MODELING TOBACCO SMOKING EFFECT ON HIV ANTIRETROVIRAL THERAPY

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Abstract. In this paper, we formulate a mathematical model to study how tobacco smoking affects antiretroviral therapy. The model is based on the fact that smoking induces metabolism of ARVs and HIV patient addiction to smoking affects adherence to drugs. Equilibrium states and effective reproduction number R_{ef} are computed. Conditions for equilibria stability are derived. The model shows that in the absence of tobacco smoking and HIV, disease free equilibrium is stable when $R_{ef} < 1$ and in the presence of tobacco smoking and HIV, endemic equilibrium is stable when $R_{ef} > 1$. The analysis shows that tobacco smoking decreases the efficacy of antiretroviral therapy and this effect is critical when smoking induces metabolism of antiretroviral drugs by 30% to 70%. Even if a HIV infected smoker remains adherent to therapy, still the effect of tobacco smoking on drugs' efficacy is inevitable. For management of HIV epidemic and its therapy, abstinence from smoking by HIV patients is recommended.

Keywords: tobacco smoking; HIV; in-host dynamics; antiretroviral therapy; T-cells; drug interaction; induction.

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1. Introduction

The world has been suffering from HIV pandemic for over three decades now, with Sub Saharan Africa which has the majority of HIV infected individuals being a focal point for the pandemic [22, 24, 33]. Lack of vaccine and life prolonging drugs has led to significantly high AIDS mortality rate among HIV infected individuals. Antiretroviral drugs have dramatically reduced HIV morbidity and mortality from opportunistic infections, they reconstitute patients' immune system and improve their lives [16, 26, 27]. Under therapy CD4+ T-cells which are mostly devastated by HIV, regain their number by increasing production in the bone marrow [14].

Administration of antiretroviral drugs blocks a specific stage of HIV life cycle within a CD4+ T-cell. During the infection, a HIV virion attaches to the cell and inserts its genetic material in the form of RNA into the cell when fusion takes place [7]. The viral RNA in the host cell is reverse transcribed into viral DNA by protein reverse transcriptase and this DNA is then integrated into the DNA of host cell by the integrase [7, 32]. Fusion inhibitors block fusion between the virus and the cell [5], Reverse Transcriptase Inhibitors (RTIs) block viral reverse transcription and Protease Inhibitors (PIs) block production of infectious virions.

Though antiretroviral drugs suppress the virus and improve quality of life [3], risk behaviour such as tobacco smoking negates and undermine the benefits of antiretroviral therapy among HIV infected individuals [10, 15]. Apart from causing anergy and unresponsiveness to T-cells [30, 31], tobacco smoking generation of poisonous, toxic and carcinogenic multi-components [4, 28] interferes with metabolism of antiretroviral drugs. Nicotine which, in particular, is a main component of tobacco smoke induces the enzymes which are involved in metabolism of antiretroviral drugs (NNRTIs and PIs) [1, 25]. Induction decreases the drugs' concentration and reduce their absorption [2].

Few cohort studies which have addressed the effect of tobacco smoking on the antiretroviral drugs concentrated on how tobacco smoking affects adherence to antiretroviral drugs [9, 15, 18, 23, 29] and ignore drug interaction. Though tobacco smoking is mentioned to affect adherence to antiretroviral drugs there have been inconsistent results as there are studies which claim the

effect of tobacco smoking on drugs' adherence [9, 10, 18] and there are some which do not claim tobacco smoking effect on drugs' adherence [23, 29].

A cohort study by Feldman et al.[10] considering a group of low-income women who are infected with HIV in highly active antiretroviral therapy era suggests that, smoking can negate antiretroviral therapy because it leads to poor viral responses, high risk of virologic rebound and immunologic failure. The study emphasizes that poor viral responses, virologic rebound and immunologic failure are due to non adherence to the therapy. According to the study, adherence to therapy is associated with high viral response and less viral and immunologic failure.

In this study mathematical modeling is used to explore the effect of tobacco smoking on antiretroviral therapy. For the best of our knowledge no study has ever used dynamical model to study the effect of tobacco smoking on antiretroviral therapy. However, mathematical models on antiretroviral therapy and its impact on HIV in-host dynamics have been developed. [14] developed a three components (Uninfected CD4+ T-cells, HIV infected CD4+ T-cells and Virus) model to determine threshold count of CD4+ T-cells for which treatment can be initiated without emergence of drug resistance. Srivastava et al.[32] extends a three components model to include pre and post-reverse transcription CD4+ T-cells. Li and Wang [17] included reverse transcriptase inhibitors in a three components model and show backward bifurcation due to viral rebound after ART stoppage. Consideration of tobacco smoking and HIV within the host differentiates our model from the rest and it the first attempt to model tobacco smoking effect on antiretroviral therapy.

This work is organized into the following order; in the next Section we formulate the model and carry out analysis, numerical analysis is done in following Section and we conclude with discussions.

2. Materials and Methods

2.1. Model formulation

In this section we formulate the model by considering antiretroviral drugs: Reverse Transcription Inhibitors (RTIs) and Protease Inhibitors (PIs). The model divides T-cells into five

classes: 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. The density of free virus is represented by V.

The expression $\Lambda - \dfrac{cV}{k+V}$ which is a decreasing function of free virus [6, 14] is a recruitment rate for T-cells. The expression $\gamma X_1 + \eta X_3$ represents smoking 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 and β_2 represent HIV infection rates for uninfected T-cells X and smoking partially impaired T-cells X_1 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 $\beta_3(1 - f_1\varepsilon)$ where ε such that $0 \le \varepsilon \le 1$ is the efficacy of RTIs in blocking reverse transcription in T-cells and $f_1(\varpi) = \dfrac{e^{-\varpi}}{\varpi + 1}$ is the smoking effect in inducing metabolism of ARVs in critically impaired T-cells, $\varpi \in (0,1)$ 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 $\sigma(1 - f\varepsilon)$ where $f = e^{-\varpi}$ models smoking inducing effect in partially impaired T-cells. Functions f and f_1 model relative smoking inducing effect in smoking partially and critically impaired T-cells as we assume smoking critically impaired T-cells experience high smoking inducing effect compared to smoking partially impaired T-cells. However, if ζ_1 denotes drugs' reverse transcription blocking rate in T-cells and ϑ adherence rate to treatment, then $\varepsilon = \zeta_1\vartheta$. 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 results into production of infectious virions at a rate $N\mu_1(1 - f_1\xi)$, $\xi = \kappa\vartheta$ such that $0 \le \xi \le 1$ 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 N is the number of infectious virions produced by each T-cell.

Free virus increase at a rate $N\mu_1(1-f_1\xi)$, they decrease due to fusion with T-cells to cause HIV infection at rates β_1VX, β_2VX_1, $\beta_3(1-f_1\varepsilon)$ and due to natural mortality at a rate μ_v.

The model assumes that, 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 as their reverse transcription is spontaneous. The model also assumes that unresponsiveness of T-cells increases with smoking rate. Interaction of variables is shown in Figure 1, state variables and model parameters are described in Tables 1 and 2
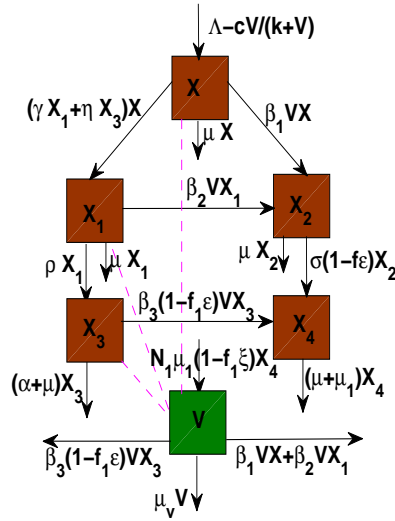

FIGURE 1. Interaction of T-cells with HIV virions and tobacco smoking in the presence of therapy.

Table 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
γ	rate of impairment from partially impaired CD4+ T-cells

Table 2 – *Continued from previous page*

Parameters	Description
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
μ_v	natural mortality rate for free virus
α	smoking induced death rate for impaired CD4+ T-cells
N_1	Number of virus released by a T-cell over the life time
ε	RTIs efficacies in T-cells
ξ	PIs efficacies in T-cells
ϖ	Smoking induction rate in metabolism of RTIs and PIs

Considering the relationship between variables, parameters and assumptions, the model is governed by the following system of differential equations;

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

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

(1c)
$$\frac{dX_2}{dt} = \beta_1 VX + \beta_2 VX_1 - (\sigma(1 - f\varepsilon) + \mu)X_2,$$

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

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

(1f)
$$\frac{dV}{dt} = N_1\mu_1(1 - f_1\xi)X_4 - \beta_1 VX - \beta_2 VX_1 - \beta_3(1 - f_1\varepsilon)VX_3 - \mu_v V,$$

TABLE 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
V	Free virus

subject to initial conditions $X(0) = X_0$, $X_1(0) = 0$, $X_2(0) = 0$, $X_3(0) = 0$, $X_4(0) = 0$, $V(0) = V_0$.

2.2. Model Analysis

2.2.1. Boundedness of solutions

Summing equations for T-cells in system (1), we obtain

$$
\begin{aligned}
\frac{d}{dt}(X + X_1 + X_2 + X_3 + X_4) \ &= \Lambda - \frac{cV}{k+V} - \mu(X + X_1 + X_2 + X_3 + X_4) \\
&\quad - \alpha X_3 - \mu X_4, \\
&\leq \Lambda - \mu(X + X_1 + X_2 + X_3 + X_4)
\end{aligned}
$$
(2)

If we denote $T_t = X + X_1 + X_2 + X_3 + X_4$, from (2) we have

$$
\frac{dT_t}{dt} \leq \Lambda - \mu T_t,
$$
(3)

which results into

$$
\frac{dT_t}{dt} + \mu T_t \leq \Lambda.
$$
(4)

Applying integration factor $e^{\mu t}$, the general solution of equation (4) is given by

$$
T_t(t) \leq \frac{\Lambda}{\mu} + \left(T_t(0) - \frac{\Lambda}{\mu} \right) e^{-\mu t}.
$$
(5)

We consider two cases to determine limiting solution in equation (5), when $T_t(0) \geq \dfrac{\Lambda}{\mu}$ and when $T_t(0) \leq \dfrac{\Lambda}{\mu}$.

(6)
$$\text{If } T_t(0) \geq \frac{\Lambda}{\mu},$$
$$\frac{\Lambda}{\mu} \leq T_t \leq \frac{\Lambda}{\mu} + \left(T_t(0) - \frac{\Lambda}{\mu} \right) e^{-\mu t}.$$

This implies that when $T_t(0) \geq \dfrac{\Lambda}{\mu}$, the RHS of equation (5) is positive and decreasing implying that $T_t(0)$ is the maximum value.

(7)
$$\text{If } T_t(0) \leq \frac{\Lambda}{\mu},$$
$$\frac{\Lambda}{\mu} + \left(T_t(0) - \frac{\Lambda}{\mu} \right) e^{-\mu t} \leq T_t \leq \frac{\Lambda}{\mu}.$$

This shows that when $T_t(0) \leq \dfrac{\Lambda}{\mu}$, the RHS of equation (5) is negative and increasing implying $\dfrac{\Lambda}{\mu}$ is the maximum value. Hence

$$(8) \qquad\qquad T_t \leq \Phi_t = max \left\{ \frac{\Lambda}{\mu}, T_t(0) \right\}.$$

Generally we see that

$$(9) \qquad\qquad X + X_1 + X_2 + X_3 + X_4 \leq \Phi_t.$$

This result implies that both uninfected and infected T-cells are bounded. It follows that

$$(10) \qquad\qquad\qquad X_4 \leq \Phi_t$$

From equation (1f), it can be shown that V is also bounded. We consider the equation

(11)
$$\frac{dV}{dt} = N_1 \mu_1 (1 - f_1 \xi) X_4 - \beta_1 V X - \beta_2 V X_1 - \beta_3 V X_3 - \mu_v V,$$
$$\leq N_1 \mu_1 (1 - f_1 \xi) X_4 - \mu_v V,$$

Using equation (10), it is seen that

$$(12) \qquad \frac{dV}{dt} + \mu_v V \leq max \left\{ \frac{\Lambda N_1 \mu_1 (1 - f_1 \xi)}{\mu}, N_1 \mu_1 (1 - f_1 \xi) T_t(0) \right\}$$

which works out to be

(13)
$$V \leq \Psi_0,$$
$$\Psi_0 = max \left\{ \frac{\Lambda N_1 \mu_1 (1 - f_1 \xi)}{\mu \mu_v}, \frac{N_1 \mu_1 (1 - f_1 \xi) T_0}{\mu_v} \right\}$$

The upper bound for free virus depends on the efficacy of PIs ξ and the magnitude of the effect of tobacco smoking f_1. We find that, the system (1) is positive invariant in the set

$$(14) \qquad \Pi_2 = \left\{ (X, X_1, X_2, X_3, X_4, V) \in R_+^6 : 0 \leq T_t \leq \Phi_t : 0 \leq V \leq \Psi_0 \right\}$$

The solutions of the model (1) which start at the boundary of the region Π_2 converge in the region. Results for existence, uniqueness and continuity hold in the region Π_2, hence the flow generated by the model (1) can now be considered in its analysis. This result is restated in the following theorem **Theorem 2.1.** The solutions of the model system (1) are bounded in the region

$$\Pi_2 = \left\{ (X, X_1, X_2, X_3, X_4, V) \in R_+^6 : 0 \leq T_t \leq \Phi_t : 0 \leq V \leq \Psi_0 \right\}$$

2.2.2. Disease Free Equilibrium and Effective reproduction Number R_{ef}

The model system (1) has disease free equilibrium given by

$$(15) \qquad \left(X^0, X_1^0, X_2^0, X_3^0, X_4^0, V^0 \right) = \left(\frac{\Lambda}{\mu}, 0, 0, 0, 0, 0 \right)$$

In this steady state, the immune system is strong and responds accordingly to infections. CD4+ T-cells perform their role as expected. To show the potentials of ARVs on HIV in the presence of tobacco smoking, we compute effective reproduction number R_{ef} in next section.

2.2.2.1. Effective reproduction Number R_{ef}

The average new impairments due to tobacco smoking and the average new infections due to HIV in the presence of antiretroviral therapy are measured by effective reproduction number R_{ef} which is computed by next generation approach [34]. The effective reproduction number R_{ef} determines how antiretroviral therapy averts new infections and measures the effect of tobacco smoking on ARVs. Using infected classes in the model system (1), the vectors for new

infections $\mathbf{H_i}$ and transfer terms $\mathbf{Z_i}$ are:

$$(16) \qquad \mathbf{H_i} = \begin{pmatrix} (\gamma X_1 + \eta X_3)X \\ \beta_1 VX + \beta_2 VX_1 \\ 0 \\ \beta_3(1 - f_1\varepsilon)VX_3 \\ N_1\mu_1(1 - f_1\xi)X_4 \end{pmatrix} \text{ and } \mathbf{Z_i} = \begin{pmatrix} (\rho + \mu)X_1 \\ (\sigma(1 - f\varepsilon) + \mu)X_2 \\ (\alpha + \mu)X_3 - \rho X_1 \\ (\mu_1 + \mu)X_4 - \sigma(1 - f\varepsilon)X_2 \\ \mu_v V \end{pmatrix}$$

The matrices $\mathbf{H}$ and $\mathbf{Z}$ work out to be

$$(17) \qquad \mathbf{H} = \begin{pmatrix} \dfrac{\gamma\Lambda}{\mu} & 0 & \dfrac{\eta\Lambda}{\mu} & 0 & 0 \\ 0 & 0 & 0 & 0 & \dfrac{\beta_1\Lambda}{\mu} \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & N_1\mu_1(1 - f_1\xi) & 0 \end{pmatrix}$$

and

$$(18) \qquad \mathbf{Z} = \begin{pmatrix} (\rho + \mu) & 0 & 0 & 0 & 0 \\ 0 & (\sigma(1 - f\varepsilon) + \mu) & 0 & 0 & 0 \\ -\rho & 0 & (\alpha + \mu) & 0 & 0 \\ 0 & -\sigma(1 - f\varepsilon) & 0 & (\mu_1 + \mu) & 0 \\ 0 & 0 & 0 & 0 & \mu_v \end{pmatrix}.$$

If we denote the effective reproduction number for T-cells by R_{ef} such that

$$(19) \qquad R_{ef} = \rho\left(\mathbf{HZ^{-1}}\right),$$

we find that

$$R_{ef} = max\{R_{eS}, R_{eA}\}, \text{ where}$$

$$(20) \qquad R_{eS} = \frac{\gamma\Lambda}{\mu(\rho + \mu)} + \frac{\eta\rho\Lambda}{\mu(\rho + \mu)(\alpha + \mu)},$$

$$R_{eA} = \sqrt{\frac{N_1\mu_1(1 - f_1\xi)\beta_1\Lambda\sigma(1 - f\varepsilon)}{\mu\mu_v(\mu_1 + \mu)(\sigma(1 - f\varepsilon) + \mu)}}.$$

The threshold quantities R_{eS} and R_{eA} are partial effective reproduction numbers due to tobacco smoking and HIV respectively. The partial effective reproduction number due to HIV R_{eA} depends on efficacies of antiretroviral therapy in blocking reverse transcription ε and production of infectious virus ξ, the rate at which smoking affects drugs' efficacy in blocking reverse transcription f and the rate at which smoking affects drugs' efficacy in blocking production of infectious virions f_1.

2.2.2.2. Analysis of partial effective reproduction number R_{eA}

To analyze partial effective reproduction number due to HIV R_{eA}, we write it as a function of efficacies of antiretroviral drugs in blocking reverse transcription and production of infectious virions, and the rate at which smoking affects the efficacy of antiretroviral drugs. The partial effective reproduction number is therefore:

$$(21) \qquad R_{eA}(\varpi, \varepsilon, \xi) = \sqrt{\frac{N_1 \mu_1 (\varpi + 1 - \xi e^{-\varpi}) \beta_1 \Lambda \sigma (1 - \varepsilon e^{-\varpi})}{\mu \mu_v (\varpi + 1)(\mu_1 + \mu)(\sigma(1 - \varepsilon e^{-\varpi}) + \mu)}}.$$

Variation of the effective reproduction number R_{eA} with respect to the efficacy of antiretroviral therapy in blocking reverse transcription in partially impaired T-cells ε gives

$$(22) \qquad \frac{\partial R_{eA}}{\partial \varepsilon} = -\frac{\beta_1 \Lambda \sigma N_1 \mu_1 e^{-\varpi}(\varpi + 1 - \xi e^{-\varpi})}{2\mu_v \sqrt{R_{eA}}(\mu_1 + \mu)(\varpi + 1)(\sigma(1 - \varepsilon e^{-\varpi}) + \mu)^2} < 0$$

and variation of R_{eA} with respect to the efficacy of antiretroviral therapy in blocking production of infectious virions ξ, gives

$$(23) \qquad \frac{\partial R_{eA}}{\partial \xi} = -\frac{N_1 \mu_1 \beta_1 \Lambda \sigma e^{-\varpi}(1 - \varepsilon e^{-\varpi})}{2\mu \mu_v \sqrt{R_{eA}}(\mu_1 + \mu)(\varpi + 1)(\sigma(1 - \varepsilon e^{-\varpi}) + \mu)} < 0.$$

Equations (22) and (23) show that if tobacco smoking does not induce metabolism of antiretroviral drugs, they can avert HIV new infections within a HIV smoker successfully. Since tobacco smoking affects antiretroviral therapy by inducing their metabolism [25] and by reducing drugs' adherence [10], we express the efficacy of the antiretroviral drugs as a product of drugs' blocking rate and adherence rate. We assess the effect of tobacco smoking on the efficacies of antiretroviral drugs by differentiating partial effective reproduction number R_{eA} with respect to the rate at which smoking induces metabolism of antiretroviral drugs ϖ and adherence rate ϑ

to obtain:

(24)
$$\frac{\partial R_{eA}}{\partial \varpi} = \frac{N_1 \mu_1 \beta_1 \Lambda \sigma e^{-\varpi}}{2\mu\mu_v g(\varpi)\sqrt{R_{eA}}} \left[1 + e^{-\varpi}(\xi + \varpi\varepsilon - 2\xi\varepsilon e^{-\varpi}) - \frac{\Gamma_1(\varepsilon,\varpi)}{(\sigma(1-\varepsilon e^{-\varpi})+\mu)(1+\varpi)} \right],$$

$$g(\varpi) = (\mu_1 + \mu)(\varpi + 1)(\sigma(1-\varepsilon e^{-\varpi})+\mu),$$

$$\Gamma_1(\varepsilon,\varpi) = (1-\varepsilon e^{\varpi})(1+\varpi-\varepsilon e^{-\varpi})[\sigma(1-\varepsilon e^{-\varpi})+\mu+\varepsilon e^{-\varpi}(1+\varpi)]$$

and

(25)
$$\frac{\partial R_{eA}}{\partial \vartheta} = \frac{N_1 \mu_1 \beta_1 \Lambda \sigma e^{-\varpi}}{2\mu\mu_v g(\varpi)\sqrt{R_{eA}}(\sigma(1-\varepsilon e^{-\varpi})+\mu)^2}[\sigma\zeta_1(\varpi+1-\kappa\vartheta e^{-\varpi})(1-\zeta_1\vartheta e^{-\varpi})$$
$$+\zeta_1\vartheta e^{-\varpi}(\kappa+1)(\sigma(1-\zeta_1\vartheta e^{-\varpi})+\mu) - (\sigma(1-\zeta_1\vartheta e^{-\varpi})+\mu)(1+\zeta_1(\varpi+1))].$$

We find that:

(26)
$$\frac{\partial R_{eA}}{\partial \varpi} > 0 \text{ iff } 1 + e^{-\varpi}(\xi + \varpi\varepsilon - 2\xi\varepsilon e^{-\varpi}) > \frac{\Gamma_1(\varepsilon,\varpi)}{(\sigma(1-\varepsilon e^{-\varpi})+\mu)(1+\varpi)},$$

and

(27)
$$\frac{R_{eA}}{\partial \vartheta} < 0 \text{ iff } \sigma\zeta_1(\varpi+1-\kappa\vartheta e^{-\varpi})(1-\zeta_1\vartheta e^{-\varpi})$$
$$+\zeta_1\vartheta e^{-\varpi}(\kappa+1)(\sigma(1-\zeta_1\vartheta e^{-\varpi})+\mu) > (\sigma(1-\zeta_1\vartheta e^{-\varpi})+\mu)(1+\zeta_1(\varpi+1))$$

If tobacco smoking continues and equation (26) holds, the efficacy of antiretroviral drugs will decrease as smoking inducing effect increases, this will result into increased HIV new infections and decreasing the number of CD4+ T-cells. However, if equation (27) holds, adherence to drugs will reduce HIV new infections significantly but as adherence drops, new infections will increase.

2.2.3. Stability Analysis of Disease Free Equilibrium

In this section local and global stabilities of disease free equilibrium are investigated using linearization method, Hurwitz criterion and comparison theorem.

2.2.3.1. Local stability of Disease free equilibrium

The system (1) is linearized at disease free equilibrium to obtain a matrix

$$(28) \quad \mathbf{J_A} = \begin{pmatrix} -\mu & -\dfrac{\gamma\Lambda}{\mu} & 0 & -\dfrac{\eta\Lambda}{\mu} & 0 & -\dfrac{\mu C + \beta_1\Lambda k}{\mu k} \\ 0 & \dfrac{\gamma\Lambda}{\mu} - w_1 & 0 & \dfrac{\eta\Lambda}{\mu} & 0 & 0 \\ 0 & 0 & -w_A & 0 & 0 & \dfrac{\beta_1\Lambda}{\mu} \\ 0 & \rho & 0 & -w_0 & 0 & 0 \\ 0 & 0 & \sigma(1-f\varepsilon) & 0 & -w_6 & 0 \\ 0 & 0 & 0 & 0 & N_1\mu_1(1-f_1\xi) & -\dfrac{\beta_1\Lambda}{\mu} - \mu_v \end{pmatrix}$$

Local stability of disease free equilibrium holds if the matrix J_A has negative eigenvalues. From the first column of the matrix J_A, we find the eigenvalue $-\mu < 0$. The matrix then reduces to

$$(29) \quad \mathbf{J_B} = \begin{pmatrix} \dfrac{\gamma\Lambda}{\mu} - w_1 & 0 & \dfrac{\eta\Lambda}{\mu} & 0 & 0 \\ 0 & -w_A & 0 & 0 & \dfrac{\beta_1\Lambda}{\mu} \\ \rho & 0 & -w_0 & 0 & 0 \\ 0 & \sigma(1-f\varepsilon) & 0 & -w_6 & 0 \\ 0 & 0 & 0 & N_1\mu_1(1-f_1\xi) & -\dfrac{\beta_1\Lambda}{\mu} - \mu_v \end{pmatrix}$$

whose characteristic equation is

$$(30) \qquad b_5\lambda^5 + b_4\lambda^4 + b_3\lambda^3 + b_2\lambda^2 + b_1\lambda + b_0 = 0,$$

where

$$b_5 = \mu^2, b_4 = \mu^2 w_0(1-R_{PT}) + \mu(\beta_1\Lambda + \mu(\mu_v + w_A + w_1 + w_6)),$$

$$b_3 = \mu^2[w_0 w_1(1-R_{eS}) + w_A w_6] + \mu(\beta_1\Lambda + mu\mu_v)(w_A + w_6)$$

$$+\mu[\Lambda\beta_1 + \mu(\mu_v + w_A + w_6)][w_1 + w_0(1-R_{PT})],$$

$$b_2 = \mu[(\Lambda\beta_1 + \mu\mu_v)(w_A + w_6) + \mu w_A w_6][w_1 + w_0(1-R_{PT})]$$

$$+\mu w_0 w_1[\Lambda\beta_1 + \mu(\mu_v + w_A + w_6)](1-R_{eS})$$

$$+\mu w_A w_6[\beta_1\Lambda + \mu\mu_v(1+R_{eA})(1-R_{eA})],$$

$$b_1 = \mu w_0 w_1[(\beta_1\Lambda + \mu\mu_v)(w_A + w_6) + \mu w_A w_6](1-R_{eS})$$

$$+\mu w_A w_6[\beta_1\Lambda + \mu\mu_v(1+R_{eA})(1-R_{eA})][w_1 + w_0(1-R_{PT})],$$

$$b_0 = \mu w_0 w_1 w_A w_6[\beta_1\Lambda + \mu\mu_v(1+R_{eA})(1-R_{eA})](1-R_{eS}).$$

The system (1) has a stable disease free equilibrium if the coefficients of the polynomial (30) obey the following conditions:

$$b_5 > 0, b_4 > 0, b_3 > 0, b_2 > 0, b_1 > 0, b_0 > 0,$$

(31)
$$b_2 b_5 - b_3 b_4 < 0 \text{ and } b_0 b_3 - b_1 b_2 < 0 \text{ or}$$

$$b_2 b_5 - b_3 b_4 < 0 \text{ and } b_0 b_3 - b_1 b_2 + b_3(b_4 - b_5) < 0.$$

From the polynomial (30), we see that

(32)
$$b_5 > 0, b_4 > 0, b_3 > 0, b_2 > 0, b_1 > 0, b_0 > 0$$

if and only if

(33)
$$R_{eS} < 1 \text{ and } R_{eA} < 1.$$

This implies that, the coefficients of a polynomial (30) do not change sign when there is low smoking rate and low HIV infection rate. Using coefficients of polynomial (30)

$$
\begin{aligned}
b_2 b_5 - b_3 b_4 \ =\ & \mu^2 [(\Lambda \beta_1 + \mu \mu_v)(w_A + w_6) + \mu w_A w_6](w_1 + w_0(1 - R_{PT})) \\
& + \mu^2 w_0 w_1 [\Lambda \beta_1 + \mu(\mu_v + w_A + w_6)](1 - R_{eS}) + \mu^2 w_A w_6 [\Lambda \beta_1 \\
& + \mu \mu_v (1 + R_{eA})(1 - R_{eA})] - \mu^3 w_0 [\Lambda \beta_1 + \mu(\mu_v + w_A + w_6)](w_1 \\
& + w_0(1 - R_{PT}))(1 - R_{PT}) - \mu^3 w_0 [\mu[w_0 w_1(1 - R_{eS}) + w_A w_6] \\
& + (\Lambda \beta_1 + \mu \mu_v)(w_A + w_6)](1 - R_{PT}) - \mu^2 [\mu[w_0 w_1(1 - R_{eS}) \\
& + w_A w_6] + (\beta_1 \Lambda + \mu \mu_v)(w_A + w_6)](\beta_1 \Lambda + \mu B) \\
& - \mu^2 (\beta_1 \Lambda + \mu(\mu_v + w_A + w_6))(\beta_1 \Lambda + \mu B)[w_1 + w_0(1 - R_{PT})], \\
B \ =\ & \mu_v + w_1 + w_A + w_6.
\end{aligned}
$$

$$b_2 b_5 - b_3 b_4 < 0 \text{ if and only if}$$

$$
\begin{aligned}
(34) \quad & [(\Lambda\beta_1 + \mu\mu_v)(w_A + w_6) + \mu w_A w_6](w_1 + w_0(1 - R_{PT})) \\
& + w_0 w_1[\Lambda\beta_1 + \mu(\mu_v + w_A + w_6)](1 - R_{eS}) + w_A w_6[\Lambda\beta_1 \\
& + \mu\mu_v(1 + R_{eA})(1 - R_{eA})] < \mu w_0[\Lambda\beta_1 + \mu(\mu_v + w_A + w_6)](w_1 \\
& + w_0(1 - R_{PT}))(1 - R_{PT}) + \mu w_0[\mu[w_0 w_1(1 - R_{eS}) + w_A w_6] \\
& + (\Lambda\beta_1 + \mu\mu_v)(w_A + w_6)](1 - R_{PT}) + [\mu[w_0 w_1(1 - R_{eS}) \\
& + w_A w_6] + (\beta_1\Lambda + \mu\mu_v)(w_A + w_6)](\beta_1\Lambda + \mu B) \\
& + (\beta_1\Lambda + \mu(\mu_v + w_A + w_6))(\beta_1\Lambda + \mu B)[w_1 + w_0(1 - R_{PT})]
\end{aligned}
$$

$$
\begin{aligned}
b_0 b_3 - b_1 b_2 \ = \ & \mu^3 w_0 w_1 w_6[\Lambda\beta_1 + \mu\mu_v(1 + R_{eA})(1 - R_{eA})][w_0 w_1(1 - R_{eS}) \\
& + w_A w_6](1 - R_{eS}) + \mu^2 w_0 w_1 w_A w_6(\beta_1\Lambda + \mu\mu_v)(w_A + w_6)[\Lambda\beta_1 \\
& + \mu\mu_v(1 + R_{eA})(1 - R_{eA})](1 - R_{eS}) + \mu^2 w_0 w_1 w_A w_6 D[\Lambda\beta_1 \\
& + \mu\mu_v(1 + R_{eA})(1 - R_{eA})](w_1 + w_0(1 - R_{PT}))(1 - R_{eS}) \\
& - \mu^2 w_0 w_1[(\beta_1\Lambda + \mu\mu_v)(w_A + w_6) + \mu w_A w_6]^2(w_1 + w_0(1 - R_{pT}))(1 - R_{eS}) \\
& - \mu^2 w_0^2 w_1^2 D[(\beta_1\Lambda + \mu\mu_v)(w_A + w_6) + \mu w_A w_6](1 - R_{eS}) \\
& - \mu^2 w_0 w_1 w_A w_6[\Lambda\beta_1 + \mu\mu_v(1 + R_{eA})(1 - R_{eA})][(\beta_1\Lambda + \mu\mu_v)(w_A + w_6) \\
& + \mu w_A w_6](1 - R_{eS}) - \mu^2 w_A w_6[(\beta_1\Lambda + \mu\mu_v)(w_A + w_6) + \mu w_A w_6][\Lambda\beta_1 \\
& + \mu\mu_v(1 + R_{eA})(1 - R_{eA})](w_1 + w_0(1 - R_{PT}))^2 - \mu^2 w_0 w_1 w_A w_6 D[\Lambda\beta_1 \\
& + \mu\mu_v(1 + R_{eA})(1 - R_{eA})](w_1 + w_0(1 - R_{PT}))(1 - R_{eS}) \\
& - \mu^2 w_A^2 w_6^2[\Lambda\beta_1 + \mu\mu_v(1 + R_{eA})(1 - R_{eA})]^2(w_1 + w_0(1 - R_{PT})), \\
D \ = \ & \Lambda\beta_1 + \mu(\mu_v + w_A + w_6).
\end{aligned}
$$

$$
b_0 b_3 - b_1 b_2 < 0 \text{ if and only if,}
$$

$$
\begin{aligned}
&\mu w_0 w_1 w_6 [\Lambda \beta_1 + \mu \mu_v (1 + R_{eA})(1 - R_{eA})][w_0 w_1 (1 - R_{eS}) \\
&+ w_A w_6](1 - R_{eS}) + w_0 w_1 w_A w_6 (\beta_1 \Lambda + \mu \mu_v)(w_A + w_6)[\Lambda \beta_1 \\
&+ \mu \mu_v (1 + R_{eA})(1 - R_{eA})](1 - R_{eS}) + w_0 w_1 w_A w_6 D[\Lambda \beta_1 \\
&+ \mu \mu_v (1 + R_{eA})(1 - R_{eA})](w_1 + w_0(1 - R_{PT}))(1 - R_{eS}) \\
&< w_0 w_1 [(\beta_1 \Lambda + \mu \mu_v)(w_A + w_6) + \mu w_A w_6]^2 (w_1 + w_0(1 - R_{pT}))(1 - R_{eS}) \\
(35) \quad &+ w_0^2 w_1^2 D[(\beta_1 \Lambda + \mu \mu_v)(w_A + w_6) + \mu w_A w_6](1 - R_{eS}) \\
&+ w_0 w_1 w_A w_6 [\Lambda \beta_1 + \mu \mu_v (1 + R_{eA})(1 - R_{eA})][(\beta_1 \Lambda + \mu \mu_v)(w_A + w_6) \\
&+ \mu w_A w_6](1 - R_{eS}) + w_A w_6 [(\beta_1 \Lambda + \mu \mu_v)(w_A + w_6) + \mu w_A w_6][\Lambda \beta_1 \\
&+ \mu \mu_v (1 + R_{eA})(1 - R_{eA})](w_1 + w_0(1 - R_{PT}))^2 + w_0 w_1 w_A w_6 D[\Lambda \beta_1 \\
&+ \mu \mu_v (1 + R_{eA})(1 - R_{eA})](w_1 + w_0(1 - R_{PT}))(1 - R_{eS}) \\
&+ w_A^2 w_6^2 [\Lambda \beta_1 + \mu \mu_v (1 + R_{eA})(1 - R_{eA})]^2 (w_1 + w_0(1 - R_{PT})).
\end{aligned}
$$

The equations (34) and (35) hold if

$$
(36) \qquad\qquad\qquad R_{eS} < 1 \text{ and } R_{eA} < 1.
$$

Local stability of disease free equilibrium is concluded in the following theorem: **Theorem 2.2.** Disease free equilibrium of the model (1) is locally asymptotically stable if equations (34) and (35) hold and $R_{eS} < 1$ and $R_{eA} < 1$, it is unstable otherwise.

2.2.3.2. Global stability of Disease free equilibrium

The global stability of disease free equilibrium is investigated by using comparison theorem as applied by Diekmann et al.[8]. We state and prove the Theorem . **Theorem 2.2.** Disease free equilibrium is globally asymptotically stable if $R_{ef} < 1$ when $(X_1, X_2, X_3, X_4, V) \to (0,0,0,0,0)$ and $X \to \dfrac{\Lambda}{\mu}$.

Proof

Using comparison theorem the infected classes of the model (1) are written as

(37)

$$
\begin{pmatrix} X_1' \\ X_2' \\ X_3' \\ X_4' \\ V' \end{pmatrix} = (H - Z) \begin{pmatrix} X_1 \\ X_2 \\ X_3 \\ X_4 \\ V \end{pmatrix} - \begin{pmatrix} (\gamma X_1 + \eta X_3)\left(\dfrac{\Lambda}{\mu} - X\right) \\ \beta_1 V \left(\dfrac{\Lambda}{\mu} - X\right) \\ 0 \\ 0 \\ \beta_1 V \dfrac{\Lambda}{\mu} + \beta_2 V X_1 + \beta_3 (1 - f_1 \varepsilon) V X_3 + \beta_1 V \left(X - \dfrac{\Lambda}{\mu}\right) \end{pmatrix}
$$

Since $X \leq \dfrac{\Lambda}{\mu}$ for $t > 0$, it follows that;

(38)
$$
\begin{pmatrix} X_1' \\ X_2' \\ X_3' \\ X_4' \\ V' \end{pmatrix} \leq (H - Z) \begin{pmatrix} X_1 \\ X_2 \\ X_3 \\ X_4 \\ V \end{pmatrix}
$$

The matrix $H - Z$ has negative eigenvalues, equation (38) will hold if and only if $X \to \dfrac{\Lambda}{\mu}$, $(X_1, X_2, X_3, X_4, V) \to (0, 0, 0, 0, 0)$ and $R_{ef} < 1$ and this completes the proof.

2.2.4. Existence and Stability of Endemic Equilibrium

2.2.4.1. Existence of Endemic Equilibrium

The two epidemics tobacco smoking and HIV are endemic when there is high rate of tobacco smoking and HIV infection. The endemic equilibrium of the model system (1) is defined by

(39) $$\Pi_2^* = \{(X^*, X_1^*, X_2^*, X_3^*, X_4^*, V^*) \geq 0\},$$

where

(40)

$$
X^* = \frac{(\beta_2 V^* + w_1)(\beta_3 V^*(1 - f_1\varepsilon) + w_0)}{\gamma(\beta_3 V^*(1 - f_1\varepsilon) + w_0) + \eta\rho},
$$

$$
X_1^* = \frac{k\Lambda + \Phi V^*}{(k + V^*)(\beta_2 V^* + w_1)} - \frac{(\beta_1 V^* + \mu)(\beta_3 V^*(1 - f_1\varepsilon) + w_0)}{\gamma(\beta_3 V^*(1 - f_1\varepsilon) + w_0) + \eta\rho},
$$

$$
X_2^* = \frac{\beta_2(k\Lambda + \Phi V^*)V^*}{w_A(k + V^*)(\beta_2 V^* + w_1)} + \frac{(\beta_3 V^*(1 - f_1\varepsilon) + w_0)(\beta_1 w_1 - \mu\beta_2)V^*}{w_A\gamma(\beta_3 V^*(1 - f_1\varepsilon) + w_0) + w_A\eta\rho},
$$

$$
X_3^* = \frac{\rho(k\Lambda + \Phi V^*)}{(k + V^*)(\beta_2 V^* + w_1)(\beta_3 V^*(1 - f_1\varepsilon) + w_0)} - \frac{\rho(\beta_1 V^* + \mu)}{\gamma(\beta_3 V^*(1 - f_1\varepsilon) + w_0) + \eta\rho},
$$

$$
X_4^* = \frac{\sigma(\beta_1 w_1 - \mu\beta_2)(1 - f\varepsilon)(\beta_3 V^*(1 - f_1\varepsilon) + w_0) - w_A\rho\beta_3(1 - f_1\varepsilon)(\beta_1 V^* + \mu)}{w_A w_6[\gamma(\beta_3 V^*(1 - f_1\varepsilon) + w_0) + \eta\rho]}
$$
$$
+ \frac{(k\Lambda + \Phi V^*)[\sigma\beta_2\beta_3(1 - f\varepsilon)(1 - f_1\varepsilon)V^* + \varepsilon_0]}{w_A w_6(k + V^*)(\beta_2 V^* + w_1)[\beta_3 V^*(1 - f_1\varepsilon) + w_0]}
$$

The expressions of X^*, X_1^*, X_2^*, X_3^* and X_4^* are in terms of free virus V^*. We obtain free virus V^* which determines the number of endemic equilibria by substituting X^*, X_1^*, X_2^*, X_3^* in the equation $\dfrac{dV}{dt}$ at equilibrium. There are multiple endemic equilibria.

2.2.4.2. Global stability of endemic equilibrium

Local stability of disease free equilibrium in Π_2 imply local stability of endemic equilibrium by reverse condition [34], we therefore proceed with global stability of endemic equilibrium. Lyapunov function and LaSalle's invariance principle have been useful in analysis of global stability of endemic equilibrium. In this work, logarithmic Lyapunov function as applied by Mpeshe et al.[20] and Mpeshe et al.[21] is used to investigate the stability of endemic equilibrium given in equation (40).

Logarithmic Lyapunov function U is defined by

(41)
$$
U = \sum a_i(X_i - X_i^* \ln X_i),
$$

where a_i are positive constants, X_i^* is an equilibrium point and X_i is a density of cells or free virus in compartment i. Using logarithmic Lyapunov function (41) while T-cells' compartments are represented by T, a system (1) is written as

(42)
$$
\begin{aligned}
U(T,V) &= a_1(X - X^* \ln X) + a_2(X_1 - X_1^* \ln X_1) + a_3(X_2 - X_2^* \ln X_2) \\
&\quad + a_4(X_3 - X_3^* \ln X_3) + a_5(X_4 - X_4^* \ln X_4) + a_6(V - V^* \ln V)
\end{aligned}
$$

Differentiation of equation (42) with respect to time gives

$$
\begin{aligned}
\frac{dU}{dt} &= a_1\left(1-\frac{X^*}{X}\right)\frac{dX}{dt} + a_2\left(1-\frac{X_1^*}{X_1}\right)\frac{dX_1}{dt} + a_3\left(1-\frac{X_2^*}{X_2}\right)\frac{dX_2}{dt} \\
&\quad + a_4\left(1-\frac{X_3^*}{X_3}\right)\frac{dX_3}{dt} + a_5\left(1-\frac{X_5^*}{X_5}\right)\frac{dX_5}{dt} + a_6\left(1-\frac{V^*}{V}\right)\frac{dV}{dt}, \\
&= a_1\left(1-\frac{X^*}{X}\right)\left[\Lambda - \frac{cV}{k+V} - (\gamma X_1 + \eta X_3)X - \beta_1 VX - \mu X\right] \\
&\quad + a_2\left(1-\frac{X_1^*}{X_1}\right)\left[(\gamma X_1 + \eta X_3)X - \beta_2 VX_1 - (\rho + \mu)X_1\right] \\
&\quad + a_3\left(1-\frac{X_2^*}{X_2}\right)\left[\beta_1 VX + \beta_2 VX_1 - (\sigma(1-f\varepsilon)+\mu)X_2\right] \\
&\quad + a_4\left(1-\frac{X_3^*}{X_3}\right)\left[\rho X_1 - \beta_3(1-f_1\varepsilon)VX_3 - (\alpha+\mu)X_3\right] \\
&\quad + a_5\left(1-\frac{X_5^*}{X_5}\right)\left[\sigma(1-f\varepsilon)X_2 + \beta_3(1-f_1\varepsilon)VX_3 - (\mu_1+\mu)X_4\right] \\
&\quad + a_6\left(1-\frac{V^*}{V}\right)\left[N_1\mu_1(1-f_1\xi)X_4 - \beta_1 VX - \beta_2 VX_1 - \beta_3 VX_3 - \mu_v V\right].
\end{aligned}
$$

At endemic equilibrium Π_2^*, we have

$$
\begin{aligned}
\frac{dU}{dt} &= a_1\left(1-\frac{X^*}{X}\right)\left[(\gamma X_1^* + \eta X_3^*)X^* + \beta_1 V^* X^* + \mu X^* - (\gamma X_1 + \eta X_3)X - \beta_1 VX - \mu X\right] \\
&\quad + a_2\left(1-\frac{X_1^*}{X_1}\right)\left[\beta_2 V^* X_1^* + (\rho+\mu)X_1^* - \beta_2 VX_1 - (\rho+\mu)X_1\right] \\
&\quad + a_3\left(1-\frac{X_2^*}{X_2}\right)\left[(\sigma(1-f\varepsilon)+\mu)X_2^* - (\sigma(1-f\varepsilon)+\mu)X_2\right] \\
&\quad + a_4\left(1-\frac{X_3^*}{X_3}\right)\left[\beta_3(1-f_1\varepsilon)V^* X_3^* + (\alpha+\mu)X_3^* - \beta_3(1-f_1\varepsilon)VX_3 - (\alpha+\mu)X_3\right] \\
&\quad + a_5\left(1-\frac{X_5^*}{X_5}\right)\left[(\mu_1+\mu)X_4^* - (\mu_1+\mu)X_4\right] \\
&\quad + a_6\left(1-\frac{V^*}{V}\right)\left[\beta_1 V^* X^* + \beta_2 V^* X_1^* + \beta_3 V^* X_3^* + \mu_v V^* - \beta_1 VX - \beta_2 VX_1 - \beta_3 VX_3 - \mu_v V\right].
\end{aligned}
$$

Simplifications and rearrangement give

$$
\begin{aligned}
\frac{dU}{dt} &= -a_1\mu X\left(1-\frac{X^*}{X}\right)^2 - a_2(\rho+\mu)X_1\left(1-\frac{X_1^*}{X_1}\right)^2 \\
&\quad -a_3(\sigma(1-f\varepsilon)+\mu)X_2\left(1-\frac{X_2^*}{X_2}\right)^2 - a_4(\alpha+\mu)X_3\left(1-\frac{X_3^*}{X_3}\right)^2 \\
&\quad -a_5(\mu_1+\mu)X_4\left(1-\frac{X_5^*}{X_5}\right)^2 - a_6\mu_v V\left(1-\frac{V^*}{V}\right)^2 + F(\Pi_2)
\end{aligned}
\tag{43}
$$

where

$$
\begin{aligned}
(44) \quad F(\Pi_2) =& \, a_1\gamma X X_1 \left(1 - \frac{X^*}{X}\right)(1 - \frac{X^*X_1^*}{XX_1}) - a_1\eta X X_3 \left(1 - \frac{X^*}{X}\right)(1 - \frac{X^*X_3^*}{XX_3}) \\
&- a_1\beta_1 V X \left(1 - \frac{X^*}{X}\right)(1 - \frac{V^*X^*}{VX}) - a_2\beta_2 V X_1 \left(1 - \frac{X_1^*}{X_1}\right)(1 - \frac{V^*X_1^*}{VX_1}) \\
&- a_4\beta_3(1 - f_1\varepsilon)V X_3 \left(1 - \frac{X_3^*}{X_3}\right)\left(1 - \frac{V^*X_3^*}{VX_3}\right) - a_6\beta_1 V X \left(1 - \frac{V^*}{V}\right)\left(1 - \frac{V^*X^*}{VX}\right) \\
&- a_6\beta_2 V X_1 \left(1 - \frac{V^*}{V}\right)\left(1 - \frac{V^*X_1^*}{VX_1}\right) - a_6\beta_3(1 - f_1\varepsilon)V X_3 \left(1 - \frac{V^*}{V}\right)\left(1 - \frac{V^*X_3^*}{VX_3}\right)
\end{aligned}
$$

Following equations (43) and (44), F is non-positive [19, 22]. Therefore it follows that $F \le 0$ for $X, X_1, X_2, X_3, X_4, V > 0$. This implies that $\frac{dU}{dt} \le 0$ for $X, X_1, X_2, X_3, X_4, V > 0$ and it is zero when $X = X^*$, $X_1 = X_1^*$, $X_2 = X_2^*$, $X_3 = X_3^*$, $X_4 = X_4^*$, $V = V^*$. This indicates that the largest compact invariant set Π_2 in which $\frac{dU}{dt} = 0$ is the singleton Π_2^* which is the endemic equilibrium. By LaSalle invariant principle, Π_2^* is globally asymptotically stable in the interior of Π_2 when $R_{ef} > 1$. We summarize this result in the following theorem

Theorem 2.1. If the effective reproduction number for T-cells $R_{ef} > 1$, then the model system (1) has a unique endemic equilibrium Π_2^* which is globally asymptotically stable in the interior of Π_2.

3. Numerical Analysis and Discussions

In this section numerical results for the model system (1) are presented and discussed by considering two scenarios; the case when tobacco smoking induces metabolism of ARVs without affecting drugs' adherence and the case when tobacco smoking induces metabolism of ARVs and affects drug adherence. However, we start with the general dynamics when smoking induces metabolism of ARVs and when it does not induce metabolism of ARVs. Using parameter values in Table 3, the model is simulated using MAT LAB (Version 7.1.0.246 (R14) Service Pack 3).

Table 3: Parameter values

Parameter	Value/Unit	Source
Λ	600 $year^{-1}$	Assumed
k	12	cite6
c	110 $year^{-1}$	[14]
λ	100 $\frac{cells}{ml\ yaer}$	[12]
γ	0.0025 $year^{-1}$	[13]
η	0.007 $year^{-1}$	Assumed
ρ	0.785 $year^{-1}$	Assumed
σ	0.45 $year^{-1}$	Assumed
μ	0.135 $year^{-1}$	[12]
β_1	0.00876 $\frac{ml}{virus\ year}$	[32]
β_2	0.0012 $\frac{ml}{virus\ year}$	[11]
β_3	0.0016 $\frac{ml}{virus\ year}$	[13]
μ_1	0.775 $year^{-1}$	Assumed
μ_v	50 $year^{-1}$	Assumed
α	0.102 $year^{-1}$	Assumed
N_1	100 $year^{-1}$	[32]
$\varpi \& \vartheta$	0.1 & 0.5	Assumed
ζ_1	0.5	Assumed
κ_1	0.9	Assumed

3.1. Tobacco smoking effect on antiretroviral therapy in the general dynamics

In this case we plot all compartments when smoking induces metabolism of ARVs and when it does not to determine its effect. When smoking does not induce metabolism of ARVs, free

virus and HIV infected classes record minimum number of virus and T-cells respectively while smoking impaired classes grow to their peak between 4 and 6 years. Uninfected T-cells record a decrease due to smoking impairment and HIV infection. However when smoking induces metabolism of ARVs, free virus and HIV infected T-cells increase because the efficacy of ARVs is attenuated by smoking. Smoking impaired classes attain their maximum number between 2 and 4 years, uninfected T-cells fall below 100 between 2 and 4 years. Figure 2 demonstrates the case when smoking induces metabolism of ARVs and when it does not.
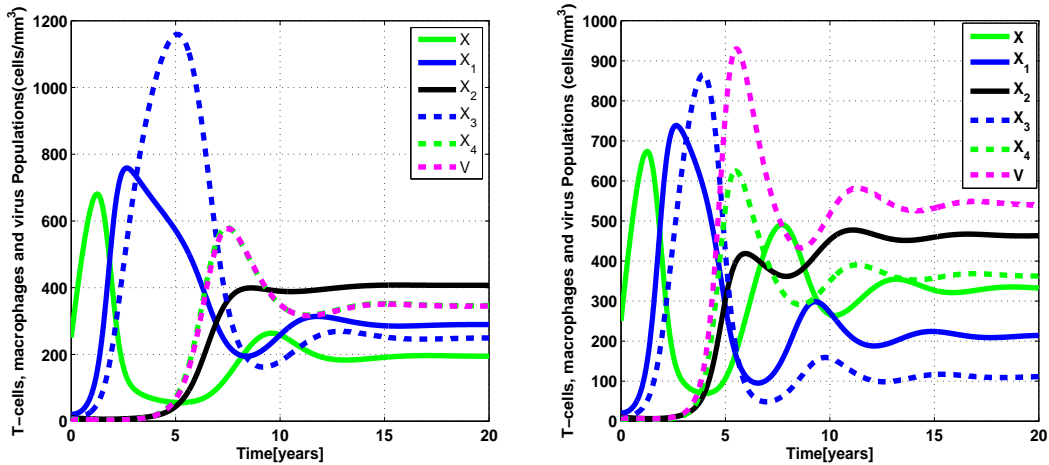
FIGURE 2. General dynamics when $\varpi = 0$ and when $\varpi = 0.5$.

3.2. The case when smoking induces metabolism of ARVs and does not affect drugs' adherence

When $\varpi = 0$ smoking has no effect to antiretroviral drugs, therefore ARVs block reverse transcription and production of infectious virions thus slows HIV infections. In this case we see more T-cells in smoking impaired classes and few HIV actively infected T-cells and free virus as demonstrated by dotted lines in Figures 3 and 4. T-cells in smoking impaired classes increase from 0 to 3 years where they attain their peak. However they decrease after 3 years, this decreasing effect is severe between 5 to 10 years as indicated by dotted line in Figure 3. Since ARVs are not 100% effective, free virus and HIV actively infected T-cells increase slowly and peak after 8 years as shown by dotted line in Figure 4. The increasing effect of free virus is associated with high HIV infection which decreases T-cells in smoking impaired classes. Both

T-cells and free virus decrease slightly after 8 years and become constant.

When tobacco smoking induces metabolism of antiretroviral drugs at a rate $\varpi = 0.3$, HIV actively infected T-cells and free virus increase correspondingly as shown by full lines in Figure 4, T-cells in smoking impaired classes decrease dramatically as demonstrated by full lines in Figure 3. Between 8 and 9 years HIV actively infected T-cells overlap when $\varpi = 0$ and $\varpi = 0.3$. This is due to the fact that, HIV actively infected T-cells when $\varpi = 0.3$ replicate first before the HIV actively infected T-cells when $\varpi = 0$, this causes HIV actively infected T-cells when $\varpi = 0.3$ to decline and overlap HIV actively infected T-cells when $\varpi = 0$. However, between 9 and 10 years, HIV actively infected T-cells when $\varpi = 0$ replicate and maintain their former position.
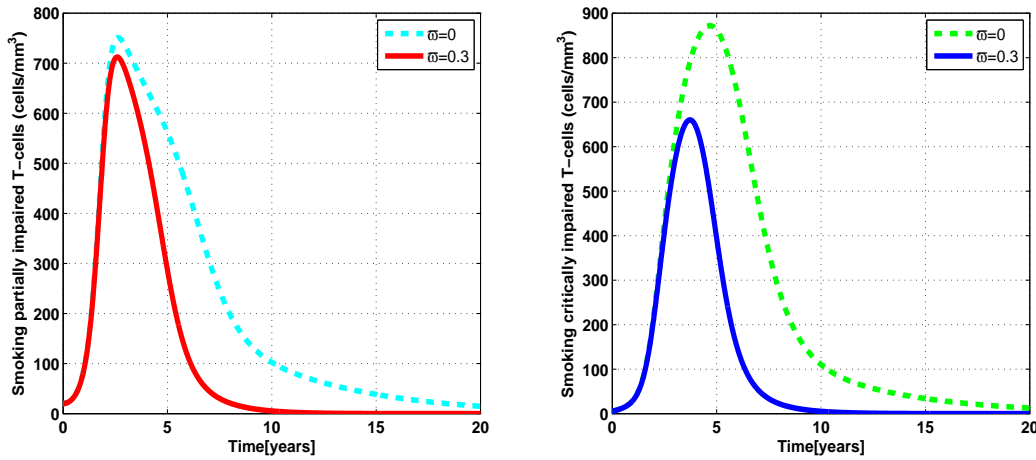

FIGURE 3. Smoking impaired classes when $\varpi = 0$ and $\varpi = 0.3$.

As smoking inducing effect increases, HIV actively infected T-cells and free virus increase and peak in 6 years. The increase in HIV actively infected T-cells is not significant and they overlap due to intracellular delay during replication. Free virus decrease slightly between 9 and 10 years due to the immune response and remain constant throughout. HIV actively infected T-cells and free virus are illustrated by Figure 6.

As HIV actively infected T-cells and free virus increase, smoking partial and critical impaired
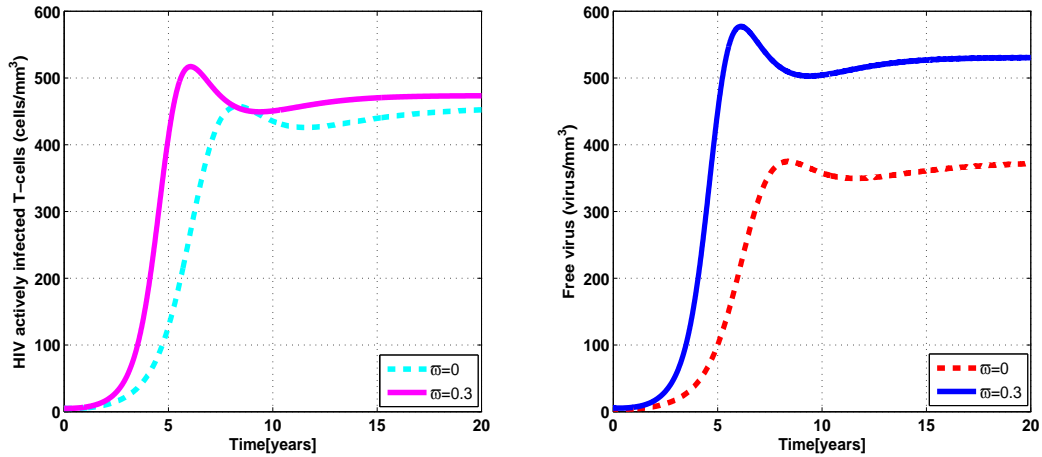
FIGURE 4. HIV actively infected T-cells and free virus when $\varpi = 0$ and $\varpi = 0.3$.
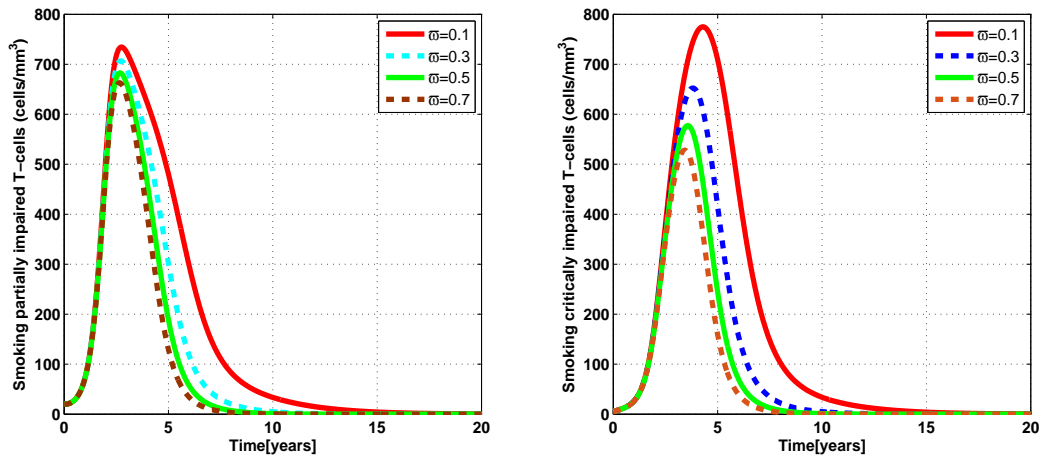

FIGURE 5. Variation of Smoking impaired classes with respect to inducing effect.

T-cells diminish from 5 years and above. HIV actively infected T-cells and free virus increase due to the fact that, as drugs' efficacy wanes, HIV actively infected T-cells replicate success-fully and produce more infectious virions as a result HIV infection rate for smoking impaired T-cells increases and reduces their number dramatically as shown in Figure 5. For $\varpi = 0.7$ and $\varpi = 0.5$ smoking partial and critical impaired classes diminish to zero before 10 years and diminish to zero in 15 years when $\varpi = 0.1$ as revealed in Figure 5.

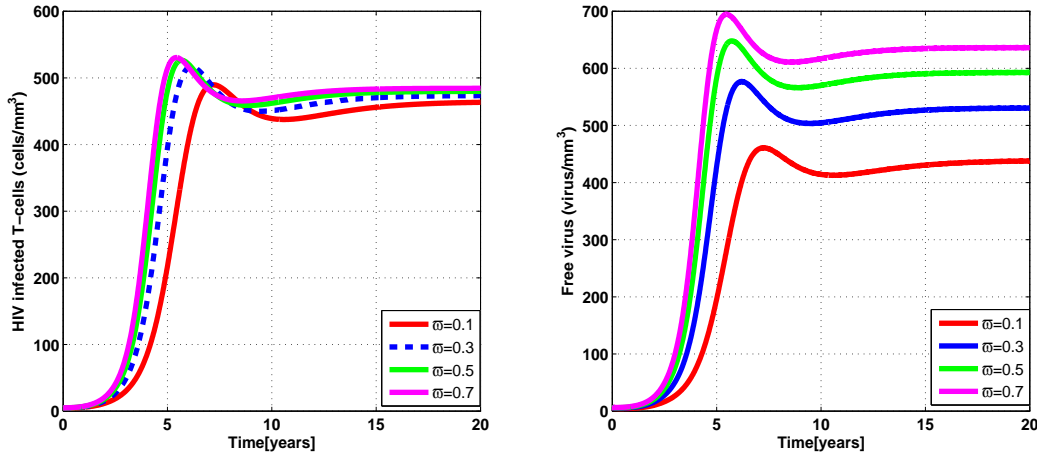## 3.3. The case when smoking induces metabolism of ARVs and affects drugs' adherence

FIGURE 6. Variation of HIV actively infected class and free virus with respect to inducing effect.

As smoking rate increases smokers become depressed and stressed hence fail to take ARVs as required, thus drug adherence drops. When smoking inducing effect increases and adherence to ARVs decreases, free virus and HIV actively infected T-cells increase. This is depicted in Figure 8. The increase of free virus and HIV actively infected T-cells is a function of smoking inducing effect and drugs' adherence rate. When $\varpi = 0.1$ and $\vartheta = 0.7$, free virus and HIV actively infected T-cells increase slowly and peak in 10 years. For the case when $\varpi = 0.4$ and $\vartheta = 0.1$, free virus and HIV actively infected T-cells increase rapidly and attain the peak in 5 years. This explains that as smoking induces metabolism of ARVs, their efficacy wanes away, free virus and HIV infected T-cells increases.

Smoking partial and critical impaired T-cells decrease as smoking inducing effect increases and adherence decreases. When $\varpi = 0.1$ and $\vartheta = 0.7$ smoking impaired T-cells decrease slowly because ARVs are still effective. As smoking inducing effect ϖ increases from 0.2 to 0.4 and adherence rate ϑ decreases from 0.5 to 0.1, smoking impaired T-cells diminish to zero before 15 years as illustrated in Figure 7.

4. Conclusion

A deterministic model for tobacco smoking effect on antiretroviral therapy is presented and analyzed to provide insights how antiretroviral therapy is affected by tobacco smoking. The
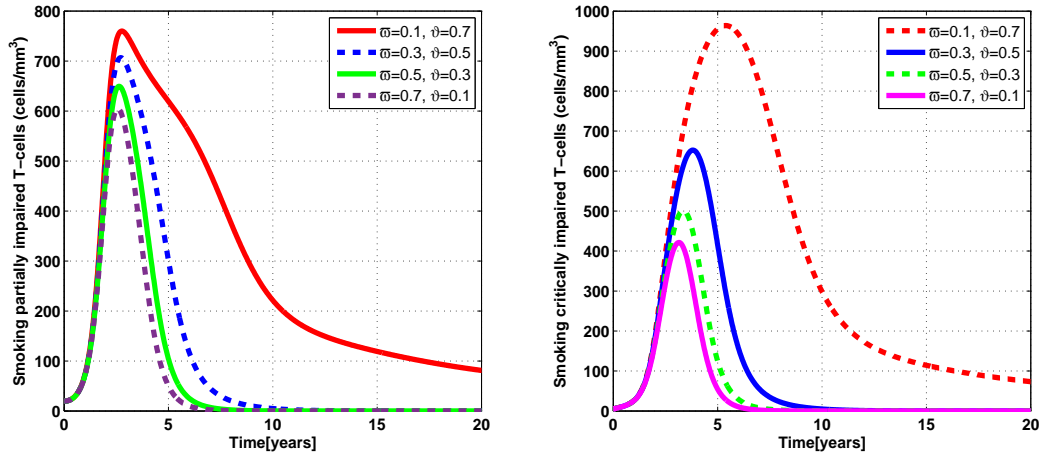
FIGURE 7. Variation of Smoking impaired classes with respect to inducing effect and drugs' adherence.
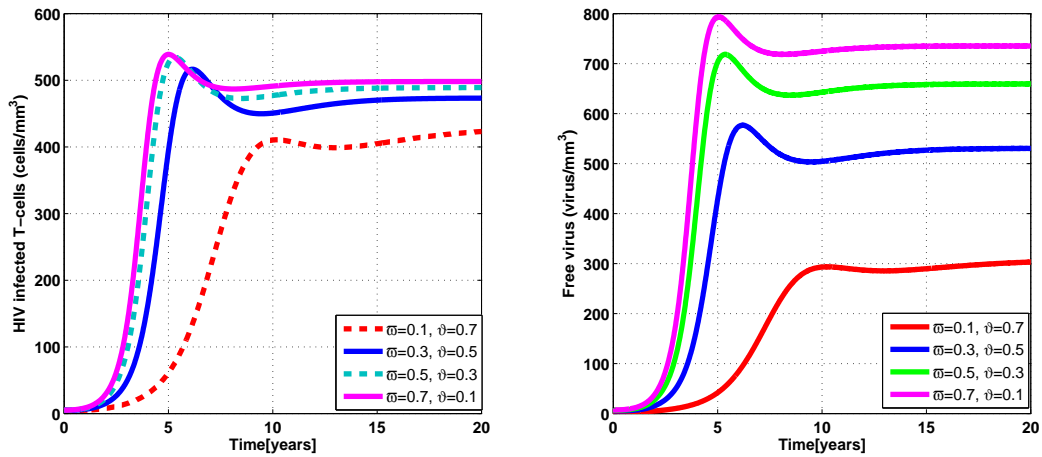

FIGURE 8. Variation of HIV actively infected class and free virus with respect to inducing effect and drugs' adherence.

model is formulated basing on the fact that, tobacco smoking induces metabolism of ARVs and has an influence on drugs' adherence. To measure and assess the effect of drugs' adherence we expressed drugs' efficacy as the product of adherence and the rate at which RTIs block reverse transcription and the product of adherence and the rate at which PIs block production of infectious virions.

The equilibrium states and effective reproduction number R_{ef} which is given as the maximum

of the partial effective reproduction numbers due to tobacco smoking R_{eS} and HIV R_{eA} is computed and analyzed. Analysis of HIV partial effective reproduction number R_{eA} indicates that tobacco smoking decreases the efficacy of ARVs because as tobacco smoking induces metabolism of ARVs, HIV new infections increases. Additionally, when drugs' adherence drops as a result of stress and depression due to high smoking rate, HIV new infections increases.

Numerical analysis guarantees a stable endemic equilibrium when $R_{ef} > 1$. The effect of tobacco smoking on ARVs is studied numerically by considering two cases; the case when smoking induces metabolism of ARVs and does not affect drugs' adherence, and the case when smoking induces metabolism of ARVs and affects drugs' adherence. For the two cases it has been found that, tobacco smoking decreases the efficacy of ARVs. This effect is significant when tobacco induces metabolism of ARVs by 30% to 70%. We consistently found that even if HIV smoker remains adherent to therapy, tobacco smoking effect on ARVs will still persist. Since tobacco smoking complicates HIV epidemic and its therapy, the study calls for HIV patients to abstain from smoking to ease management of the epidemic and its therapy.

Conflict of Interests

The authors declare that there is no conflict of interests.

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