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MODELING TOBACCO SMOKING EFFECT ON HIV ANTIRETROVIRA THERAPY AND STABILITY ANALYSISL

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Abstract. Tobacco smoking effect on ARVs remains a topic under investigation. In this paper, a deterministic model is formulated by considering smoking interference in metabolism of ARVs and its effect on one's adherence to drugs in order to assess stability of equilibrium states and determine how tobacco smoking affects antiretroviral drugs. Equilibrium states and effective reproduction number R_{eff} are computed and stability condition for equilibrium states established. Using linearization method and comparison theorem, analysis shows that disease free equilibrium is globally stable when $R_{eff} < 1$ and it is unstable when $R_{eff} > 1$. However, due to high smoking impairment effective reproduction number R_{eff} cannot be less than unity and the classical requirement $R_{eff} < 1$ for global stability of disease free equilibrium cannot be realized. Therefore tobacco smoking affects stability of disease free equilibrium. By applying logarithmic Lyapunov function, endemic equilibrium is asymptotically stable when $R_{eff} > 1$. The analysis shows that, as tobacco smoking interference with metabolism of ARVs increases, HIV infected T-cells and macrophages, and free virus record a corresponding increase and this shows that tobacco smoking decreases the efficacy of ARVs. To improve patient's immune system and manage HIV epidemic and its therapy, integration of smoking cessation programs in HIV care services is recommended.

1. Introduction

Tobacco smoking remains a top health agenda among HIV infected patients whether they are under therapy or not. Contents of tobacco smoke have a devastating effect in HIV therapy and exacerbate pathogenesis of HIV in the in-vivo dynamics (23). The benefits of ARVs in reducing mortality and suffering among HIV infected individuals are negated by tobacco smoking (5; 19). In addition to causing immune system defective, tobacco smoking also interferes with metabolism of ARVs and causes drug interaction (2). Drug interaction reduces concentration of the drugs' and cuts down their absorption which entails reduced efficacy.

To gain insight on the effect of tobacco smoking when a HIV smoker is under therapy, we use mathematical modeling to study the behaviour of HIV within a host when ARVs are administered. Mathematical models play an important role in studying and understanding the dynamics of infectious diseases and their intervention strategies (13). In this study, the model for tobacco

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smoking effect on antiretroviral therapy is formulated by considering HIV in vivo dynamics and smoking effect on T-cells and macrophages. Stability analysis of the model equilibrium states is performed to determine the qualitative behaviour of the dynamics.

Stability analysis of the model steady states is one of the fundamental problem in mathematical epidemiology (21) as it reveals important features for persistence or eradication of the disease. Understanding of these features which drive a particular disease helps researchers and health practitioners to design treatment and intervention strategies (28). Apart from designing treatment and control strategies, stability analysis also offers alert and precautions for disease outbreak.

To perform stability analysis of equilibrium states to determine behaviour of the disease in consideration, different approaches have been proposed. However among the approaches, some are useful in analysis of local stability and some for global stability. Linearization method (11; 24) is useful in the analysis of local stability. Under this approach a system is linearized at equilibrium state to obtain a Jacobian matrix. From Jacobian matrix, we compute eigenvalues. If the eigenvalues of the Jacobian matrix are negative or have negative real parts, the equilibrium state is proved stable. However, the equilibrium state is proved unstable when at least one of the eigenvalues is positive or has positive real part.

Sometimes it is difficult to obtain eigenvalues directly from Jacobian matrix. Whenever it is impossible to compute the eigenvalues from the Jacobian matrix, linearization method offers alternative methods to test the signs of eigenvalues without computing them. These methods include trace and determinant method, and Hurwitz criterion. Negative trace and positive determinant indicate that, the Jacobian matrix has negative eigenvalues. In Hurwitz criterion, we derive a characteristic equation and test the signs for coefficients. If coefficients do not change sign, necessary condition hold. However, sufficient condition depends on the degree of the characteristic equation. Linearization method is also used to analyze local stability of endemic equilibrium.

Comparison theorem (4) and Metzler matrix (12) are used in analysis of global stability of disease free equilibrium. Comparison theorem proves infected classes are diminishing as uninfected classes are growing to attain the disease free equilibrium point. Metzler matrix forms two matrices from uninfected and infected classes. The method concludes global stability if the matrix from uninfected classes has negative eigenvalues and the elements of the main diagonal in the matrix of the infected classes are negative. However, since global stability implies local stability the approaches may also be used to establish local stability.

Lyapunov method can be used to establish stability of disease free and endemic equilibriums. The Lyapunov functions which are used in the analysis of disease free equilibrium are unique depending on the nature of the model under consideration. However, the analysis of endemic

equilibrium uses general Lyapunov functions which are reviewed as follows. Explicit Lyapunov function was constructed for the analysis of SEIR and SEIS epidemic models (15; 16). Logarithmic Lyapunov function was used to analyze Lotka-Voltera systems (6). Later it was used in the analysis of endemic equilibrium for SIR, SIRS and SIS epidemic models (17). Composite quadratic Lyaponuv function was proposed and used to determine stability of endemic equilibrium for SIR, SIRS and SIS epidemic models (30). Later the composite-Volterra function was used in the analysis of endemic equilibrium for the model with relapse (30).

As stability is a requirement for the model application in a real setting, this study analyzes stability of a mathematical model for tobacco smoking effect on antiretroviral therapy using linearization method, comparison theorem and Lyapunov function. This work is organized as follows: we describe the model in the next Section, analysis of the model is presented after the next Section, Numerical analysis and Conclusion mark the end.

2. Model formulation

The model divides T-cells into five classes and macrophages into four classes. Antiretroviral drugs under consideration are reverse transcription inhibitors (RTIs) and Protease Inhibitors (PIs). In T-cells, X represents density of uninfected T-cells, X_1 density of smoking partially impaired T-cells, X_2 density of HIV latently infected T-cells, X_3 density of smoking critically impaired T-cells and X_4 density of HIV productively infected T-cells. For the case of macrophages, Y represents density of healthy macrophages, Y_1 density of smoking partially impaired macrophages, Y_2 density of HIV infected macrophages, Y_3 density of smoking critically impaired macrophages and density of free virus is represented by V.

A function $\Lambda - \dfrac{cV}{k+V}$ which decreases due to the presence of free virus (14; 3) is a recruitment rate for T-cells. The expression $\gamma X_1 + \eta X_3$ represents smoking T-cells' impairment rate with $\gamma < \eta$ being relative smoking impairment rates of X_1 and X_3 due to the fact that, smoking critically impaired T-cells have high concentration of tobacco smoke poisonous and carcinogenic compounds. Parameters β_1, β_2 and τ represent HIV infection rates for uninfected T-cells X, smoking partially impaired T-cells X_1 and HIV infection rate of uninfected T-cells X from HIV infected macrophages Y_2 respectively. Since reverse transcription in smoking critically impaired T-cells X_3 is assumed to be spontaneous, in the presence of ARVs, HIV infects smoking critically impaired T-cells at a rate $\beta_3(1-f_1\epsilon)$ where ϵ such that $0 \leq \epsilon \leq 1$ is the efficacy of RTIs in blocking reverse transcription in T-cells and $f_1(\varpi) = \dfrac{e^{-\varpi}}{\varpi+1}$ is a smoking effect in inducing metabolism of ARVs in smoking critically impaired T-cells and macrophages, $\varpi \in (0,1)$ is the rate at which smoking induces metabolism of ARVs. When $\varpi = 0$, smoking does not induce metabolism of ARVs and when $\varpi = 1$, smoking induces metabolism of ARVs at a highest rate.

Smoking partially impaired T-cells X_1 progress to smoking critically impaired T-cells X_3 at a rate ρ. HIV latently infected T-cells X_2 due to the presence of smoking partially impaired T-cells, progress to productively infected T-cells X_4 following successful reverse transcription at a rate $\sigma(1-f\epsilon)$ where $f = e^{-\varpi}$ models smoking effect in inducing metabolism of ARVs in smoking partially impaired T-cells and macrophages. Functions f and f_1 model relative smoking inducing effect in smoking partially and critically impaired cells as we assume smoking critically impaired cells experience high smoking inducing effect compared to smoking partially impaired cells. However, if ζ_1 denotes drugs' reverse transcription blocking rate in T-cells and ϑ adherence rate to treatment, then $\epsilon = \zeta_1\vartheta$. Parameter α is smoking induced mortality in critically impaired T-cells and μ_1 is a HIV induced mortality in HIV productively infected T-cells which produce infectious virions at a rate $N_1\mu_1(1-f_1\xi)$. The parameter $\xi = \kappa\vartheta$ such that $0 \leq \xi \leq 1$ is the efficacy of PIs in blocking production of infectious virions in T-cells, κ is the rate at which PIs block production of infectious virions in T-cells and ϑ is drugs' adherence rate.

Macrophages are recruited at a rate λ. Expressions $\beta_4(1-\epsilon_1)$, $\beta_5(1-f\epsilon_1)$ and $\beta_6(1-f_1\epsilon_1)$ are HIV infection rates for healthy macrophages Y, smoking partially impaired macrophages Y_1 and smoking critically impaired macrophages Y_3, where $\epsilon_1 = \zeta_2\vartheta$ such that $0 \leq \epsilon_1 \leq 1$ is the efficacy of RTIs in macrophages and ζ_2 is the rate at which RTIs block reverse transcription in macrophages. Expression $\nu Y_1 + \theta Y_3$ is a smoking impairment rate with relative impairment of Y_1 and Y_3 given by ν and θ, we assume that $\nu < \theta$ because smoking critically impaired macrophages have high concentration of tobacco smoke poisonous and carcinogenic compounds. Smoking critically impaired macrophages suffer smoking induced mortality at a rate α_1. HIV infected macrophages suffer HIV induced mortality at rate δ and produce infectious virions at a rate $N_2\delta(1-f_1\xi_1)$ where $\xi_1 = \kappa_1\vartheta$ such that $0 \leq \xi_1 \leq 1$ is the efficacy of PIs in blocking production of infectious virions in macrophages and κ_1 is the rate at which PIs' block production of infectious virions. Parameters μ_y and μ_v represent natural mortalities for macrophages' compartments and free virus respectively.

The model assumes that RTIs and PIs have different efficacies in T-cells and macrophages (1). Metabolism of RTIs and PIs occurs at a cellular level. Tobacco smoking induces metabolism of RTIs and PIs uniformly. On HIV infection, smoking partially impaired T-cells join HIV latently infected compartment because their reverse transcription is not spontaneous and critically impaired T-cells join productively HIV infected T-cells due to their spontaneous reverse transcription. The model also assumes that unresponsiveness of T-cells and impairment of macrophages increase with smoking. Interaction of variables is demonstrated by Figure 2.1, state variables and model parameters are described in Tables 2.1 and 2.2 respectively.

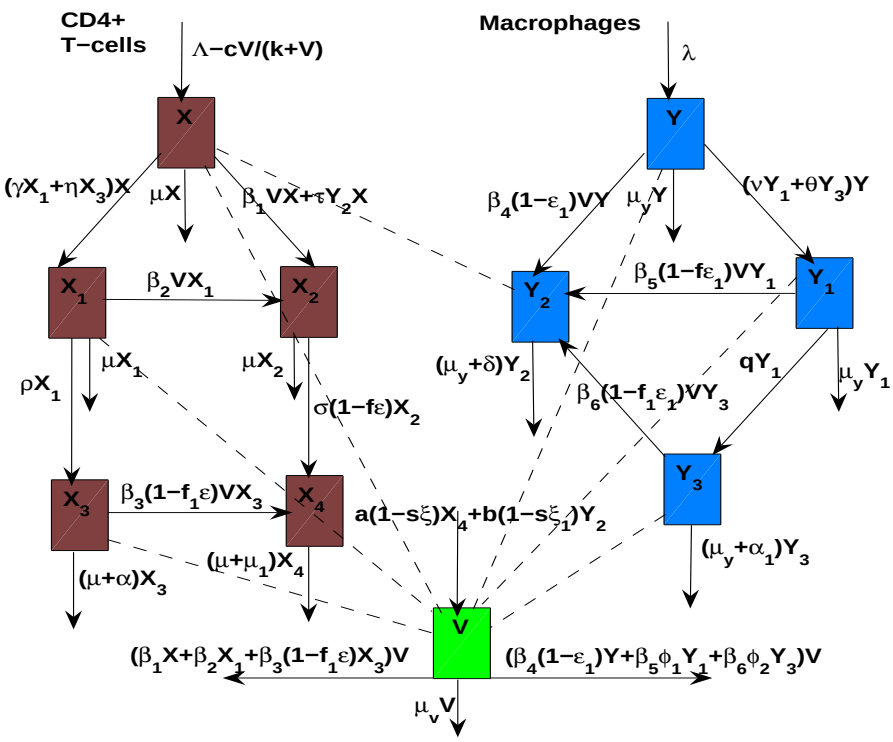

FIGURE 2.1. Interaction of T-cells and macrophages with free virus and tobacco smoking in the presence of therapy.

TABLE 2.1. Variables description

Variable	Description
X	Uninfected CD4+ T-cells
X_1	Smoking partially impaired CD4+ T-cells
X_2	HIV latently infected CD4+ T-cells
X_3	Smoking critically impaired CD4+ T-cells
X_4	HIV productively infected CD4+ T-cells
Y	Healthy macrophages
Y_1	smoking partially impaired macrophages
Y_2	HIV infected macrophages
Y_3	Smoking critically impaired macrophages
V	Free virus

Table 2.2: Parameters descriptions

Parameters	**Description**
Λ	CD4+ T-cells recruitment in the absence of HIV
k	half saturation constant
c	rate at which HIV reduces newly produced CD4+ T-cells
λ	recruitment rate for macrophages
γ	rate of impairment from partially impaired CD4+ T-cells
η	rate of impairment from critically impaired CD4+ T-cells
ρ	progression rate from partially to critically impaired CD4+ T-cells
σ	progression rate from HIV latent to actively infected CD4+ T-cells
μ	natural mortality rate for CD4+ T-cells
β_1	HIV infection rate for uninfected CD4+ T-cells
β_2	HIV infection rate for partially impaired CD4+ T-cells
β_3	HIV infection rate for critically impaired T-cells
β_4	HIV infection rate for uninfected macrophages
β_5	HIV infection rate for partially impaired macrophages
β_6	HIV infection rate for partially impaired macrophages
ν	smoking impairment rate from partially impaired macrophages
θ	rate of impairment from critically impaired macrophages
μ_1	HIV induced death rate for CD4+ T-cells
μ_y	natural mortality rate for macrophages
δ	HIV induced death rate for macrophages
μ_v	natural mortality rate for free virus
α_1	smoking induced death rate for impaired macrophages
α	smoking induced death rate for impaired CD4+ T-cells
τ	HIV transmission rate by infected macrophages to CD4+ T-cells
q	progression rate from partially to critically impaired macrophages
N_1 & N_2	Number of virus released by a T-cell and a macrophage over the life time
ϵ & ϵ_1	RTIs efficacies in T-cells and macrophages
ξ& ξ_1	PIs efficacies in T-cells and macrophages
ϖ	Smoking induction rate in metabolism of RTIs and PIs

From the flow diagram 2.1, the model is governed by the following system of differential equations:

$$\frac{dX}{dt} = \Lambda - \frac{cV}{k+V} - (\gamma X_1 + \eta X_3)X - \beta_1 VX - \tau Y_2 X - \mu X, \tag{1a}$$

$$\frac{dX_1}{dt} = (\gamma X_1 + \eta X_3)X - \beta_2 VX_1 - (\rho + \mu)X_1, \tag{1b}$$

$$\frac{dX_2}{dt} = \beta_1 VX + \tau Y_2 X + \beta_2 VX_1 - (\sigma(1 - f\epsilon) + \mu)X_2, \tag{1c}$$

$$\frac{dX_3}{dt} = \rho X_1 - \beta_3(1 - f_1\epsilon)VX_3 - (\alpha + \mu)X_3, \tag{1d}$$

$$\frac{dX_4}{dt} = \sigma(1 - f\epsilon)X_2 + \beta_3(1 - f_1\epsilon)VX_3 - (\mu_1 + \mu)X_4, \tag{1e}$$

$$\frac{dY}{dt} = \lambda - \beta_4(1 - \epsilon_1)VY - (\nu Y_1 + \theta Y_3)Y - \mu_y Y, \tag{1f}$$

$$\frac{dY_1}{dt} = (\nu Y_1 + \theta Y_3)Y - \beta_5(1 - f\epsilon_1)VY_1 - (q + \mu_y)Y_1, \tag{1g}$$

$$\frac{dY_2}{dt} = \beta_4(1 - \epsilon_1)VY + \beta_5(1 - f\epsilon_1)VY_1 + \beta_6(1 - f_1\epsilon_1)VY_3 - (\delta + \mu_y)Y_2, \tag{1h}$$

$$\frac{dY_3}{dt} = qY_1 - \beta_6(1 - f_1\epsilon_1)VY_3 - (\alpha_1 + \mu_y)Y_3, \tag{1i}$$

$$\begin{aligned}\frac{dV}{dt} &= N_1\mu_1(1 - f_1\xi)X_4 + N_2\delta(1 - f_1\xi_1)Y_2 - \beta_1 VX - \beta_2 VX_1 - \beta_3(1 - f_1\epsilon)VX_3 \\ &\quad - \beta_4(1 - \epsilon_1)VY - \beta_5(1 - f\epsilon_1)VY_1 - \beta_6(1 - f_1\epsilon_1)VY_3 - \mu_v V,\end{aligned} \tag{1j}$$

subject to initial conditions $X(0) = X_0$, $X_1(0) = X_10$, $X_2(0) = 0$, $X_3(0) = 0$, $X_4(0) = 0$, $Y(0) = Y_0$, $Y_1(0) = Y_10$, $Y_2(0) = 0$, $Y_3(0) = 0$, and $V(0) = V_0$.

3. Model Analysis

In this section the region under which the solutions of model (1) are bounded is deduced and we compute equilibrium states, effective reproduction number and determine condition for equilibria stability.

3.1. **Boundedness of Solutions.**

To prove boundedness of solutions we consider T-cells, macrophages and free virus separately. If T_t represents sum of T-cells in all compartments, we have:

$$\begin{aligned}\frac{dT_t}{dt} &= \Lambda - \tfrac{cV}{k+V} - \mu T_t - \alpha X_3 - \mu_1 X_4, \\ \frac{dT_t}{dt} &\leq \Lambda - \mu T_t\end{aligned}$$

Rearrangement gives the following equation:

$$\frac{dT_t}{dt} + \mu T_t \leq \Lambda \tag{2}$$

whose general solution is given by

$$T_t \leq \frac{\Lambda}{\mu} + \left(T_t(0) - \frac{\Lambda}{\mu}\right) e^{-\mu t}. \tag{3}$$

Considering the two cases when $T_t(0) > \dfrac{\Lambda}{\mu}$ and when $T_t(0) < \dfrac{\Lambda}{\mu}$, we have:

$$\begin{aligned} &T_t \leq \Phi_t, \text{ where} \\ &\Phi_t = max\left\{T_t(0), \frac{\Lambda}{\mu}\right\}. \end{aligned} \tag{4}$$

However, since T_t represents the sum of all T-cells, it follows that:

$$X_4 \leq \Phi_t. \tag{5}$$

For the case of macrophages if M_t represents the sum of macrophages in all compartments and we apply the same procedures as for T-cells, we have

$$M_t \leq \Phi_m = max\left\{M_t(0), \frac{\lambda}{\mu_y}\right\}. \tag{6}$$

Since M_t is the sum of macrophages in all compartments, it follows that

$$Y_2 \leq \Phi_m. \tag{7}$$

We now consider equation (1j), so that

$$\begin{aligned} \frac{dV}{dt} &= N_1\mu_1(1-f_1\xi)X_4 + N_2\delta(1-f_1\xi_1)Y_2 - \beta_1 VX - \beta_2 VX_1 - \beta_3(1-f_1\epsilon)VX_3 \\ &\quad -\beta_4(1-\epsilon_1)VY - \beta_5(1-f\epsilon_1)VY_1 - \beta_6(1-f_1\epsilon_1)VY_3 - \mu_v V, \\ \frac{dV}{dt} &\leq N_1\mu_1(1-f_1\xi)X_4 + N_2\delta(1-f_1\xi_1)Y_2 - \mu_v V. \end{aligned}$$

Substitution of X_4 and Y_2 in equation

$$\frac{dV}{dt} \leq N_1\mu_1(1-f_1\xi)X_4 + N_2\delta(1-f_1\xi_1)Y_2 - \mu_v V, \tag{8}$$

yields solution which shows that free virus are also bounded. The solution is given by

$$V(t) \leq \Psi_{01}, \tag{9}$$

where

$$\Psi_{01} = Max\left\{\frac{N_1\mu_1(1-f_1\xi)T_t(0)}{\mu_v} + \frac{N_2\delta(1-f_1\xi_1)M_t(0)}{\mu_v}, \frac{N_1\mu_1(1-f_1\xi)\Lambda}{\mu\mu_v} + \frac{N_2\delta(1-f_1\xi_1)\lambda}{\mu_y\mu_v}\right\}.$$

The solutions of the model system are bounded in the region

$$\Upsilon = \left\{(T, Y, M, V) \in R_+^{10} :\leq T \leq \Phi_t : 0 \leq M \leq \Phi_m : 0 \leq V \leq \Psi_{01}\right\} \tag{10}$$

where T and M represent T-cells' and macrophages' compartments respectively.
Any solution on the boundary of Υ converges and remains in the region. Existence, uniqueness and continuity of solutions of the model (1) hold in Υ.

3.2. **Disease Free Equilibrium and Effective Reproduction Number R_{eff}.**

The disease free equilibrium of the model (1) when there is no tobacco smoking and HIV is given by

$$\chi^0\left(X, X_1, X_2, X_3, X_4, Y, Y_1, Y_2, Y_3, V\right) = \left(\frac{\Lambda}{\mu}, 0, 0, 0, 0, \frac{\lambda}{\mu_y}, 0, 0, 0, 0\right) \tag{11}$$

We use disease free equilibrium to compute effective reproduction number R_{eff} in the next section.

3.2.1. *Effective Reproduction Number R_{ff}. If we consider the infected classes in a model system* (1) *so that the new infections and transfer terms are defined by* $\mathbf{M_i}$ *and* $\mathbf{N_i}$ *respectively, the matrix* $\mathbf{M}$ *and* $\mathbf{N}$ *are defined by*

$$\mathbf{M} = \frac{\partial M_i}{\partial X_j}(\chi^0) \text{ and } \mathbf{N} = \frac{\partial N_i}{\partial X_j}(\chi^0). \tag{12}$$

According to (29), the effective reproduction number R_{eff} is given by

$$R_{eff} = \rho\left(\mathbf{MN^{-1}}\right) \tag{13}$$

which is the maximum eigenvalue of the matrix $\mathbf{MN^{-1}}$. *From the model* (1), *we define the new infections and transfer terms to be*

$$\mathbf{M_i} = \begin{pmatrix} (\gamma X_1 + \eta X_3)X \\ \beta_1 VX + \tau Y_2 X + \beta_2 V X_1 \\ 0 \\ \beta_3(1 - f_1\epsilon)VX_3 \\ (\nu Y_1 + \theta Y_3)Y \\ \beta_4(1-\epsilon_1)VY + \beta_5(1 - f\epsilon_1)VY_1 + \beta_6(1 - f_1\epsilon_1)VY_3 \\ 0 \\ N_1\mu_1(1 - f_1\xi)X_4 + N_2\delta(1 - f_1\xi_1 Y_2 \end{pmatrix} \tag{14}$$

and

$$\mathbf{N_i} = \begin{pmatrix} (\rho + \mu)X_1 \\ (\sigma(1 - f\epsilon) + \mu)X_2 \\ (\alpha + \mu)X_3 - \rho X_1 \\ (\mu_1 + \mu)X_4 - \sigma(1 - f\epsilon)X_2 \\ (q + \mu_y)Y_1 \\ (\delta + \mu_y)Y_2 \\ (\alpha_1 + \mu_y)Y_3 - qY_1 \\ \mu_v V \end{pmatrix} \tag{15}$$

From equation (13)*, the effective reproduction number* R_{eff} *works out to be:*

$$R_{eff} = max\{R_{eff_1}, R_{eff_2}\} \tag{16}$$

where

$$\begin{aligned} R_{eff_1} &= \frac{\Lambda\gamma}{\mu(\rho+\mu)} + \frac{\Lambda\eta\rho}{\mu(\rho+\mu)(\alpha+\mu)}, \\ R_{eff_2} &= \frac{\lambda\nu}{\mu_y(q+\mu_y)} + \frac{\lambda\nu q}{\mu_y(q+\mu_y)(\alpha_1+\mu_y)}. \end{aligned}$$

The effective reproduction number R_{eff} *is given as the maximum of partial effective reproductive number due to tobacco smoking in T-cells* R_{ff1} *and partial effective reproductive number due to tobacco smoking in macrophages* R_{ff2}*. Tobacco smoking dominates HIV in producing new infections. The partial effective reproductive numbers* R_{ff1} *and* R_{ff2} *can be written as the sum of new infections which are caused by smoking partially impaired cells and those caused by smoking critically impaired cells. If the new infections which are caused by smoking partially impaired T-cells are defined by* R_{ePT} *and those caused by smoking critically impaired T-cells by* R_{eCT} *then*

$$\begin{aligned} &R_{eff1} = R_{ePT} + R_{eCT}, \\ &\text{where } R_{ePT} = \frac{\Lambda\gamma}{\mu(\rho+\mu)} \text{ and } R_{eCT} = \frac{\Lambda\eta\rho}{\mu(\rho+\mu)(\alpha+\mu)}. \end{aligned} \tag{17}$$

Similarly for the case of macrophages, if the new infections which are caused by smoking partially impaired macrophages are defined by R_{ePM} *and those which are caused by smoking critically impaired macrophages by* R_{eCM} *then*

$$\begin{aligned} &R_{eff2} = R_{ePM} + R_{eCM}, \\ &\text{where} \\ &R_{ePM} = \frac{\lambda\nu}{\mu_y(q+\mu_y)} \text{ and } R_{eCM} = \frac{\lambda\nu q}{\mu_y(q+\mu_y)(\alpha_1+\mu_y)}. \end{aligned} \tag{18}$$

We use effective reproduction number R_{eff} *to determine stability of disease free equilibrium.*

3.2.2. *Local stability of a Disease Free Equilibrium* χ^0*. When tobacco smoking impairs less than one cell (T-cells or macrophages) and HIV infects less than one cell (T-cells or macrophages) a case in which* $R_{eff} < 1$*, disease free equilibrium is locally asymptotically stable. It becomes unstable when tobacco smoking impairs more than one cell (T-cells or macrophages) and HIV infects more than one cell (T-cells or macrophages) the case in which* $R_{eff} > 1$*. To find condition for local stability of disease free equilibrium, we state and prove the following theorem.*

Theorem 1. : *Disease free equilibrium is locally asymptotically stable when* $R_{eff} < 1$ *and unstable when* $R_{eff} > 1$*.*

To prove the theorem, we linearize the model system (1) *at disease free equilibrium to obtain a matrix*

$$\mathbf{J}(\chi^{\mathbf{0}}) = \begin{pmatrix} -\mu & -\frac{\gamma\Lambda}{\mu} & 0 & -\frac{\gamma\eta}{\mu} & 0 & 0 & 0 & -\frac{\tau\Lambda}{\mu} & 0 & -\frac{c}{k} - \frac{\beta_1\Lambda}{\mu} \\ 0 & \frac{\gamma\Lambda}{\mu} - w_1 & 0 & \frac{\eta\Lambda}{\mu} & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & -w_A & 0 & 0 & 0 & 0 & \frac{\tau\Lambda}{\mu} & 0 & \frac{\beta_1\Lambda}{\mu} \\ 0 & \rho & 0 & -w_0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & \sigma(1-f\epsilon) & 0 & -w_6 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & -\mu_y & -\frac{\nu\lambda}{\mu_y} & 0 & -\frac{\theta\lambda}{\mu_y} & -\frac{d_3}{\mu_y} \\ 0 & 0 & 0 & 0 & 0 & 0 & \frac{\nu\lambda}{\mu_y} - w_3 & 0 & \frac{\theta\lambda}{\mu_y} & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & -w_4 & 0 & \frac{d_3}{\mu_y} \\ 0 & 0 & 0 & 0 & 0 & 0 & q & 0 & -w_2 & 0 \\ 0 & 0 & 0 & 0 & d_1 & 0 & 0 & d_2 & 0 & -\frac{\beta_1\Lambda}{\mu} - \frac{d_3}{\mu_y} - \mu_v \end{pmatrix} \tag{19}$$

where

$$d_1 = N_1\mu_1(1 - f_1\xi),\ d_2 = N_2\delta(1 - f_1\xi_1),\ d_3 = \beta_4\lambda(1 - \epsilon_1).$$

Negative eigenvalues from matrix $J(\chi^0)$ *will mean stable disease free equilibrium. Negative trace and positive determinant of the matrix* $J(\chi^0)$ *also means that the eigenvalues of the matrix* $J(\chi^0)$ *are negative and disease free equilibrium is stable. After identifying two negative eigenvalues* $-\mu$ *and* $-\mu_y$ *in first and sixth columns, the matrix reduces to*

$$\mathbf{J_1}(\chi^{\mathbf{0}}) = \begin{pmatrix} \frac{\gamma\Lambda}{\mu} - w_1 & 0 & \frac{\eta\Lambda}{\mu} & 0 & 0 & 0 & 0 & 0 \\ 0 & -w_A & 0 & 0 & 0 & \frac{\tau\Lambda}{\mu} & 0 & \frac{\beta_1\Lambda}{\mu} \\ \rho & 0 & -w_0 & 0 & 0 & 0 & 0 & 0 \\ 0 & \sigma(1-f\epsilon) & 0 & -w_6 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & \frac{\nu\lambda}{\mu_y} - w_3 & 0 & \frac{\theta\lambda}{\mu_y} & 0 \\ 0 & 0 & 0 & 0 & 0 & -w_4 & 0 & \frac{d_3}{\mu_y} \\ 0 & 0 & 0 & 0 & q & 0 & -w_2 & 0 \\ 0 & 0 & 0 & d_1 & 0 & d_2 & 0 & -\frac{\beta_1\Lambda}{\mu} - \frac{d_3}{\mu_y} - \mu_v \end{pmatrix} \tag{20}$$

If we denote trace and determinant of matrix $J_1(\chi^0)$ *by* trJ_1 *and* $detJ_1$*, then trace and determinant are given by*

$$\begin{aligned} trJ_1 &= w_1(R_{ePT} - 1) + w_3(R_{eMP} - 1) - \frac{\beta_1\Lambda}{\mu} - \frac{\beta_4(1-\epsilon_1)}{\mu_y} - \mu_v - w_0 - w_2 \\ &\quad -w_4 - w_A - w_6, \end{aligned} \tag{21}$$

and

$$
\begin{aligned}
detJ_1 &= \Phi\left[\frac{\beta_1\Lambda}{\mu\mu_v}+\frac{\beta_4(1-\epsilon_1)\lambda}{\mu_y\mu_v}+1-R_{eH}\right](1-R_{eff_1})(1-R_{eff_2}),\\
\text{where } R_{eH} &= \frac{\left(\tau\beta_4(1-\epsilon_1)+\beta_1\mu\mu_y w_4\right)\sigma\Lambda N_1\mu_1(1-f_1\xi)(1-f\epsilon)}{\mu\mu_y\mu_v w_A w_4 w_6}\\
&\quad+\frac{N_2\delta(1-f_1\xi_1)\beta_4(1-\epsilon_1)\lambda}{\mu_y\mu_v w_4},\ \Phi=\mu_v w_A w_0 w_1 w_2 w_3 w_4 w_6.
\end{aligned}
\tag{22}
$$

The expressions for R_{ePT} and R_{eMP} are given in (17) *and* (18) *respectively. We find that*

$$
trJ_1<0 \text{ if and only if } R_{ePT}<1 \text{ and } R_{eMP}<1,
\tag{23}
$$

and

$$
\begin{aligned}
&detJ_1>0 \text{ if and only if } R_{eff1}<1,\ R_{eff2}<1\\
&\text{and } R_{eH}<\frac{\beta_1\Lambda}{\mu\mu_v}+\frac{\beta_4(1-\epsilon_1)\lambda}{\mu_y\mu_v}+1.
\end{aligned}
\tag{24}
$$

Non-negative determinant and negative trace represent a model system with locally asymptotically stable disease fee equilibrium when $R_{eff}<1$. However since R_{eff} is the maximum of R_{eff_1} and R_{eff_2}, stable disease free equilibrium will not be realized when $R_{eff_1}>1$ and $R_{eff_2}>1$.

3.2.3. *Global Stability of a Disease Free Equilibrium χ^0. Global stability analysis of a disease free equilibrium is usually done by Lyaponuv functions as applied in (27), (31), (25) and (26), and by comparison theorem as used in (4; 9) and (32). Since Lyapunov functions are not unique and present a challenge in construction, this work adopts comparison theorem in global stability analysis for disease free equilibrium.*

Considering infected classes alone in the model (1)*, we write the system without uninfected compartments by*

$$
(25)\qquad \begin{pmatrix} X_1' \\ X_2' \\ X_3' \\ X_4' \\ Y_1' \\ Y_2' \\ Y_3' \\ V' \end{pmatrix} = (\mathbf{M}-\mathbf{N}) \begin{pmatrix} X_1 \\ X_2 \\ X_3 \\ X_4 \\ Y_1 \\ Y_2 \\ Y_3 \\ V \end{pmatrix} - \begin{pmatrix} (\gamma X_1 + \eta X_3)\left(\frac{\Lambda}{\mu} - X\right) \\ (\tau Y_2 + \beta_1 V)\left(\frac{\Lambda}{\mu} - X\right) \\ 0 \\ 0 \\ (\nu Y_1 + \theta Y_3)\left(\frac{\lambda}{\mu_y} - Y\right) \\ \beta_4 V\left(\frac{\lambda}{\mu_y} - Y\right) \\ 0 \\ L + \beta_1 V\left(X - \frac{\Lambda}{\mu}\right) + \beta_4(1-\epsilon_1)V\left(Y - \frac{\lambda}{\mu_y}\right) \end{pmatrix}
$$

$L = \beta_1 V\frac{\Lambda}{\mu} + \beta_4(1-\epsilon_1)V\frac{\lambda}{\mu_y} + \beta_2 V X_1 + \beta_3(1-f_1\epsilon)VX_3 + \beta_5(1-f\epsilon_1)VY_1 + \beta_6 V(1-f_1\epsilon_1)Y_3.$

Matrices $\mathbf{M}$ *and* $\mathbf{N}$ *represent new infections and transfer terms respectively. For* $t > 0$, $X \leq \frac{\Lambda}{\mu}$ *and* $Y \leq \frac{\lambda}{\mu_y}$ *we see that*

$$
(26)\qquad \begin{pmatrix} X_1' \\ X_2' \\ X_3' \\ X_4' \\ Y_1' \\ Y_2' \\ Y_3' \\ V' \end{pmatrix} \leq (\mathbf{M}-\mathbf{N}) \begin{pmatrix} X_1 \\ X_2 \\ X_3 \\ X_4 \\ Y_1 \\ Y_2 \\ Y_3 \\ V \end{pmatrix}
$$

Since the matrix $\mathbf{M}-\mathbf{N}$ *has negative eigenvalues, equation* (26) *represents a stable disease free equilibrium whereby* $(X,Y) \to \left(\frac{\Lambda}{\mu}, \frac{\lambda}{\mu_y}\right)$ *and* $(X_1, X_2, X_3, X_4, Y_1, Y_2, Y_3, V) \to (0,0,0,0,0,0,0,0)$ *as* $t \to \infty$. *This shows that a disease free equilibrium is globally asymptotically stable. We summarize this result in Theorem 2.*

Theorem 2. : *The disease equilibrium* χ^0 *is globally asymptotically stable when* $(X,Y) \to \left(\frac{\Lambda}{\mu}, \frac{\lambda}{\mu_y}\right)$ *and* $(X_1, X_2, X_3, X_4, Y_1, Y_2, Y_3, V) \to (0,0,0,0,0,0,0,0)$ *for which* $R_{eff} < 1$

3.2.4. *Global stability of endemic equilibrium. By reverse condition as stated by (29) the endemic equilibrium* Υ^* *is locally stable. Lyapunov functions and LaSalle invariant principle are used to analyze global stability of endemic equilibrium* Υ^*. *Using a system* (1), *we define a logarithmic*

Lyapunov function by

$$U_2(T, M, V) = b(T - T^* \ln T) + c(M - M^* \ln M) + d(V - V^* \ln V), \tag{27}$$

T, M and V represent T-cells, macrophages and free virus respectively and T^*, M^* and V^* represent T-cells, macrophages and free virus at endemic equilibrium point. In full, function $U_2(T, M, V)$ is written as

$$\begin{aligned} U_2(T, M, V) &= b_1(X - X^* \ln X) + b_2(X_1 - X_1^* \ln X_1) + b_3(X_2 - X_2^* \ln X_2) \\ &+ b_4(X_3 - X_3^* \ln X_3) + b_5(X_4 - X_4^* \ln X_4) + b_6(Y - Y^* \ln Y) \\ &+ b_7(Y_1 - Y_1^* \ln Y_1) + b_8(Y_2 - Y_2^* \ln Y_2) + b_9(Y_3 - Y_3^* \ln Y_3) \\ &+ b_{10}(V - V^* \ln V). \end{aligned} \tag{28}$$

Derivative of equation (28) *with respect to time, gives*

$$\begin{aligned} \frac{dU_2}{dt} &= b_1\left(1 - \frac{X^*}{X}\right)\frac{dX}{dt} + b_2\left(1 - \frac{X_1^*}{X_1}\right)\frac{dX_1}{dt} + b_3\left(1 - \frac{X_2^*}{X_2}\right)\frac{dX_2}{dt} \\ &+ b_4\left(1 - \frac{X_3^*}{X_3}\right)\frac{dX_3}{dt} + b_5\left(1 - \frac{X_4^*}{X_4}\right)\frac{dX_4}{dt} + b_6\left(1 - \frac{Y^*}{Y}\right)\frac{dY}{dt} \\ &+ b_7\left(1 - \frac{Y_1^*}{Y_1}\right)\frac{dY_1}{dt} + b_8\left(1 - \frac{Y_2^*}{Y_2}\right)\frac{dY_2}{dt} + b_9\left(1 - \frac{Y_3^*}{Y_3}\right)\frac{dY_3}{dt} \\ &+ b_{10}(1 - \frac{V^*}{V})\frac{V}{dt}, \end{aligned} \tag{29}$$

Substitution of the rate of change for each variable at endemic equilibrium, simplification and rearrangements give

$$\begin{aligned} \frac{dU_2}{dt} &= -b_1\mu X\left(1 - \frac{X^*}{X}\right)^2 - b_2w_1X_1\left(1 - \frac{X_1^*}{X_1}\right)^2 - b_3w_AX_2\left(1 - \frac{X_2^*}{X_2}\right)^2 \\ &- b_4w_0X_3\left(1 - \frac{X_3^*}{X_3}\right)^2 - b_5w_6X_4\left(1 - \frac{X_4^*}{X_4}\right)^2 - b_6\mu_yY\left(1 - \frac{Y^*}{Y}\right)^2 \\ &- b_7w_3Y_1\left(1 - \frac{Y_1^*}{Y_1}\right)^2 - b_8w_4Y_2\left(1 - \frac{Y_2^*}{Y_2}\right)^2 - b_9w_2Y_3\left(1 - \frac{Y_3^*}{Y_3}\right)^2 \\ &- b_{10}\mu_vV\left(1 - \frac{V^*}{V}\right)^2 + F_2(X, X_1, X_2, X_3, X_4, Y, Y_1, Y_2, Y_3, V), \end{aligned} \tag{30}$$

where

$$
\begin{aligned}
F_2 = & -b_1\gamma XX_1\left(1-\frac{X^*}{X}\right)\left(1-\frac{X^*X_1^*}{XX_1}\right)-b_1\eta XX_3\left(1-\frac{X^*}{X}\right)\left(1-\frac{X^*X_3^*}{XX_3}\right)\\
& -b_1\beta_1 VX\left(1-\frac{X^*}{X}\right)\left(1-\frac{V^*X^*}{VX}\right)-b_1\tau Y_2X\left(1-\frac{X^*}{X}\right)\left(1-\frac{Y_2^*X^*}{Y_2X}\right)\\
& -b_2\beta_2 VX_1\left(1-\frac{X_1^*}{X_1}\right)\left(1-\frac{V^*X_1^*}{VX}\right)-b_4\beta_3(1-f_1\epsilon)VX_3\left(1-\frac{X_3^*}{X_3}\right)\left(1-\frac{V^*X_3^*}{VX_3}\right)\\
& -b_6\beta_4(1-\epsilon_1)VY\left(1-\frac{Y^*}{Y}\right)\left(1-\frac{V^*Y^*}{VY}\right)-b_6\nu YY_1\left(1-\frac{Y^*}{Y}\right)\left(1-\frac{Y^*Y_1^*}{YY_1}\right)\\
& -b_6\theta YY_3\left(1-\frac{Y^*}{Y}\right)\left(1-\frac{Y^*Y_3^*}{YY_3}\right)-b_7\beta_5(1-f\epsilon_1)VY_1\left(1-\frac{Y_1^*}{Y_1}\right)\left(1-\frac{V^*Y_1^*}{VY_1}\right)\\
& -b_9\beta_6(1-f_1\epsilon_1)VY_3\left(1-\frac{Y_3^*}{Y_3}\right)\left(1-\frac{V^*Y_3^*}{VY_3}\right)-b_{10}\beta_1 VX\left(1-\frac{V^*}{V}\right)\left(1-\frac{V^*X^*}{VX}\right)\\
& -b_{10}\beta_2 VX_1\left(1-\frac{V^*}{V}\right)\left(1-\frac{V^*X_1^*}{VX_1}\right)-b_{10}\beta_3 VX_3\left(1-\frac{V^*}{V}\right)\left(1-\frac{V^*X_3^*}{VX_3}\right)\\
& -b_{10}\beta_4 VY\left(1-\frac{V^*}{V}\right)\left(1-\frac{V^*Y^*}{VY}\right)-b_{10}\beta_5 VY_1\left(1-\frac{V^*}{V}\right)\left(1-\frac{V^*Y_1^*}{VY_1}\right)\\
& -b_{10}\beta_6 VY_3\left(1-\frac{V^*}{V}\right)\left(1-\frac{V^*Y_3^*}{VY_3}\right).
\end{aligned}
\tag{31}
$$

Following the approach in (22) and (20), F_2 is non-positive. Function $F_2 \leq 0$ for $X, X_1, X_2, X_3, X_4, Y, Y_1, Y_2, Y_3, V > 0$. The time derivative $\frac{dU_2}{dt} \leq 0$ when $X, X_1, X_2, X_3, X_4, Y, Y_1, Y_2, Y_3, V > 0$, for $X = X^*$, $X_1 = X_1^*$, $X_2 = X_2^*$, $X_3 = X_3^*$, $X_4 = X_4^*$, $Y = Y^*$, $Y_1 = Y_1^*$, $Y_2 = Y_2^*$, $Y_3 = Y_3^*$, $V = V^*$, $\frac{dU_2}{dt} = 0$. This indicates that, the largest invariant set Υ for which $\frac{dU_2}{dt} = 0$ is a singleton Υ^* which is endemic equilibrium. Using LaSalle Invariant Principle (18), Υ^* is globally stable in the interior of Υ when $R_{eff} > 1$. This result is summarized in the following theorem

Theorem 3. : *If $R_{eff} > 1$, then the model system (1) has unique endemic equilibrium Υ^* which is globally asymptotically stable in the interior of Υ^*.*

4. Numerical Analysis

In this section we illustrate the effect of tobacco smoking on antiretroviral therapy, and we show existence and stability of equilibrium states numerically. As smoking interferes with metabolism of antiretroviral drugs, stability of equilibrium states is assessed by considering infected and non infected classes. The simulation results on how smoking affects ARVs on the dynamics of HIV among T-cells and macrophages are discussed. We use parameter values in Table 4.1 to simulate the model using MATLAB (Version 7.1.0.246 (R14) Service Pack 3).

Table 4.1: Parameter values

Parameter	**Value/Unit**	**Source**
Λ	600 $year^{-1}$	*Assumed*
k	12	*(3)*
c	110 $year^{-1}$	*(14)*
λ	100 $\frac{cells}{ml\ yaer}$	*(8)*
γ	0.0025 $year^{-1}$	*(10)*
η	0.007 $year^{-1}$	*Assumed*
ρ	0.785 $year^{-1}$	*Assumed*
σ	0.45 $year^{-1}$	*Assumed*
μ	0.135 $year^{-1}$	*(8)*
β_1	0.00876 $\frac{ml}{virus\ year}$	*(26)*
β_2	0.0012 $\frac{ml}{virus\ year}$	*(7)*
β_3	0.0016 $\frac{ml}{virus\ year}$	*(10)*
β_4	0.0002 $\frac{ml}{virus\ year}$	*(8)*
β_5	0.0004 $\frac{ml}{virus\ year}$	*(8)*
β_6	0.0005 $\frac{ml}{virus\ year}$	*(8)*
ν	0.0016 $year^{-1}$	*Assumed*
θ	0.003 $year^{-1}$	*Assumed*
μ_1	0.775 $year^{-1}$	*Assumed*
μ_y	0.0351 $year^{-1}$	*(10)*
δ	0.25 $year^{-1}$	*(8)*
μ_v	50 $year^{-1}$	*Assumed*
α_1	0.03 $year^{-1}$	*Assumed*
α	0.102 $year^{-1}$	*Assumed*
τ	0.000365 $year^{-1}$	*(14)*
q	0.38 $year^{-1}$	*Assumed*
N_1	100 $year^{-1}$	*(26)*
N_2	100 $year^{-1}$	*(8)*
$\varpi \& \vartheta$	0.1 & 0.5	*Assumed*
$\zeta_1 \& \zeta_2$	0.5 &0.6	*Assumed*
$\kappa_1 \& \kappa_2$	0.9 &0.92	*Assumed*

In this section, we begin by plotting the general dynamics for model (1)*. Figure 4.1 shows the dynamics among HIV in T-cells and macrophages when smoking induces metabolism of ARVs*

at a rate 0.3. *The dynamics show the existence of unstable disease free equilibrium between* 0 *and* 2 *years. During this time interval, uninfected T-cells and healthy macrophages grow slightly. However, smoking compartments indicate a fast growth compared to HIV compartments which take over later.*

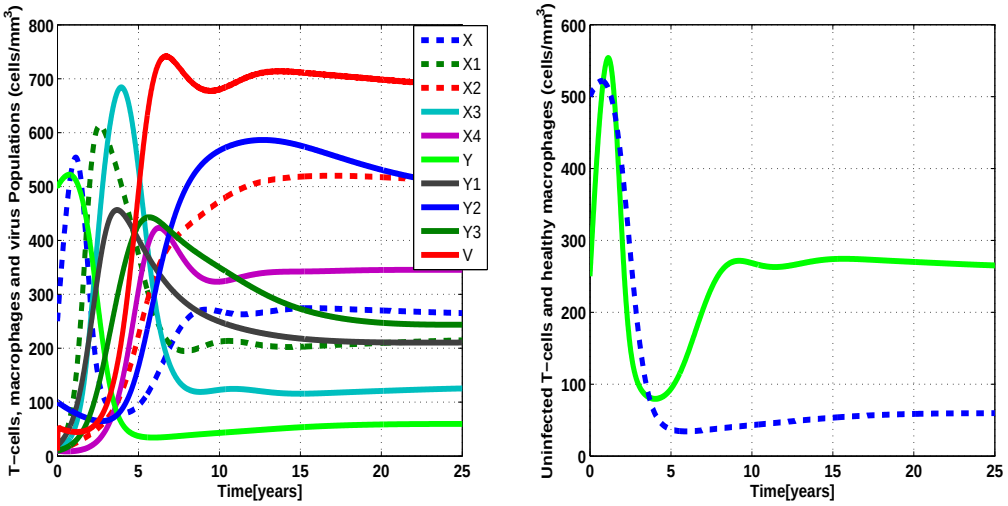

FIGURE 4.1. Variation of cells' populations in the general dynamics when a HIV smoker is under therapy.

To show the endemic equilibrium, we plot HIV infected and smoking impaired classes and they are shown in Figure 4.2. Smoking impaired classes increase between 0 *and* 5 *years and on their downfall HIV infected classes and free virus increases.*

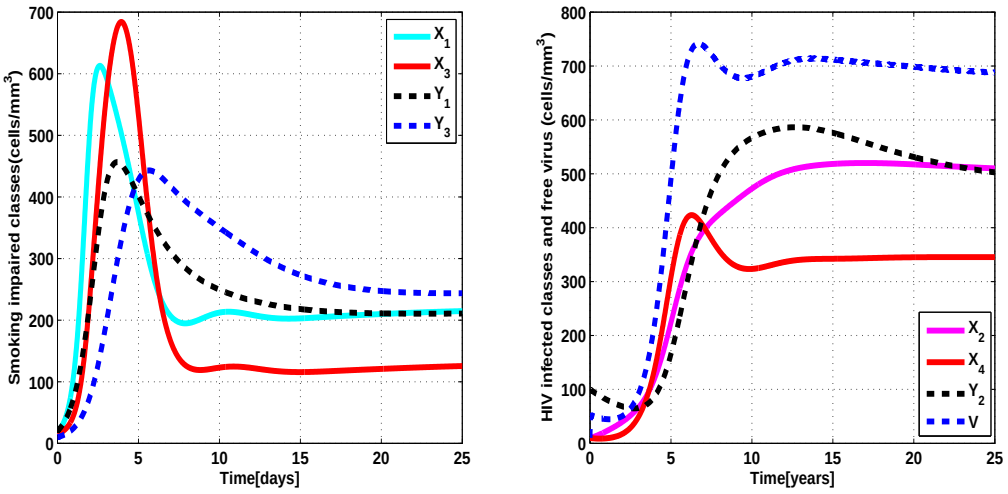

FIGURE 4.2. Variation of HIV infected and smoking impaired classes with time.

We have shown unstable disease free and endemic equilibriums, now we assess the effect of tobacco smoking on the antiretroviral drugs by looking into how HIV latently and actively infected T-cells, HIV infected macrophages and free virus behave when smoking interferes metabolism of

ARVs.

In Figures 4.3 and 4.4, HIV actively infected T-cells, HIV infected macrophages and free virus increase correspondingly with increasing in interference of ARVs' metabolism. This shows that smoking interference in metabolism of ARVs reduces drugs' efficacy. For HIV latently infected T-cells as antiretroviral drugs are taken, they increase from 0 *to* 10 *years. However from* 10 *years and above HIV latently infected T-cells decreases as smoking interference with metabolism of ARVs increases. This is the time when ARVs becomes ineffective due to tobacco smoking.*

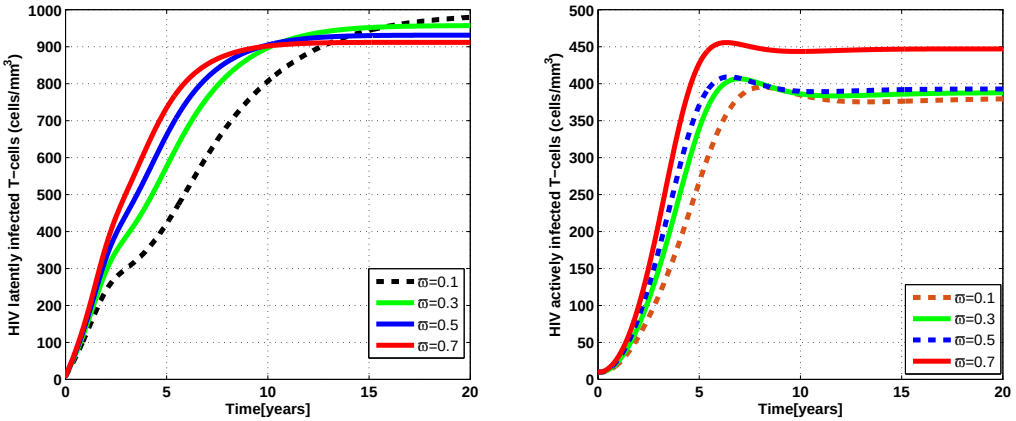

FIGURE 4.3. Variation of HIV actively and latently infected T-cells with respect to smoking inducing effect.

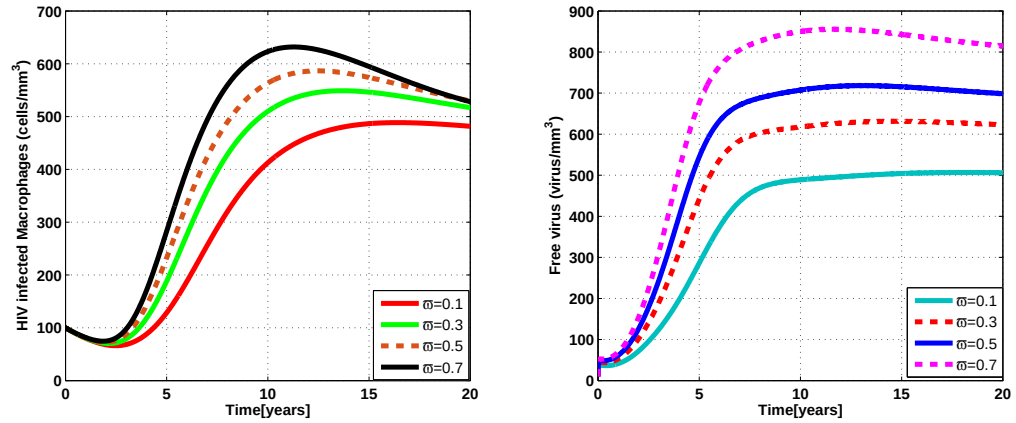

FIGURE 4.4. Variation of HIV infected macrophages and free virus with respect to smoking inducing effect.

We study stability of endemic equilibrium in the dynamics of HIV in T-cells and macrophages by considering uninfected T-cells and macrophages, smoking partially and critically impaired classes, HIV infected T-cells and macrophages and free virus. Figures 4.5, 4.6, 4.7 and 4.8 show the trajectories for mentioned compartments. The trajectories for different initial conditions converge to a single point as time goes on. This indicate the existence of endemic equilibrium which we

already established earlier. Convergence for trajectories indicates that endemic equilibrium exists, and it is globally asymptotically stable whenever it exists.

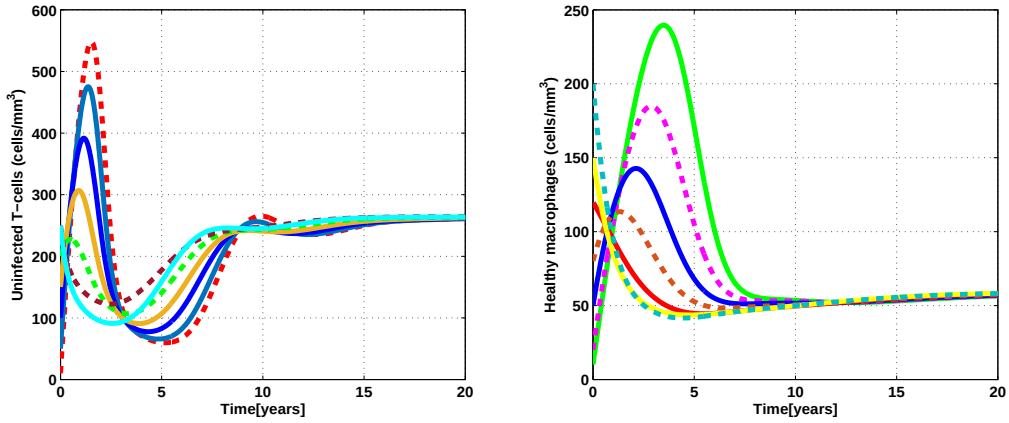

FIGURE 4.5. Trajectories of uninfected T-cells and healthy macrophages.

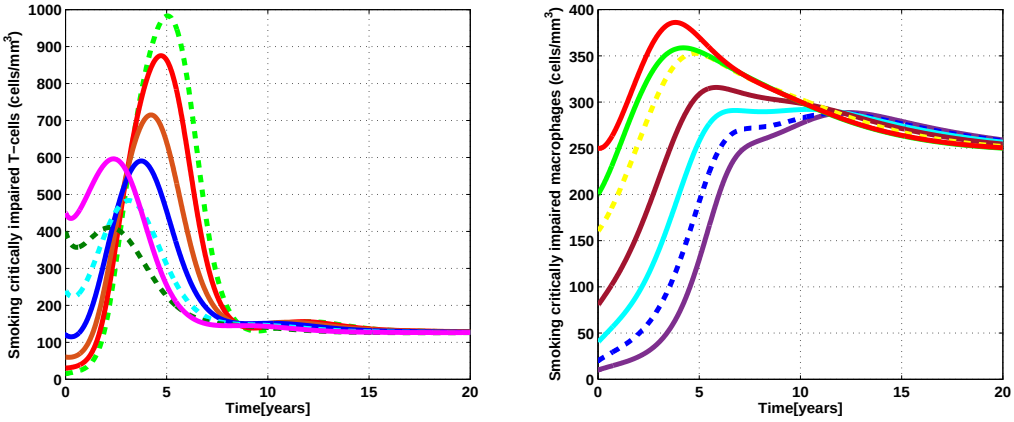

FIGURE 4.6. Trajectories of Smoking critically impaired T-cells and macrophages.

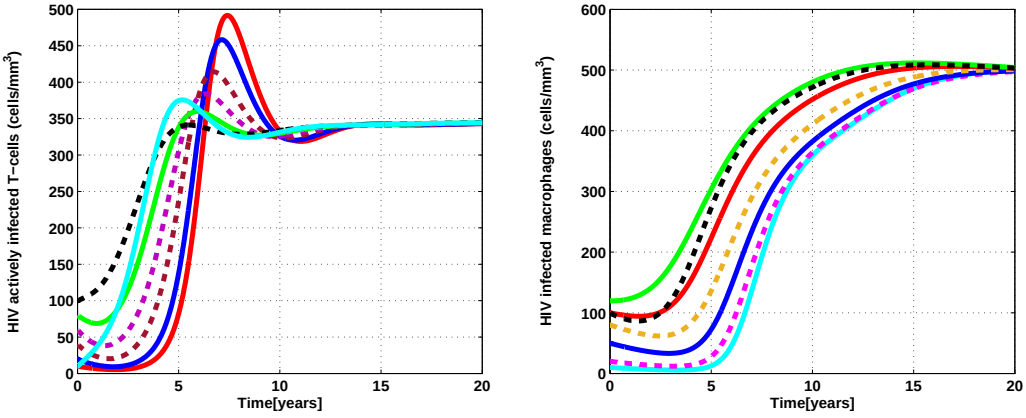

FIGURE 4.7. Trajectories of HIV actively infected T-cells and macrophages.

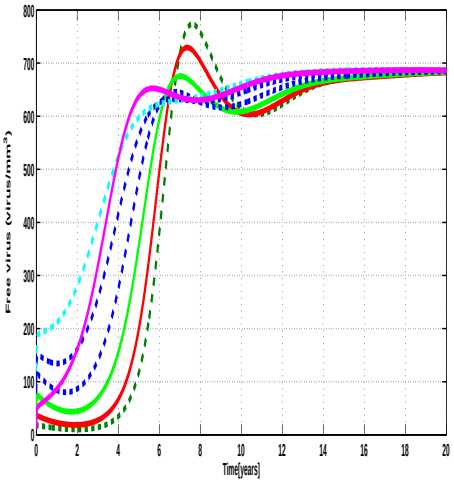

FIGURE 4.8. Trajectories of free virus.

5. CONCLUSION

A mathematical model to determine the effect of tobacco smoking on antiretroviral therapy and assess stability of equilibrium states is presented and analyzed. The effective reproduction number R_{eff} *is computed by using next generation approach (29) and it is given as the maximum of partial effective reproduction numbers due to tobacco smoking in T-cells* R_{eff_1} *and macrophages* R_{eff_2}*. The disease free equilibrium is shown to be globally asymptotically stable when* $R_{eff} < 1$*. However with the parameters that we have used in simulation,* R_{eff_1} *and* R_{eff_2} *are not less than unit. Since* R_{eff} *is the maximum of* R_{eff_1} *and* R_{eff_2}*, it will never be less than unity and the classical requirement of* $R_{eff} < 1$ *for global stability of disease free equilibrium cannot be achieved. Therefore tobacco smoking affects stability of disease free equilibrium.*

Numerical simulation indicates that the unstable disease free equilibrium and stable endemic equilibrium exist. Convergence of trajectories in Figures 4.5, 4.6, 4.7 and 4.8 proves the existence of endemic equilibrium and its stability. Endemic equilibrium is asymptotically stable whenever it exists when $R_{eff} > 1$*. Simulation indicates that tobacco smoking reduces the efficacy of antiretroviral therapy. This is reflected by increase of free virus, HIV infected T-cells and macrophages when smoking induces metabolism of ARVs.*

Conflict of interest

The authors declare no conflict of interest.

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