gamma\mu) \right],$$

$$a_3 = \theta \left[(\Psi_1 + \Psi_2) (2\Psi_0\delta v^2\Psi_3\Psi_1\Psi_2 - \delta\varepsilon\Lambda v\sigma\psi\Psi_3 - \beta\mu v^2 N_2\Psi_0\Psi_4) \right]$$

$$\begin{aligned}
& + \left. \beta\mu v N_2 (\Lambda\sigma\psi\varepsilon - v\Psi_0\Psi_1\Psi_2) \right] - \gamma\mu v\psi\Psi_3(\Psi_1 + \Psi_2), \\
a_4 & = \left[\delta v\Psi_1\Psi_2\Psi_3(\Lambda\varepsilon\sigma\psi + v\Psi_0\Psi_1\Psi_2) + \Psi_4\beta\mu v N_2 (\Lambda\varepsilon\sigma\psi - v\Psi_0\phi_1\Psi_2) \right] \\
& - \gamma\mu v\psi\Psi_1\Psi_2, \Psi_3
\end{aligned}$$

in which $\Psi_0 = (\mu + \psi)$, $\Psi_1 = (\varepsilon + \mu)$, $\Psi_2 = (\mu - r\varepsilon)$, $\Psi_3 = (\mu + \psi + \phi)$, $\Psi_4 = (\mu + \varepsilon - r\varepsilon)$ and $\Psi_5 = (1 + \eta V_H)$.

To establish the nature of the roots for polynomial (10) we use Descartes' rule of signs due to its intractability, hence, we state the following Lemma;

Lemma 1. *The fourth-order polynomial function*

$$f(K) = a_0K^4 + a_1K^3 + a_2K^2 + a_3K + a_4$$

is subject to the following conditions;

(1) *The polynomial has only one unique positive root provided that either*

$a_0 > 0, a_1 < 0, a_2 < 0, a_3 < 0$ and $a_4 < 0$, or $a_0 > 0, a_1 > 0, a_2 < 0, a_3 < 0$ and $a_4 < 0$, or $a_0 > 0, a_1 > 0, a_2 > 0, a_3 < 0$ and $a_4 < 0$, or $a_0 > 0, a_1 > 0, a_2 > 0, a_3 > 0$ and $a_4 < 0$,

(2) *The polynomial has no positive roots provided that $a_0 > 0, a_1 > 0, a_2 > 0, a_3 > 0$ and $a_4 > 0$,*

(3) *The polynomial has more than one positive root otherwise.*

4.4. The immune reproduction number, for the co-infection model. We define the immune response reproduction number, \mathcal{R}_K , as the average number of immune response cells that each actively infected cell, I_2 , can activate and therefore, \mathcal{R}_K , is expressed in terms of, I_2^e as follows;

$$(11) \quad \mathcal{R}_K = \frac{\sigma I_2^e}{v} = \frac{\sigma\Lambda(1 + \eta\bar{V}_H)\psi\varepsilon(\mathcal{R}_0 - 1)[\gamma\mu + \Lambda(1 + \eta\bar{V}_H)]}{v(\mu + \psi)(\mu - r\varepsilon)(\varepsilon + \mu)\mathcal{A}_1},$$

where, $\frac{1}{v}$, is the average life of an immune response cell and I_2^e is the number of infected cells at E_1 . Therefore, for the CTL-free equilibrium to be stable the following conditions should hold;

(1) E_1 , is globally asymptotically stable provided that $\mathcal{R}_0 > 1$ and $\mathcal{R}_K \leq 1$,

(2) E_1 , is unstable when $\mathcal{R}_0 > 1$ and $\mathcal{R}_K \geq 1$, while E_2 is globally asymptotically stable.

5. LOCAL STABILITY OF E_0

To prove the stability of the infection-free equilibrium, (E_0) we state following theorem;

Theorem 2. *The infection-free equilibrium for the co-infection model system (5) is locally asymptotically stable provided that $\mathcal{R}_0 < 1$ and unstable otherwise.*

Proof. The Jacobian matrix for model (5) evaluated at the E_0 is given by;

$$J(E_0) = \begin{bmatrix} -\mu & \phi & 0 & 0 & -q_1 & 0 \\ 0 & -q_2 & 0 & 0 & q_1 & 0 \\ 0 & \psi & -q_3 & 0 & 0 & 0 \\ 0 & 0 & \varepsilon & -q_4 & 0 & 0 \\ 0 & 0 & N_2\mu & N_2\mu & -\delta & 0 \\ 0 & 0 & 0 & 0 & 0 & -v \end{bmatrix},$$

where $q_1 = -\frac{\Lambda(1+\eta\bar{V}_H)\beta}{\gamma\mu + \Lambda(1+\eta\bar{V}_H)}$, $q_2 = (\mu + \psi + \phi)$, $q_3 = (\varepsilon + \mu)$, $q_4 = (\mu - r\varepsilon)$.

Finding the determinant yields;

$$\begin{aligned} Det (J(E_0)) &= -v [N_2\mu^2\psi q_1(\mu - r\varepsilon) + N_2\mu^2\psi q_1\varepsilon - \delta\mu(\mu + \psi + \phi)(\varepsilon + \mu)(\mu - r\varepsilon)], \\ (12) \quad &= \delta\mu(\mu + \psi + \phi)(\varepsilon + \mu)(\mu - r\varepsilon) [1 - \mathcal{R}_0]. \end{aligned}$$

If $\mathcal{R}_0 < 1$ then $Det (J(E_0)) > 0$ and $\text{trace } J(E_0) = -4\mu - \phi - \psi - \varepsilon(1 - r) - \delta - v < 0$, since all parameters are positive and $(\mu - r\varepsilon) > 0$. Hence it follows that the infection-free equilibrium is locally asymptotically stable when $\mathcal{R}_0 < 1$. This completes the proof. \square

5.1. Global stability analysis of E_0 . To prove that the infection-free equilibrium is globally asymptotically stable we state and prove the following theorem;

Theorem 3. *The infection-free equilibrium for model (5) is globally asymptotically stable provided that $\mathcal{R}_0 < 1$.*

Proof. Let $\mathcal{X} = T_s \in \mathbb{R}$ be the susceptible healthy epithelial cells and the infected population be represented by $\mathcal{Z} = (L, I_1, I_2, V)$. Hence We rewrite model system (5) as;

$$(13) \quad \begin{aligned} \frac{d\mathcal{X}}{dt} &= F(\mathcal{X}, \mathcal{Z}), \\ \frac{d\mathcal{Z}}{dt} &= G(\mathcal{X}, \mathcal{Z}), \quad G(\mathcal{X}, 0) = 0, \end{aligned}$$

where

$$\begin{aligned} F(\mathcal{X}, \mathcal{Z}) &= \Lambda(1 + \eta\bar{V}_H) + \phi L - \left[\frac{\beta V}{(\gamma + T_s)} + \mu \right] T_s, \\ G(\mathcal{X}, \mathcal{Z}) &= \begin{bmatrix} \frac{\beta V T_s}{(\gamma + T_s)} - (\mu + \psi + \phi)L, \\ \psi L - (\varepsilon + \mu + \theta K)I_1, \\ \varepsilon I_1 + r\varepsilon I_2 - (\mu + \theta K)I_2, \\ N_2\mu(I_1 + I_2) - \delta V \end{bmatrix}. \end{aligned}$$

Let the infection-free equilibrium point for the system be given by $\mathcal{Q}_0 = (\mathcal{X}^*, 0)$ where

$$\mathcal{X}^* = \left[\frac{\Lambda(\eta\bar{V}_H + 1)}{\mu}, 0, 0, 0, 0, 0 \right].$$

Therefore,

$$(14) \quad \left. \frac{d\mathcal{X}}{dt} \right|_{\mathcal{Z}=0} = \Lambda(1 + \eta\bar{V}_H) - \mu \mathcal{X},$$

Solving differential equation (14) yields

$$T_s(t) = \frac{\Lambda(1 + \eta\bar{V}_H)}{\mu} + \left(T_s(0) - \frac{\Lambda(1 + \eta\bar{V}_H)}{\mu} \right) \exp^{-\mu t}.$$

and it is clear that as $t \rightarrow \infty$, $T_s \rightarrow \mathcal{X}^*$. Now to guarantee global stability of model system (5), the following three conditions should hold

- (1) For $\frac{d\mathcal{X}}{dt} = F(\mathcal{X}, 0)$, \mathcal{X}^* is globally asymptotically stable,
- (2) $G(\mathcal{X}, \mathcal{Z}) = \mathcal{A}\mathcal{Z} - \hat{G}(\mathcal{X}, \mathcal{Z})$, $\hat{G}(\mathcal{X}, \mathcal{Z}) \geq 0$ for $(\mathcal{X}, \mathcal{Z}) \in \Omega$,

- (3) $\mathcal{A} = D_{\mathcal{X}}G(\mathcal{X}^*, 0)$ is an M-matrix whose off diagonal elements are non-negative and Ω is the region where the model is biologically feasible.

By linearizing $G(\mathcal{X}, \mathcal{Z})$ we obtain the following matrix

$$\mathcal{A} = \begin{bmatrix} -(\mu + \phi + \psi) & 0 & 0 & \frac{\beta\Lambda(1 + \eta\bar{V}_H)}{\gamma\mu + \Lambda(1 + \eta\bar{V}_H)} \\ \psi & -(\varepsilon + \mu) & 0 & 0 \\ 0 & \varepsilon & -(\mu - r\varepsilon) & 0 \\ 0 & N_2\mu & N_2\mu & -\delta \end{bmatrix}$$

and

$$\mathcal{A}\mathcal{Z} = \begin{bmatrix} \frac{\beta V\Lambda(1 + \eta\bar{V}_H)}{\gamma\mu + \Lambda(1 + \eta\bar{V}_H)} - (\mu + \psi + \phi)L, \\ \psi L - (\varepsilon + \mu)I_1, \\ \varepsilon I_1 - (\mu - r\varepsilon)I_2, \\ N_2\mu(I_1 + I_2) - \delta V \\ \sigma I_2 K - \nu K \end{bmatrix}$$

and so

$$\hat{G}(\mathcal{X}, \mathcal{Z}) = \mathcal{A}\mathcal{Z} - G(\mathcal{X}, \mathcal{Z}) = \begin{bmatrix} \frac{\beta V\gamma(T_{s0} - T_s)}{(\gamma + T_{s0})(\gamma + T_s)}, \\ \theta K I_1, \\ \theta K I_2, \\ 0 \end{bmatrix}.$$

Provided that $I_1 \geq 0, I_2 \geq 0, K \geq 0$ and $T_{s0} \geq T_s$, hence it follows that $\hat{G}(\mathcal{X}, \mathcal{Z}) \geq 0$. Hence, the infection-free equilibrium is globally asymptotically stable whenever $\mathcal{R}_0 < 1$. This concludes the proof. \square

5.2. Local stability of E_1 . To prove the local stability of the first endemic equilibrium point, E_1 , we use the bifurcation theory by Castillo Chavez and Song [18]. Therefore we state and prove the following theorem;

Theorem 4. *Model system (5) has an asymptotically stable CTL-inactivated endemic equilibrium point, E_1 , whenever $\mathcal{R}_0 > 1$ and is unstable otherwise.*

Proof. To investigate the existence of a forward bifurcation, we rewrite model system (5) as

$$(15) \quad \begin{cases} \dot{x}_1 = f_1 = \Lambda(1 + \eta\bar{V}_H) + \phi x_2 - \left[\frac{\beta x_5}{(\gamma + x_1)} + \mu \right] x_1, \\ \dot{x}_2 = f_2 = \frac{\beta x_5 x_1}{(\gamma + x_1)} - (\mu + \psi + \phi)x_2, \\ \dot{x}_3 = f_3 = \psi x_2 - (\varepsilon + \mu + \theta x_6)x_3, \\ \dot{x}_4 = f_4 = \varepsilon x_3 + r\varepsilon x_4 - (\mu + \theta x_6)x_4, \\ \dot{x}_5 = f_5 = N_2\mu(x_3 + x_4) - \delta x_5, \\ \dot{x}_6 = f_6 = \sigma x_4 x_6 - \nu x_6, \end{cases}$$

where $T_s = x_1$, $L = x_2$, $I_1 = x_3$, $I_2 = x_4$, $V = x_5$, $K = x_6$. We consider the case where the bifurcation parameter of interest is the transmission rate $\beta = \beta^*$ and by solving for β^* given that $\mathcal{R}_0 = 1$ yields

$$(16) \quad \beta = \beta^* = \frac{\delta(\mu - r\varepsilon)(\mu + \varepsilon)(\mu + \psi + \phi) [\gamma\mu + \Lambda(1 + \eta\bar{V}_H)]}{N_2\mu\psi\Lambda(1 + \eta\bar{V}_H)(\mu + \varepsilon - r\varepsilon)}.$$

The Jacobian for system (5) evaluated at the infection-free equilibrium is given

$$J(E_{\mathcal{R}_0=1}) = \begin{bmatrix} -\mu & \phi & 0 & 0 & -q_0 & 0 \\ 0 & -q_1 & 0 & 0 & q_0 & 0 \\ 0 & \psi & -q_2 & 0 & 0 & 0 \\ 0 & 0 & \varepsilon & -q_3 & 0 & 0 \\ 0 & 0 & N_2\mu & N_2\mu & -\delta & 0 \\ 0 & 0 & 0 & 0 & 0 & -\nu \end{bmatrix},$$

where $q_0 = -\frac{\beta^*\Lambda(1 + \eta\bar{V}_H)}{\gamma\mu + \Lambda(1 + \eta\bar{V}_H)}$, $q_1 = (\mu + \psi + \phi)$, $q_2 = (\varepsilon + \mu)$, $q_3 = (\mu - r\varepsilon)$ and β^* is the bifurcation parameter. Based on the local stability theorem when $\mathcal{R}_0 = 1$, the Jacobian, $J(E_{\mathcal{R}_0=1})$ has a zero eigenvalue and all other eigenvalues have negative real parts provided the conditions stated are met, so the Center Manifold theory can be applied. The right eigenvalues for $J(E_{\mathcal{R}_0=1})$ are given by $\mathbf{w} = (\omega_1, \omega_2, \omega_3, \omega_4, \omega_5, \omega_6)$, where

$$(17) \quad \omega_1 = -\frac{1}{(\mu + \psi)}, \quad \omega_2 = \frac{1}{\psi}, \quad \omega_3 = \frac{1}{(\mu - r\varepsilon)}, \quad \omega_4 = \frac{1}{\varepsilon}, \quad \omega_5 = \frac{(\mu + \psi + \phi)(x_1^* + \gamma)}{\psi\beta^*x_1^*}, \quad \omega_6 = 0,$$

and $x_1^* = \frac{\Lambda(1 + \eta\bar{V}_h)}{\mu}$. The left eigenvalues for $J(E_{\mathcal{R}_0=1})$ are given by $\mathbf{u} = (u_1, u_2, u_3, u_4, u_5, u_6)$ where

$$(18) \quad u_1 = 0, \quad u_2 = \frac{\psi}{(\mu + \varepsilon - r\varepsilon)(\mu + \psi + \phi)}, \quad u_3 = \frac{1}{(\mu + \varepsilon - r\varepsilon)}, \quad u_4 = \frac{1}{(\varepsilon + \mu)},$$

$$u_5 = \frac{\beta^* \psi x_1^*}{\delta(\gamma + x_1^*)(\mu + \psi + \phi)(\mu + \varepsilon - r\varepsilon)}, \quad u_6 = 0.$$

Therefore, the non-zero partial derivatives for f_i for $i = 1, 2, \dots, 6$ are given by

$$(19) \quad \frac{\partial^2 f_2}{\partial x_1 x_5} = \frac{\partial^2 f_2}{\partial x_5 x_1} = \frac{\beta^* \gamma}{(\gamma + x_1^*)^2}, \quad \frac{\partial^2 f_2}{\partial x_5 \beta^*} = \frac{\partial^2 f_2}{\partial \beta^* x_5} = \frac{x_1^*}{\gamma + x_1^*}$$

Computing the bifurcation coefficients a and b yield

$$(20) \quad a = -\frac{N_2 \mu \psi}{\delta(\mu + \varepsilon)(\mu - r\varepsilon)(\mu + \psi + \phi)(\mu + \psi)} < 0$$

$$b = \frac{N_2 \mu \psi \Lambda(\eta\bar{V}_H + 1)}{\delta(\mu - r\varepsilon)(\mu + \varepsilon)(\mu + \phi + \psi) [\gamma\mu + \Lambda(1 + \eta\bar{V}_h)]} > 0.$$

We state the following theorem;

Theorem 5. *Provided that $a < 0$ and $b > 0$, the model system (5) will undergo a transcritical forward bifurcation at $\mathcal{R}_0 = 1$.*

From Theorem (5) we establish that there is a change in stability when $\mathcal{R}_0 < 1$ but close to unity. The implication of this is that when $\mathcal{R}_0 \leq 1$ we have the only extremum that exists being the infection-free equilibrium and this equilibrium is globally stable. On the other hand when $\mathcal{R}_0 \geq 1$ but close to unity we have the endemic equilibrium being the only extremum that is locally stable. Therefore in this case reducing the reproduction below unity guarantees that HPV within an HIV-infected population can be controlled. This concludes the proof. \square

5.3. Global stability of E_1 . To prove the global stability of the CTL-inactive endemic equilibrium for the co-infection model, we state and prove the following theorem;

Theorem 6. *The CTL-inactive endemic equilibrium point, E_1 , is globally asymptotically stable provided that $\mathcal{R}_0 > 1$, $\mathcal{R}_K \leq 1$ and unstable otherwise.*

Proof. To prove the global asymptotic stability of the endemic equilibrium, E_1 , we define a Lyapunov function of the form

$$(21) \quad \begin{aligned} \mathcal{W} &= T_s - T_s^e - T_s^e \ln \frac{T_s}{T_s^e} + L - L^e - L^e \ln \frac{L}{L^e} + I_1 - I_1^e - I_1^e \ln \frac{I_1}{I_1^e} + I_2 - I_2^e - I_2^e \ln \frac{I_2}{I_2^e} \\ &+ V - V^e - V^e \ln \frac{V}{V^e} + \frac{\theta}{\sigma} K. \end{aligned}$$

Differentiating \mathcal{W} yields

$$(22) \quad \mathcal{W}' = T_s'(1 - \frac{T_s^e}{T_s}) + L'(1 - \frac{L^e}{L}) + I_1'(1 - \frac{I_1^e}{I_1}) + I_2'(1 - \frac{I_2^e}{I_2}) + V'(1 - \frac{V^e}{V}) + \frac{\theta}{\sigma} K'.$$

and by substitution of $T_s', L', I_1', I_2', V', K'$ we obtain

$$\begin{aligned} \mathcal{W}' &= \left[\Lambda(\eta V_H + 1) + \phi L - \left(\frac{\beta V}{\gamma + T_s} + \mu \right) T_s \right] \left(1 - \frac{T_s^e}{T_s} \right) + \left[\frac{\beta V T_s}{\gamma + T_s} - (\mu + \psi + \phi) L \right] \\ &\times \left(1 - \frac{L^e}{L} \right) + [\psi L - (\varepsilon + \mu + \theta K) I_1] \left(1 - \frac{I_1^e}{I_1} \right) + [\varepsilon I_1 + r \varepsilon I_2 - (\mu + \theta K) I_2] \left(1 - \frac{I_2^e}{I_2} \right) \\ &+ [N_2 \mu (I_1 + I_2) - \delta V] \left(1 - \frac{V^e}{V} \right) + \frac{\theta}{\sigma} [\sigma I_2 K - v K]. \\ &= \Lambda(\eta V_H + 1) + \phi L - \mu T_s - \frac{\Lambda(\eta V_H + 1) T_s^e}{T_s} - \frac{\phi L T_s^e}{T_s} + \frac{\beta V T_s^e}{\gamma + T_s} + \mu T_s^e - (\mu + \psi + \phi) L \\ &- \frac{\beta V T_s^e L^e}{(\gamma + T_s) L} + (\mu + \psi + \phi) L^e + \psi L - (\varepsilon + \mu + \theta K) - \frac{\psi L I_1^e}{I_1} + (\varepsilon + \mu + \theta K) I_1^e + \varepsilon I_1 + r \varepsilon I_2 \\ &- (\mu + \theta K) I_2 - \frac{\varepsilon I_1 I_2^e}{I_2} - r \varepsilon I_2^e + (\mu + \theta K) I_2^e + N_2 \mu (I_1 + I_2) - \delta V - \frac{N - 2\mu(I_1 + I_2)V^e}{V} + \delta V^e \\ &+ \theta I_2 K - \frac{\theta v}{\sigma}. \end{aligned}$$

At the endemic equilibrium, we have

$$(23) \quad \begin{aligned} \Lambda(\eta V_H + 1) &= \mu T_s^e + (\mu + \psi) L^e, \quad \frac{\beta V T_s^e}{\gamma + T_s^e} = (\mu + \psi + \phi) L^e, \\ \psi L^e &= (\varepsilon + \mu) I_1^e, \quad \varepsilon I_1^e = (\mu - r \varepsilon) I_2^e, \quad N_2 \mu (I_1^e + I_2^e) = \delta V^e. \end{aligned}$$

We further obtain at the endemic equilibrium

$$\begin{aligned}
\mathcal{W}' &= \mu T_s^e + (\mu + \psi)L^e + \pi L - \mu T_s - (\mu T_s^e + (\mu + \psi)L^e) \frac{T_s^e}{T_s} - \frac{\phi L T_s^e}{T_s} + \frac{\beta V T_s^e}{\gamma + T_s} \mu T_s^e - (\mu + \psi + \phi)L \\
&- \frac{\beta V T_s L^e}{(\gamma + T_s)L} + (\mu + \psi + \phi)L^e + \psi L - (\mu + \varepsilon + \theta K)I_1 - \frac{\psi L I_1^e}{I_1} + (\mu + \varepsilon + \theta K)I_1^e + \varepsilon I_1 + r \varepsilon I_2 \\
&- (\mu + \theta K)I_2 - \frac{\varepsilon I_1 I_2^e}{I_2} - r \varepsilon I_2^e + (\mu + \theta K)I_2^e + N_2 \mu (I_1 + I_2) - \delta V - \frac{N_2 \mu (I_1 + I_2) V^e}{V} \\
&+ N_2 \mu (I_1^e + I_2^e) + \theta I_2 K - \frac{\theta v}{\sigma}.
\end{aligned}$$

Further simplification yields

$$\begin{aligned}
\mathcal{W}' &= \mu T_s^e \left[2 - \frac{T_s}{T_s^e} - \frac{T_s^e}{T_s} \right] + \mu L^e \left[2 - \frac{T_s^e}{T_s} - \frac{L}{L^e} \right] + \psi L^e \left[2 - \frac{T_s^e}{T_s} - \frac{L I_1^e}{L^e I_1} \right] \\
&+ \mu I_2^e \left[1 + \frac{I_1^e}{I_2^e} - \frac{I_1}{I_2^e} - \frac{I_2}{I_2^e} \right] + \frac{\beta V T_s^e}{\gamma + T_s} \left[1 - \frac{T_s L^e}{T_s^e L} \right] + \varepsilon I_1^e \left[1 - \frac{I_1 I_2^e}{I_1^e I_2} \right] + r \varepsilon I_2^e \left[1 - \frac{I_2}{I_2^e} \right] \\
(24) \quad &+ N_2 (I_1^e + I_2^e) \left[1 - \frac{V}{V^e} \right] + N_2 \mu (I_1 + I_2) \left[1 - \frac{V^e}{V} \right] + \theta K \left[I_2^e - \frac{v}{\sigma} \right].
\end{aligned}$$

Since the arithmetic mean is greater than the geometric mean it follows that

$$2 - \frac{T_s}{T_s^e} - \frac{T_s^e}{T_s} \leq 0, \quad 2 - \frac{T_s^e}{T_s} - \frac{L}{L^e} \leq 0, \quad 2 - \frac{T_s^e}{T_s} - \frac{L I_1^e}{L^e I_1} \leq 0$$

and for the CTL-inactive endemic equilibrium state we have $\mathcal{R}_K < 1$ whenever $\mathcal{R}_0 > 1$. Then it means that the condition $(I_2^e - \frac{v}{\sigma} \leq 0)$ must be satisfied so that $\mathcal{W}' \leq 0$. We also note that $\mathcal{W}' = 0$ for $T_s = T_s^e$, $L = L^e$, $I_1 = I_1^e$, $I_2 = I_2^e$, $V = V^e$, thus, the largest compact invariant set $\{T_s^e, L^e, I_1^e, I_2^e, V^e \in \Omega : \mathcal{W}' = 0\}$, is the singleton $\{E_1\}$. Therefore by LaSalle's invariance principle [19], the CTL-inactive endemic equilibrium is globally asymptotically stable provided that $\mathcal{R}_0 > 1$ and $\mathcal{R}_K < 1$. This completes the proof \square

Stability analysis of the CTL-active equilibrium is demonstrated using numerical simulations.

6. NUMERICAL SIMULATIONS

In our numerical simulations, we extend the model to include vaccination against HPV and ART treatment of HIV-positive individuals. The HPV vaccines currently available inhibit the occurrence of new infections and hence to model this we introduce the parameter ε_I which is

the efficacy of the HPV vaccine. When $\varepsilon_I = 0$, the HPV vaccine is considered to have failed while when $\varepsilon_I = 1$, the vaccine is 100% effective. To model the dynamics of HIV treatment we consider the action of the reverse transcriptase inhibitor, (RIs) and the protease inhibitors (PIs). The effect of the reverse transcriptase inhibitors is represented in the model by, ε_R while the protease inhibitors are represented by parameter, ε_P . The conditions for the RIs and the PIs are that when $\varepsilon_R, \varepsilon_P = 0$ then there is no treatment effect and when $\varepsilon_R, \varepsilon_I = 1$ then treatment is 100% effective. The new extended model is given by

$$(25) \quad \left\{ \begin{array}{l} T'_h(t) = s - (1 - \varepsilon_R)\kappa V_h T_h - d_1 T_h, \\ L'_h(t) = \rho(1 - \varepsilon_R)\kappa V_h T_h - (\zeta + d_2)L_h, \\ I'_h(t) = (1 - \rho)(1 - \varepsilon_R)\kappa V_h T_h + \zeta L_h - d_3 I_h, \\ V'_h(t) = N_1 d_3 (1 - \varepsilon_P) I_h - c V_h, \\ T'_s(t) = \Lambda(1 + \eta \bar{V}_h) + \phi L - \left(\frac{(1 - \varepsilon_I)\beta V}{\gamma + T_s} + \mu \right) T_s, \\ L'(t) = \frac{(1 - \varepsilon_I)\beta V T_s}{\gamma + T_s} - (\mu + \psi + \phi)L, \\ I'_1(t) = \psi L - (\varepsilon + \mu + \theta K)I_1, \\ I'_2 = \varepsilon I_1 + r\varepsilon I_2 - (\mu + \theta K)I_2, \\ V'(t) = N_2 \mu (I_1 + I_2) - \delta V, \\ K'(t) = \sigma I_2 K - \nu K, \end{array} \right.$$

and the control reproduction number is given by

$$\mathcal{R}_c = \frac{\beta(1 - \varepsilon_I)(1 - \varepsilon_R)(1 - \varepsilon_P)N_2 \mu \psi \Lambda(1 + \eta \bar{V}_h)(\mu + \varepsilon - r\varepsilon)}{\delta(\mu - r\varepsilon)(\mu + \varepsilon)(\mu + \psi + \phi)[\Lambda(1 + \eta \bar{V}_h) + \gamma\mu]}.$$

Parameter values used in the simulations were either obtained from published literature, calculated, or closely approximated. To estimate the parameters for the HIV model the following calculations were performed;

$$(26) \quad \bar{L}_H = \frac{\rho \kappa \bar{V}_H \bar{T}_H}{\zeta + d_2}, \quad \bar{I}_H = \frac{c \bar{V}_H}{N_1 d_3}, \quad \kappa = \frac{c(\zeta + d_2)}{\bar{T}_H N_1 [\zeta + d_2(1 - \rho)]}, \quad s = (\kappa \bar{V}_H + d_1) \bar{T}_H$$

The initial HIV concentrations used are: $\bar{T}_H = 5 \times 10^5$ cells/ml [7], $\bar{V}_H = 4.8 \times 10^4$ cells/ μ l [1] while using expression (26) we calculate the remaining concentrations which yields $\bar{L}_H = 237.62$ cells/ μ l, $\bar{I}_H = 1.04 \times 10^3$ cells/ μ l, $\kappa = 5 \times 10^{-8}$ virions per day and $s = 6.2 \times 10^3$ cells/ μ l/day. A summary of the parameter values and their description is given in Table 1.

TABLE 1. Parameters values for the HIV/HPV co-infection model.

Parameter	Value	Source
s	$6.2 \times 10^3/\mu\text{l/day}$	Calculated
κ	$5 \times 10^{-8} /\mu\text{l/ day}$	Calculated
d_1, d_2, d_3	$[0.03, 0.001, 1]/\mu\text{l/ day}$	[20],[1]
ζ	0.1 per μl per day	[20]
ρ	0.02 per μl per day	[20]
N_1	$[1000-1250]/\mu\text{l/day}$	[20], [1]
c	$[20-23]/\mu\text{l/day}$	[20], [1],[1]
η	varied	varied
Λ	36000 cells/ $\mu\text{l/day}$	[15]
β	0.0067 μl virions per day	[1]
δ	0.05 cells per day	Est.
μ	0.048 per day	[21]
N_2	1000 virions per cell	[1]
θ	0.01 day^{-1}	[22]
γ	10^6	[21]
ψ	0.03 day^{-1}	[23]
σ	0.001 cells per ml	Est.
ν	0.5 cells/ ml	Est.
ε	varied between $[0 - 1]$	[21]
r	0.01	[21]
ϕ	0.6 day^{-1}	[23]
ε_I	varied	varied
η_P	varied	varied
η_R	varied	varied

6.1. Convergence of equilibrium points. Figure 2 presents the convergence of the infection-free equilibrium. The results presented support the theoretical analysis presented earlier. We observe that when $\mathcal{R}_0 < 1$ the system approaches, $E_0 = (1.837 \times 10^6, 0, 0, 0, 0, 0)$ for, $\eta > 0$, (*tat* protein present) and it approaches the equilibrium $E_0 = (7.5 \times 10^5, 0, 0, 0, 0, 0)$ for, $\eta = 0$, (*tat* protein absent). Clearly, the presence of *tat* protein increases latently infected cells, $L(t)$, actively infected cells, $I_1(t)$, self-proliferating cells, $I_2(t)$ and HPV virions as opposed to the absence of *tat* protein.

Figure 3 presents the convergence of the CTL-free endemic equilibrium, E_1 . When $\mathcal{R}_0 > 1, \mathcal{R}_K < 1$, the model converges to $E_1 = (2.765 \times 10^5, 1,114 \times 10^6, 5.76 \times 10^5, 1.20 \times 10^5, 6.68 \times 10^8, 0)$, hence, the endemic equilibrium, E_1 , is globally asymptotically stable provided $\mathcal{R}_0 > 1$ and $\mathcal{R}_K < 1$, supporting the theoretical analysis presented earlier. Figure 3 presents the convergence of the CTL-active equilibrium, E_2 . It is observed that the endemic equilibrium E_2 is globally asymptotically stable when $\mathcal{R}_0 > 1$ and $\mathcal{R}_K > 1$. We observe a delay in the activation of immune response cells between (0 – 100) days. A decrease in the I_2 cells and HPV virions is observed as the CTL-cells dock and kill infected cells. The gradual decline observed leads to the endemic equilibrium point, $E_2 = (3.45 \times 10^5, 1.403 \times 10^6, 4433, 5000, 9.064 \times 10^6, 40.3)$.

6.2. Vaccination effects on the dynamics of HIV/HPV co-infection. We consider two cases; the case where co-infection exists and in the absence of vaccination and when there is vaccination as presented in Figures 4(a-e). Simulations indicate that HPV vaccination among HIV positive women is beneficial in preventing new HPV infections from occurring. This is shown by a significant increase in the susceptible epithelial cells and a decrease in actively infected cells when a 90% vaccine efficacy is applied. The absence of vaccination increases the probability of HPV infection as evidenced by the dynamics of I_1 (blue dashed line) and this is because HIV exacerbates HPV persistence. On the other hand the presence of vaccination effectively reduces new infections as evidenced by the dynamics of I_1 cells (red dashed line). Clinical data from the study by Konopnicki *et al.* and Table 1 was used to produce the dynamics in Figure 5.

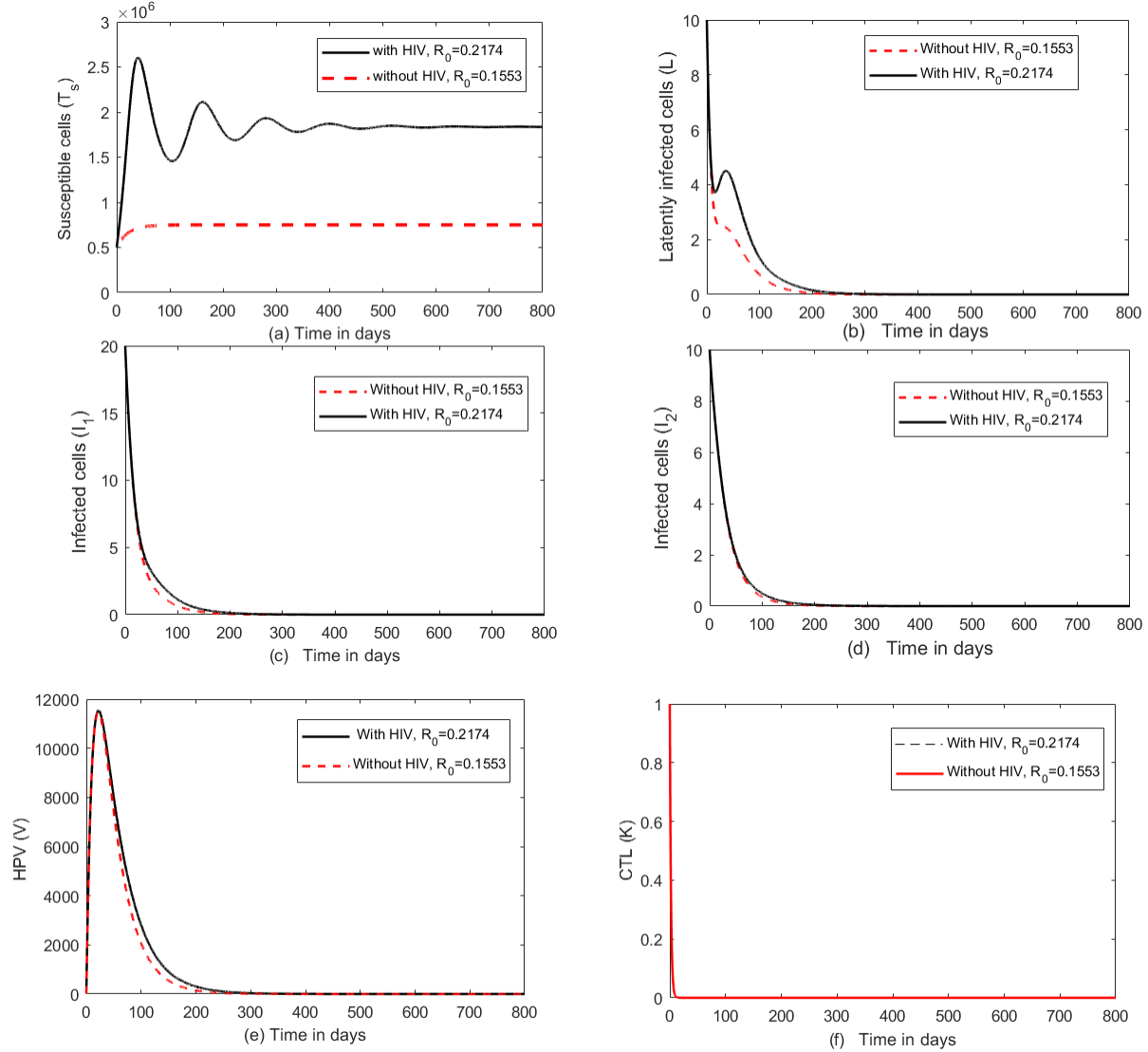


FIGURE 2. The stability of the infection-free equilibrium for $\mathcal{R}_0 = 0.1553 < 1$, (*tat* protein absent, $\eta = 0$) and $\mathcal{R}_0 = 0.2174 < 1$ (*tat* protein present, $\eta = 2.0833 \times 10^{-5}$). The initial conditions used were $T_s(0) = 500000$, $L(0) = 100$, $I_1(0) = 200$, $I_2(0) = 100$, $V(0) = 100$, $K(0) = 1$ and the rest of the parameters are from Table 1.

Tat protein is normally not in effect when the CD4+ T-cell count is > 500 cells/ μl and therefore we assume that $\eta \bar{V}_H = 0$, [1]. Stages where the CD4+ T-cell count is < 500 cells/ μl there is the action of *tat* protein hence $\eta \bar{V}_H = 1$. For the first 50 days Figure 5(a) indicates an increase in I_1 cells as the CD4+ T-cell count is low. Due to this Figure 5(b) indicates that a rise in I_1 cells exacerbates the production of I_2 cells and this consequently HPV viral production is

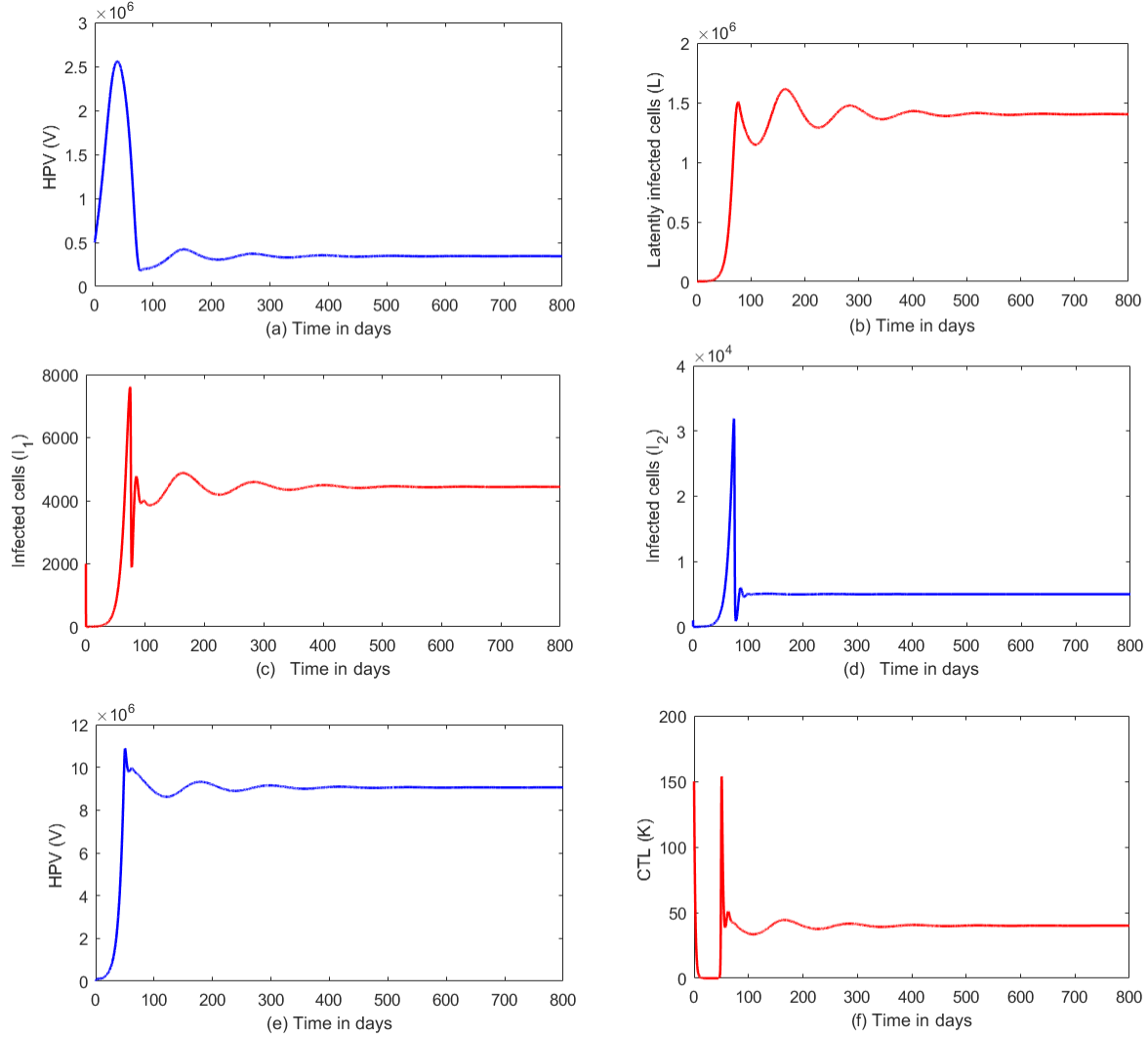


FIGURE 3. Stability of the CTL-free equilibrium E_1 , with $\mathcal{R}_0 = 24.0351$ and $\mathcal{R}_K = 17.6668$ and $\beta = 0.0067$, $\sigma = 0.00001$, $\eta = 2.0833 \times 10^{-5}$. The initial conditions used are $T_s(0) = 500000$, $L(0) = 1000$, $I_1(0) = 2000$, $I_2(0) = 1000$, $V(0) = 1000$, $K(0) = 150$ and the rest of the parameters are obtained in Table 1.

also affected by the CD4+ T-cell count as shown by Figure 5 (c). So a healthy HIV-infected individual has an immune system that can effectively reduce HPV. Also, during the first 50 days a delay in the immune response is also observed and this is assumed to be as a result of immune evasion. The consequence of this is a sharp increase in infected cells and the HPV viral load as shown in Figures 5(a-c). The dynamics of infection change after a period of 50

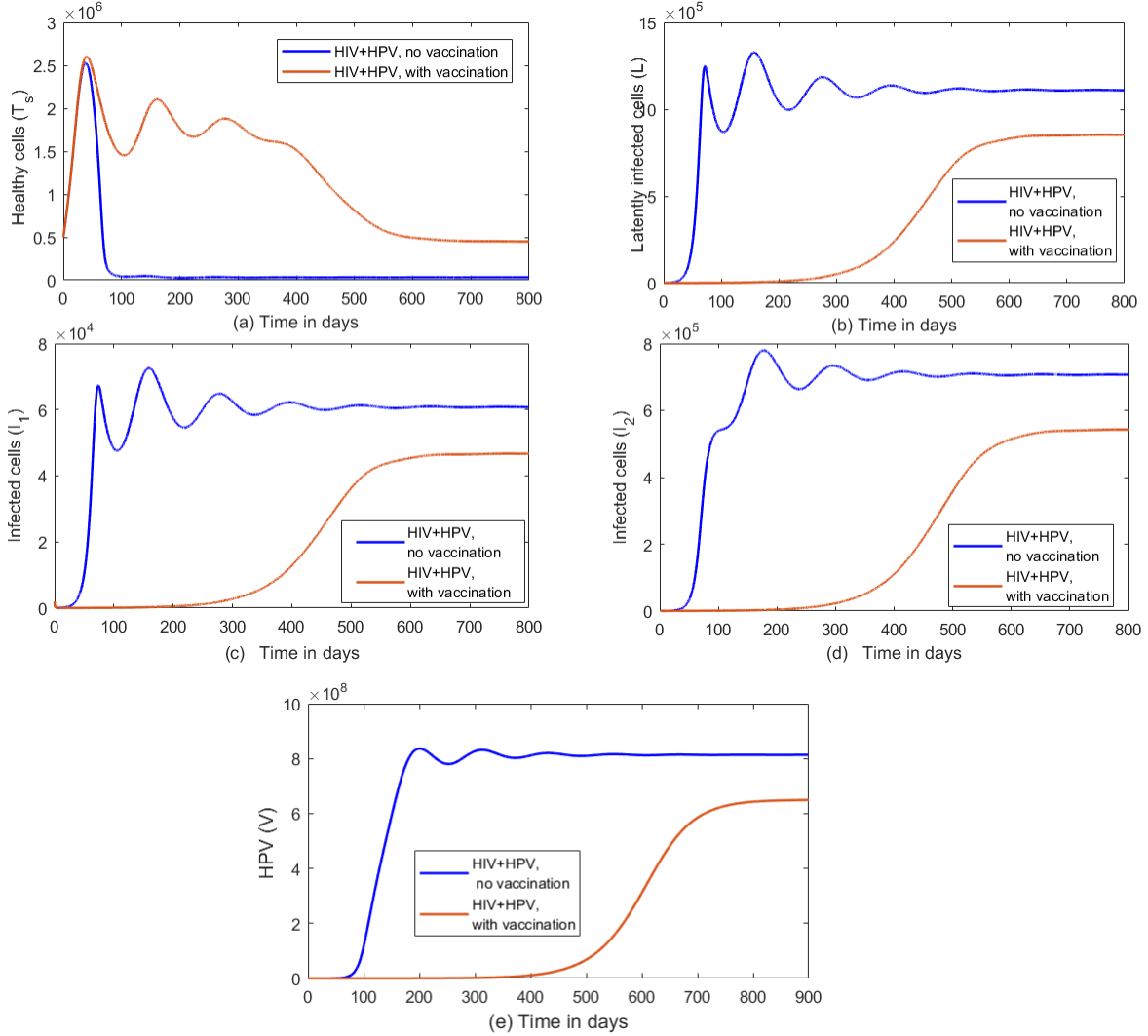


FIGURE 4. Dynamics of HPV/HIV co-infection model in the presence of vaccination with; $\eta\bar{V}_H = 1, \varepsilon_I = 0$, (ii) $\eta\bar{V}_H = 1, \varepsilon_I = 0.90$, with initial conditions $T_s(0) = 1000, L(0) = 100, I_1(0) = 200, I_2(0) = 100, V(0) = 100, K(0) = 150$. In all cases, $\mathcal{R}_c > 1$ and $\mathcal{R}_K < 1$ and the rest of parameters are taken from Table 1.

days. We observe the action of the immune response and a gradual decrease in the number of infected cells and these approach some equilibrium.

6.3. HIV/HPV co-infection in the presence of treatment. To simulate the contribution of cART we assume that all infected individuals are highly adherent to cART and have initiated it well in time. Adherence is crucial in the reduction of HPV infection in HIV-positive women.

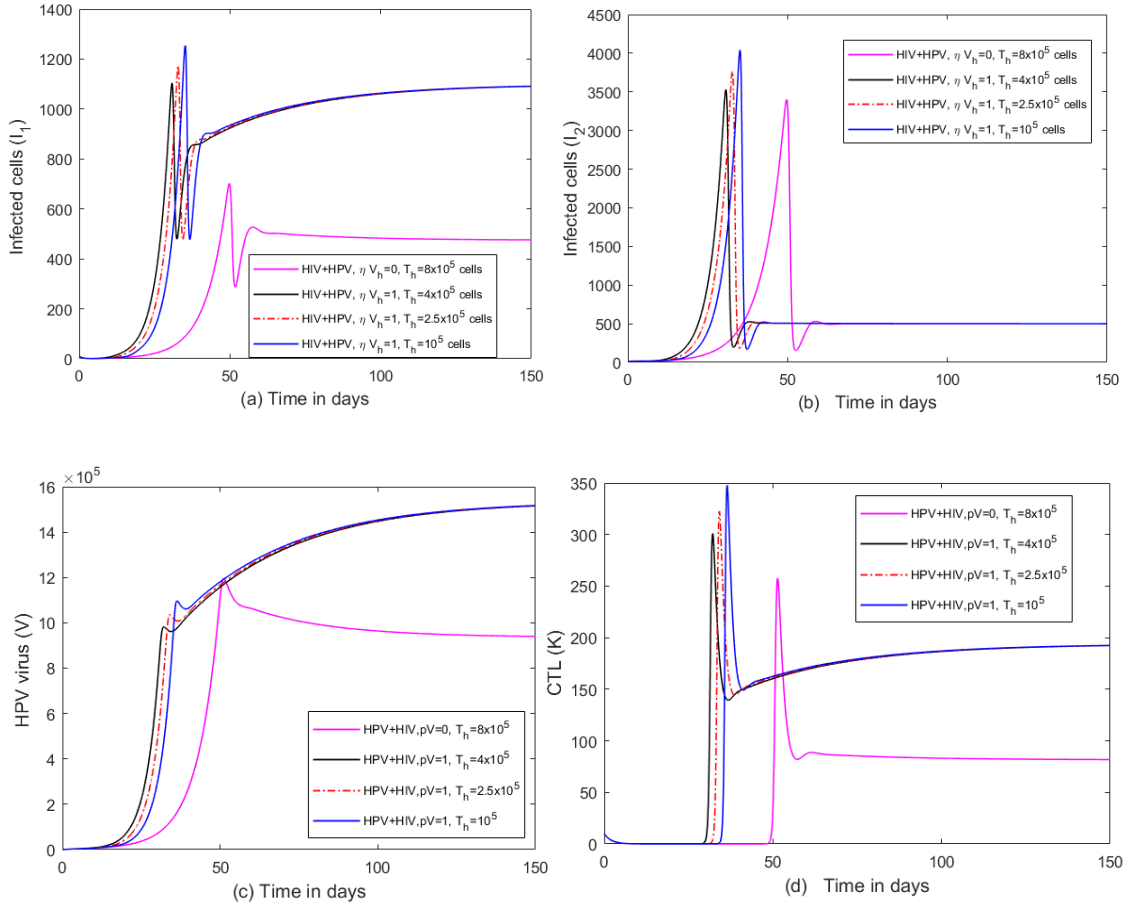


FIGURE 5. The HPV/HIV co-infection dynamics, for (i) $T_H = 8 \times 10^5$ and $\eta\bar{V}_H = 0$, (ii) $T_H = 4 \times 10^5$, $\eta\bar{V}_H = 1$ (iii) $T_H = 2.5 \times 10^5$, $\eta\bar{V}_H = 1$ and (iv) $T_H = 10^5$, $\eta\bar{V}_H = 1$, $\mathcal{R}_0 > 1$. The rest of the parameters are taken from Table 1. It is also assumed that; healthy CD4+ T-cell count is 8×10^5 cells/ μl , the chronic HIV stage CD4+T-cell count is 4×10^5 cells/ μl and 2.5×10^5 cells/ μl respectively and the chronic AIDS stage is 10^5 cells/ μl .

Simulations in Figure 6 show two cases that is; “ineffective cART case” ($\varepsilon_P = 0$, $\varepsilon_R = 0.01$) and “effective cART case” ($\varepsilon_P = 0.5$, $\varepsilon_R = 0.95$). Results indicate that adherence to treatment (effective cART case) is indeed crucial in the reduction of HPV prevalence. We therefore recommend that women and girls living with HIV be educated on the benefits of adherence to treatment in relation to the reduction in HPV related infections.

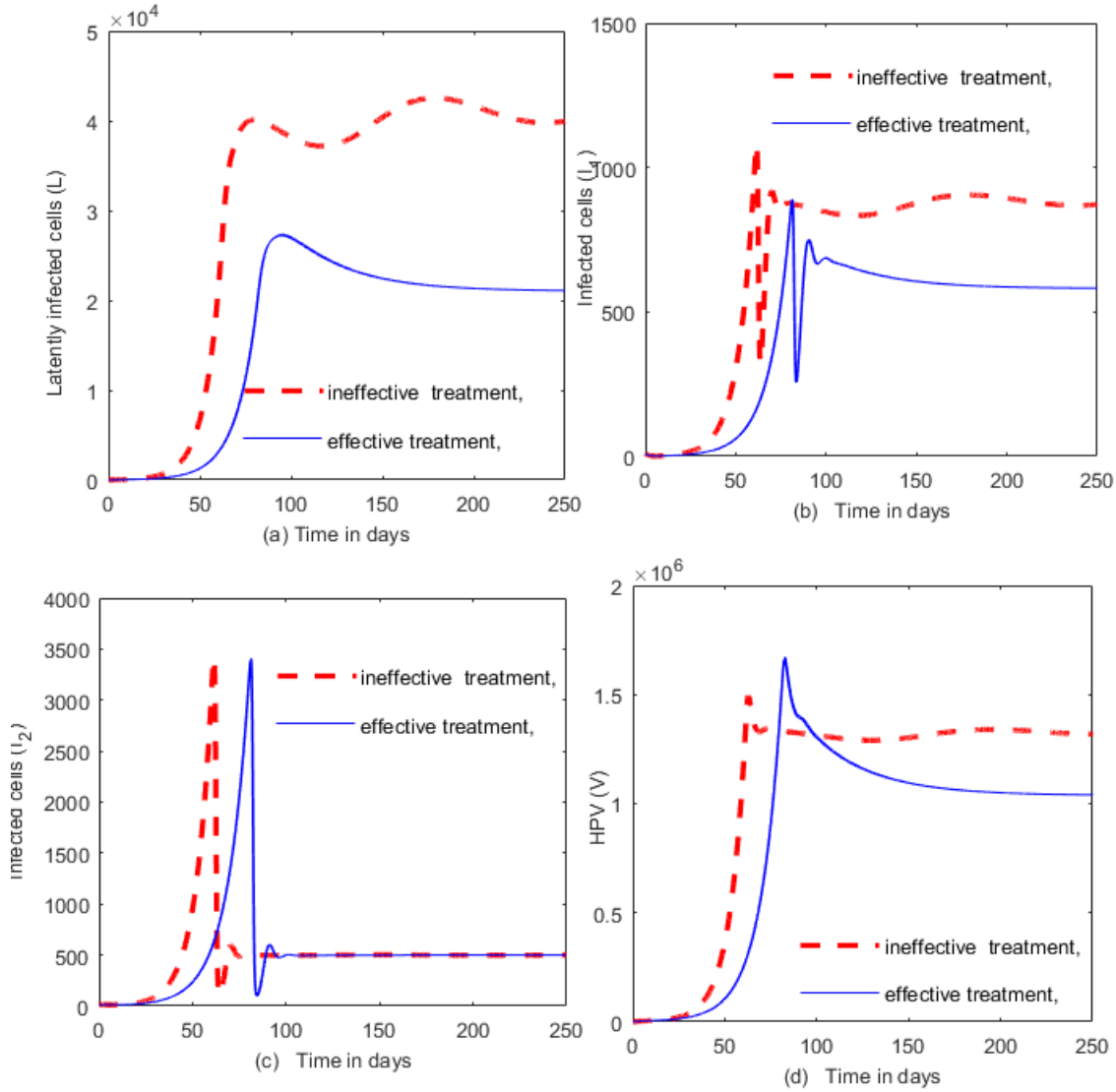


FIGURE 6. HIV/HPV co-infection in the presence of cART, where “ineffective cART” implies $\varepsilon_P = 0$, $\varepsilon_R = 0.01$ and “effective cART” implies $\varepsilon_P = 0.5$ and $\varepsilon_R = 0.95$. The rest of the parameters are from Table 1.

7. CONCLUSION

In this study, we investigated the dynamics of HIV/HPV co-infection, building upon the work by [1, 11]. Our model specifically considered the impact of latent HPV infections on the persistence of infection among women living with HIV/AIDS. Through mathematical analysis, we identified three equilibrium points: the disease-free equilibrium, CTL-free endemic equilibrium, and CTL-active endemic equilibrium. We established both the global and local stabilities

of these equilibrium points and provided the conditions for their stability. Notably, the stability of these points depended on two key parameters: the basic reproduction number, \mathcal{R}_0 , and the immune response reproduction number, \mathcal{R}_K . An essential finding of our analysis was the observation of a forward bifurcation when $\mathcal{R}_0 > 1$ but close to one. This implies that reducing \mathcal{R}_0 to below unity will effectively control HPV among women living with HIV. To gain further insights, we conducted numerical simulations, which explored the dynamics of the model under two scenarios: vaccination and the presence of cART. The results highlighted the benefits of vaccinating women living with HIV, especially when the vaccine's efficacy exceeds 60%, aligning with the current HPV vaccine efficacy levels. Additionally, combining vaccination with proper adherence to cART proved to be effective in reducing HPV infection. In conclusion, our model emphasises the importance of widespread vaccination for women and girls, early initiation of cART, and adherence to cART in combating HPV infection among women. We believe that these findings contribute significantly to a better understanding of HPV dynamics in immune-compromised individuals.

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CONFLICT OF INTERESTS

The authors declare that there is no conflict of interests.

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