A MATHEMATICAL MODEL FOR HIV-TB CO-INFECTION: THE EFFECT OF TREATMENT

SACHIN KUMAR AND **SHIKHA JAIN**

ABSTRACT. We propose a population model for HIV-TB co-infection dynamics by considering treatments for HIV infection, active tuberculosis and co-infection. The HIV only and TB only models are analyzed separately, as well as full model. The basic reproduction numbers for TB ($\mathcal{R}_0^T$) and HIV ($\mathcal{R}_0^H$) and overall reproduction number for the system $\mathcal{R}_0 = \max\{\mathcal{R}_0^T, \mathcal{R}_0^H\}$ are computed. The equilibria and their stability are studied. We explore the effect of early and late HIV treatment on disease induced death during the TB treatment course. Mathematical analysis of our model shows that successful disease eradication requires treatment of single disease, that is, treatment for HIV only and TB only infected individuals with addition to co-infection treatment.

1. Introduction

According to WHO, Tuberculosis is one of the top 10 causes of death worldwide [22, 25]. Tuberculosis (TB) is a bacterial disease which is primarily caused by the bacteria *Mycobacterium Tuberculosis* and is usually acquired by inhaling TB bacteria from surrounding air. All the infected people are not equally infectious and generally, it is only people with TB of the throat or lungs who are infectious. The bacteria get released in air by a carrier with active TB through coughing, sneezing or talking. Most infections do not have symptoms, in that case it is known as latent tuberculosis and people with latent TB do not spread the disease. Inhaling only a few of these germs are sufficient to get infected. *About one third of the world's population is infected with TB* [21], while most are in latent phase.

HIV, the Human Immunodeficiency Virus infects cells of immune system, destroying their function. HIV infects vital cells in the human immune system such as helper T cells (specifically CD4+ T cells), macrophages, and dendritic cells. As it hijacks the T cells that help keep the immune system working, HIV is particularly devastating to immune health. In the process of replication, the virus destroys increasing numbers of T cells. The T cells of an important part of the immune system are annihilated, leaving the body open to opportunistic infections. The immune system is thus deteriorated and no longer fulfils its role of fighting infections and diseases. Acquired immunodeficiency syndrome (AIDS) is a term for the most advanced stages of HIV infection. HIV can be transmitted through unprotected sexual intercourse, and oral sex with an infected person, transfusion of contaminated blood and sharing of contaminated needles, syringes, surgical equipment or other sharp instruments. It may also be transmitted between a mother and her infant during

pregnancy, childbirth and breastfeeding. In 2015, an estimated 44% of new infections occurred among key populations and their partners [26].

TB is a leading killer of HIV-positive people: in 2015, 35% of HIV deaths were due to TB [21]. Lowered immunity due to HIV infection increases the susceptibility to TB infection. People infected with HIV are 20 to 30 times more likely to develop active TB disease than the uninfected ones. TB is a treatable and curable disease but it is important to complete the entire course of medications even after one feels well. Between 2000 to 2015, an estimated 49 million lives were saved through TB diagnosis and treatment [21]. Though HIV infection has no permanent treatment, ART (Antiretroviral Therapy) can slow down the progression of HIV in the body to near a halt. ART reduces the risk of TB morbidity and mortality among people living with HIV. When ART is combined with TB preventive therapy, it can have a significant impact on TB prevention. Since TB can be cured effectively with treatment and complete treatment course being short, the usual recommendation is to start it immediately. The DOTS strategy makes no distinction between settings with different levels of HIV infection, yet outcomes will inevitably differ according to the epidemiology of HIV infection [6]. Initiating ART soon after the beginning of TB treatment increases the risk of IRIS (Immune Reconstruction Inflammatory Syndrome) which worsens TB infection and causes severe medical complications, while its delay until completion of TB treatment course increases the risk of death due to HIV. Therefore, it is difficult to identify the correct initiation of ART with TB treatment.

The negative impact of synergic interactions between TB and HIV have caused worldwide concern. Mathematical modelling of HIV, TB and HIV/TB co-infections have been reported by several researchers. Guzzetta et. al [10] proposed an age-structured, socio-demographic individual based model (IBM) with a realistic, time-evolving structure of preferential contacts in a population. Trauer et. al [23] presented a mathematical model to simulate tuberculosis (TB) transmission in highly endemic regions of the Asia-Pacific, where epidemiology does not appear to be primarily driven by HIV-coinfection. Long et. al [13] proposed a co-epidemical model for HIV-TB infection and presented an analysis in the population of India. Roeger et. al [17] proposed an 8 compartmental model of HIV-TB co-infection in which qualitative analysis of the model has been done. They discussed the stability and disease prevalence in the model. Silva et. al [19] proposed a population model for HIV-TB/AIDS co-infection transmission dynamics, which considers antiretroviral therapy for HIV infection and treatments for latent and active tuberculosis. Bhunu et. al [1] developed a model that in-corporates all aspects of TB transmission dynamics as well as aspects of HIV transmission dynamics to come with a distinct detailed co-infection model for HIV and TB. Naresh et. al [15] developed a HIV/TB co-epidemic model assuming that AIDS cases are non- infectious and did not include all stages of HIV and TB infection. Gakkhar and Chavda [9] formulated a simple epidemic HIV-TB co-infection model. Kaur et. al [12] developed a deterministic non-linear HIV-TB co-infection model which discusses the role of screening and treatment in the transmission dynamics of HIV/AIDS and tuberculosis co-infection. Mallela et. al [14] developed an eight compartmental model and studied the effect of HIV treatment in different phases of TB treatment.

Work done by Mallela et. al is the motivation for the present paper. In the present paper necessity of single disease infection treatments that is treatment for TB only and HIV only patients is also studied with the HIV treatment during different phases of TB treatment.

The paper is organised as follows: in Section 2, a twelve compartmental model for HIV-TB co-infection and treatment has been developed and positivity and boundedness of the solutions is proved. In Sections 3 and 4, TB and HIV sub-models are analyzed respectively and the respective reproduction numbers are calculated. The existence and stability conditions of equilibria are also deduced. In Section 5, the main model is discussed with its reproduction number and stability of equilibria. In Section 6, numerical computations of the model are performed to explore the HIV-TB co-infection dynamics. The effect of reproduction number on the infected population is studied. The effect of early or late initiation of HIV treatment during TB treatment course and the necessity of single disease infection treatment are discussed. We summarize our results with conclusion in Section 7.

2. **Model formulation and basic properties**

The model subdivides the human population into twelve mutually-exclusive compartments, namely susceptible individuals (S), TB-latently infected individuals (T_L), TB-infected individuals who are infectious and have active TB (T_I), TB-infected individuals who are under treatment for TB (T_T), HIV infected individuals (H), HIV infected individuals co-infected with latent TB (H_L), HIV infected individuals under treatment for HIV infection (H^T), co-infected Individuals with active TB (C), co-infected individuals with active TB under early phase of treatment for TB (C_1), co-infected individuals with active TB under late phase of treatment for TB (C_2), co-infected individuals with active TB under early phase of TB treatment as well as going through ART (C_1^T) and co-infected individuals with active TB under late phase of TB treatment along with ART (C_2^T). The total population at time t, denoted by $N(t)$, is given by

$$N(t) = S(t) + T_L(t) + T_I(t) + H(t) + H_L(t) + H^T(t) + C(t)$$
$$+ C_1(t) + C_2(t) + C_1^T(t) + C_2^T(t) + T_T(t).$$

We assume that all individuals in a given compartment are identically infectious, which might ignore potential effects caused due to variation among individuals. The susceptible cannot get HIV and TB infection simultaneously that means there is no direct transmission from the class of susceptible to the class of individuals co-infected with HIV and TB. The susceptible population is increased by the constant recruitment rate Λ. All individuals in different compartments suffer from natural death rate d while d_T and d_H are disease induced death rates due to TB and HIV separately. We ignore the temporal immunity to recover from latent TB because nowdays modern lifestyle has lowered the immunity [2] and consider direct and endogenous reinfection only. Since initiation of ART with TB treatment alters the disease induced death rate, therefore we consider it to be d_H^T and α is the probability of developing IRIS during different phases of co-treatment given by γ and $\frac{\gamma \rho_1}{\rho_1 + \rho_2}$ for compartments C_1^T and C_2^T respectively where γ is the rate of developing IRIS [14]. We assume σ and e are per capita contact rates for HIV and TB respectively. We assume β to be the probability of TB infection per contact with a person with active TB and λ is the probability of HIV infection per contact with a HIV infectious person. We assume that people under treatment for any disease are not infectious for spreading that disease since they are aware of their illness, so are precautious to the spread of disease. Secondly, treatment of TB reduces its infectiousness
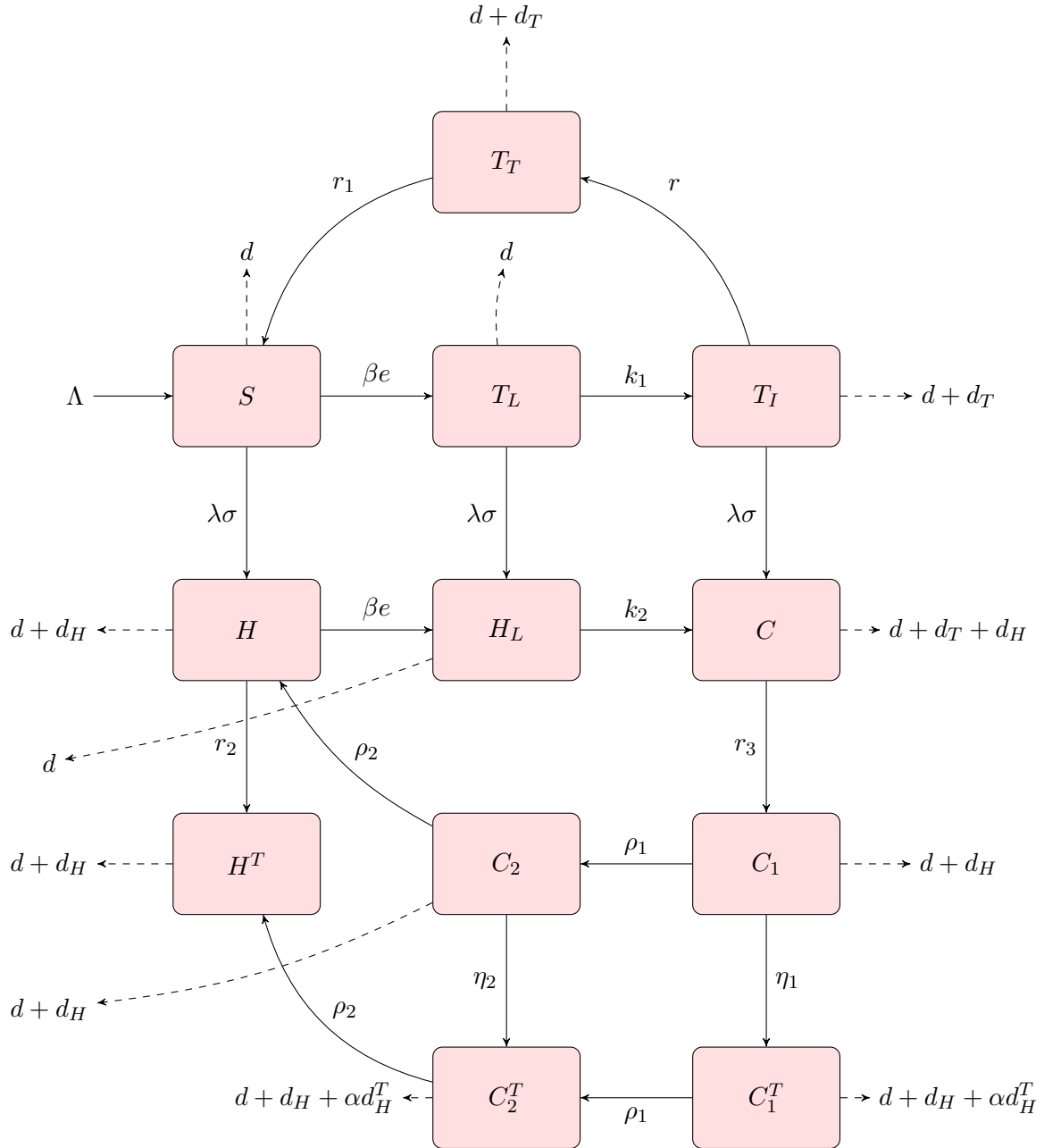
FIGURE 1. Schematic Diagram

exponentially [18]. In this model, we do not consider the treatment of latent TB and only sexual transmission of HIV is considered. The force of infection λ_T associated with TB is given by

$$\lambda_T = \beta e \frac{(T_I + C)}{N}. \tag{2.1}$$

The force of infection λ_H associated with HIV is given by

$$\lambda_H = \lambda \sigma \frac{(H + H_L + C + C_1 + C_2)}{N}. \tag{2.2}$$

We further assume that co-infected individuals under TB-treatment die of HIV or IRIS only. We assume k_1 is the progression rate from latent to active TB with no HIV while k_2 is the progression rate from latent to active TB with HIV, r is the per capita TB treatment rate with no HIV and r_1 is the recovery rate by treatment from TB with no HIV. The people successfully treated with TB return to class of susceptible since TB can reoccur [21]. Let r_2 be the per capita HIV treatment rate with no TB while r_3 is the per-capita TB treatment rate in co-infected individuals. We assume ρ_1 and ρ_2 to be the transition rates of TB treatment from early phase to late phase and from late phase to completion phase respectively while η_1 and η_2 are the rates at which HIV treatment begins during early phase of TB treatment and late phase of TB treatment respectively. The assumptions result in the following differential equations that describe the interaction of the two disease model as:

$$\frac{dS}{dt} = \Lambda - \beta e S \frac{(T_I + C)}{N} - dS - \lambda \sigma S \frac{(H + H_L + C + C_1 + C_2)}{N} + r_1 T_T,$$

$$\frac{dT_L}{dt} = \beta e S \frac{(T_I + C)}{N} - (d + k_1) T_L - \lambda \sigma T_L \frac{(H + H_L + C + C_1 + C_2)}{N},$$

$$\frac{dT_I}{dt} = k_1 T_L - (d + d_T) T_I - \lambda \sigma T_I \frac{(H + H_L + C + C_1 + C_2)}{N} - r T_I,$$

$$\frac{dH}{dt} = \lambda \sigma S \frac{(H + H_L + C + C_1 + C_2)}{N} - r_2 H - (d + d_H) H - \beta e H \frac{(T_I + C)}{N} + \rho_2 C_2,$$

$$\frac{dH_L}{dt} = \lambda \sigma T_L \frac{(H + H_L + C + C_1 + C_2)}{N} + \beta e H \frac{(T_I + C)}{N} - (k_2 + d + d_H) H_L,$$

$$\frac{dC}{dt} = k_2 H_L + \lambda \sigma T_I \frac{(H + H_L + C + C_1 + C_2)}{N} - (d + d_T + d_H) C - r_3 C, \tag{2.3}$$

$$\frac{dC_1}{dt} = r_3 C - \rho_1 C_1 - (d + d_H) C_1 - \eta_1 C_1,$$

$$\frac{dC_2}{dt} = \rho_1 C_1 - \rho_2 C_2 - (d + d_H) C_2 - \eta_2 C_2,$$

$$\frac{dC_1^T}{dt} = \eta_1 C_1 - \rho_1 C_1^T - (d + d_H + \alpha d_H^T) C_1^T,$$

$$\frac{dC_2^T}{dt} = \eta_2 C_2 + \rho_1 C_1^T - (d + d_H + \alpha d_H^T) C_2^T,$$

$$\frac{dH^T}{dt} = \rho_2 C_2^T + r_2 H - (d + d_H) H^T,$$

$$\frac{dT_T}{dt} = rT_I - r_1 T_T - (d + d_T)T_T.$$

The model flow diagram is shown in figure 1. The solid arrows show the flow within the system while dashed arrows show flow out from the system. The model has initial conditions given by:

$$
\begin{aligned}
S(0) &= S_0 \geqslant 0, & T_L(0) &= T_{L_0} \geqslant 0, & T_I(0) &= T_{I_0} \geqslant 0, & H(0) &= H_0 \geqslant 0, \\
H_L(0) &= H_{L_0} \geqslant 0, & C(0) &= C_0 \geqslant 0, & C_1(0) &= C_{1_0} \geqslant 0, & C_2(0) &= C_{2_0} \geqslant 0, & (2.4) \\
C_1^T(0) &= C_{1_0}^T \geqslant 0, & C_2(0) &= C_{2_0} \geqslant 0, & H^T(0) &= H_0^T \geqslant 0, & T_T(0) &= T_{T_0} \geqslant 0.
\end{aligned}
$$

2.1. **Positivity and boundedness of solutions.** Since the system deals with human population which can not be negative, we need to show that all the variables are always non-negative as well as the solutions of system (2.3) remain positive always with positive initial conditions in the bounded region defined by

$$D = \left\{ (S, T_L, T_I, H, H_L, C, C_1, C_2, C_1^T, C_2^T, H^T, T_T) \in \mathbb{R}_+^{12} : N(t) \leqslant \frac{\Lambda}{d} \right\}.$$

Theorem 2.1. *For the initial conditions given by (2.4), the solutions S, T_L, T_I, H, H_L, C, C_1, C_2, C_1^T, C_2^T, H^T, T_T of the system (2.3) are positive when $t \geqslant 0$ and the region D is positively invariant.*

Proof. For the given initial conditions, it is easy to prove that all the components of solutions of the system (2.3) are positive. The rate of change of total population is given by

$$
\begin{aligned}
\frac{dN}{dt} =\ & \Lambda - dS - dT_L - (d + d_T)T_I - (d + d_H)H - (d + d_H)H_L \\
& - (d + d_T + d_H)C - (d + d_H)C_1 - (d + d_H)C_2 \\
& - (d + d_H + \alpha d_H^T)C_1^T - (d + d_H + \alpha d_H^T)C_2^T - dT_T - d_T T_T, \\
=\ & \Lambda - dN - d_H H - d_H H_L - (d_H + d_T)C - d_H C_1 \\
& - d_H C_1 - d_H C_2 - d_H^1 C_1^T - d_H^1 C_2^T - d_T T_T, \\
\leq\ & \Lambda - dN.
\end{aligned}
$$

Clearly, if $N > \frac{\Lambda}{d}$, then $\frac{dN}{dt} < 0$. Thus, we get

$$N(t) \leq N(0)\exp(-dt) + \frac{\Lambda}{d}(1 - \exp(-dt)).$$

In particular, $N(t) \leq \frac{\Lambda}{d}$ if $N(0) \leq \frac{\Lambda}{d}$. For the system (2.3), the solutions that start in D remain there. This can be verified as follows: Suppose for example, at some time $t > 0$, the variable T_L becomes zero. i.e. $T_L(\bar{t}) = 0$, while all other variables are positive. Then from the equation (2) of the system (2.3), $\frac{dT_L(\bar{t})}{dt} > 0$. Thus, $T_L(t)$ remains positive. Similarly, it can be proved for other variables. Thus, D is positively invariant. $\qquad \square$

3. **TB Sub-model**

We have the TB sub-model when $H = H_L = C = C_1 = C_2 = C_1^T = C_2^T = H^T = 0$, which is given by:

$$\frac{dS}{dt} = \Lambda - \frac{\beta e S}{N} T_I - dS + r_1 T_T,$$

$$\frac{dT_L}{dt} = \frac{\beta e S}{N} T_I - dT_L - k_1 T_L,$$

$$\frac{dT_I}{dt} = k_1 T_L - (d + d_T) T_I - r T_I, \tag{3.1}$$

$$\frac{dT_T}{dt} = r T_I - r_1 T_T - dT_T - d_T T_T$$

with $S(0) = S_0 \geqslant 0$, $T_L(0) = T_{L_0} \geqslant 0$, $T_I(0) = T_{I_0} \geqslant 0$, $T_T(0) = T_{T_0} \geqslant 0$ as initial conditions and $\lambda_T = \frac{\beta e T_I}{N}$ is the force of infection. The total population is given by

$$N(t) = S(t) + T_L(t) + T_I(t) + T_T(t).$$

Considering biological constraints, the system (3.1) will be studied in the following region:

$$D_1 = \left\{ (S, T_L, T_I, T_T) \in \mathbb{R}_+^4 : N(t) \leqslant \frac{\Lambda}{d} \right\}.$$

It can be easily shown that the solutions S, T_L, T_I, T_T of the system are bounded and positively invariant in D_1.

3.1. **Disease free equilibrium and stability analysis.** The disease free equilibrium is given by

$$E_0^T = (S_0, T_{L_0}, T_{I_0}, T_{T_0}) = \left(\frac{\Lambda}{d}, 0, 0, 0 \right).$$

The basic reproduction number is defined as the average number of new cases of an infection caused by one typical infected individual in a population consisting of susceptibles only [7, 8, 11]. Here reproduction number, $\mathcal{R}_0^T$, is defined as the number of TB infections produced by an active TB case. We use the next generation matrix method to find basic reproduction number. Thus, we have the transmission matrix T and transition matrix Σ as follows:

$$T = \begin{bmatrix} \frac{\beta e \Lambda}{Nd} & 0 \\ 0 & 0 \end{bmatrix} \text{ and } \Sigma = \begin{bmatrix} 0 & -d - k_1 \\ -d - d_T - r & k_1 \end{bmatrix},$$

$$K = -T\Sigma^{-1} = \begin{bmatrix} \frac{-\beta e k_1 \Lambda}{Nd(d+k_1)(d+r+d_T)} & \frac{-\beta e \Lambda}{Nd(d+r+d_T)} \\ 0 & 0 \end{bmatrix}.$$

$\mathcal{R}_0^T$ is the spectral radius i.e. the dominant eigenvalue of K,

$$\mathcal{R}_0^T = \rho(k) = \frac{\beta e k_1 \Lambda}{Nd(d^2 + dr + dd_T + dk_1 + rk_1 + d_T k_1)}. \tag{3.2}$$

We now discuss the stability of disease free equilibrium.

Theorem 3.1. *The disease-free equilibrium, E_0^T is locally asymptotically stable when $\mathcal{R}_0^T < 1$ and unstable when $\mathcal{R}_0^T > 1$.*

Proof. The Jacobian matrix of the system (3.1) at E_0^T is given by

$$J(E_0^T) = \begin{bmatrix} -d & 0 & -\frac{\beta e \Lambda}{Nd} & r_1 \\ 0 & -d-k_1 & \frac{\beta e \Lambda}{Nd} & 0 \\ 0 & k_1 & -(d+d_T+r) & 0 \\ 0 & 0 & r & -(r_1+d+d_T) \end{bmatrix}. \tag{3.3}$$

The characteristic polynomial is given by

$$(x+d)(x+d+d_T+r_1)\left(x^2 + (2d+r+d_T+k_1)x + (d^2+dr+dd_T+dk_1+rk_1+d_Tk_1) - \frac{e\beta\Lambda k_1}{Nd}\right). \tag{3.4}$$

The first two factors are linear and give eigenvalues $-d$ and $-(d+d_T+r_1)$ for (3.4), which have negative real parts. For the remaining quadratic factor we use Routh-Hurwitz stability criterion by which disease free equilibrium is locally asymptotically stable if all the coefficients of quadratic polynomial in (3.4) are positive.

Comparing the quadratic factor in (3.4) with the general quadratic form $a_2 x^2 + a_1 x + a_0$, we get
$a_2 = 1$,
$a_1 = (2d+r+d_T+k_1)$,
$a_0 = (d^2+dr+dd_T+dk_1+rk_1+d_Tk_1) - \frac{e\beta\Lambda k_1}{Nd}$.
Clearly, $a_2 = 1 > 0$ and $a_1 = (2d+r+d_T+k_1) > 0$. But $a_0 > 0$, if

$$(d^2+dr+dd_T+dk_1+rk_1+d_Tk_1) - \frac{e\beta\Lambda k_1}{Nd} > 0,$$

$$\frac{e\beta\Lambda k_1}{Nd(d^2+dr+dd_T+dk_1+rk_1+d_Tk_1)} < 1,$$

$$\Rightarrow \mathcal{R}_0^T < 1.$$

Since all the coefficients of (3.4) are positive, by Routh-Hurwitz criterion $J(E_0^T)$ is locally asymptotically stable for $\mathcal{R}_0^T < 1$ [16]. □

We now list two conditions that are sufficient to guarantee the global stability of the disease free equilibrium point. Following Castillo-Chavez et al. [4], we rewrite the model system (3.1) as

$$\frac{d\mathbf{S}}{dt} = F(\mathbf{S}, \mathbf{I}), \qquad G(\mathbf{S}, \mathbf{0}) = 0, \tag{3.5}$$
$$\frac{d\mathbf{I}}{dt} = G(\mathbf{S}, \mathbf{I}),$$

where $\mathbf{S} \in \mathbb{R}^2$ denotes the number of uninfected individuals and $\mathbf{I} \in \mathbb{R}^2$ denotes the number of infected individuals. $\mathbf{E}_0 = (X^*, 0)$ denotes the disease free equilibrium of system (3.5). The conditions $(H1)$ and $(H2)$ below must be satisfied to guarantee a local asymptotic stability.
(H1) For $\frac{d\mathbf{S}}{dt} = F(\mathbf{S}, 0), S^*$ is globally asymptotically stable,
(H2) $G(\mathbf{S}, \mathbf{I}) = A\mathbf{I} - \hat{G}(\mathbf{S}, \mathbf{I}), \hat{G}(\mathbf{S}, \mathbf{I}) \geq 0$ for $(\mathbf{S}, \mathbf{I}) \in G_2$,

where $A = D_{\mathbf{I}}G(S^*, 0)$ is an M-matrix (the off diagonal elements are non negative) and G is the region where the model makes biological sense. If the system (3.1) satisfies the above two conditions, then the theorem holds.

Theorem 3.2. *The fixed point $E_0^T = (S^*, 0)$ is a globally asymptotically stable equilibrium of system (3.1) if $\mathcal{R}_0^T < 1$ and the assumptions in (3.5) are satisfied.*

Proof. We have already proved in theorem (3.1) that for $\mathcal{R}_0^T < 1$, E_0^T is locally asymptotically stable. Consider

$$\frac{dS}{dt} = \Lambda - \frac{\beta e S}{N}T_I - dS + r_1 T_T = F(S, I),$$
$$\frac{dI}{dt} = G(S, I), \tag{3.6}$$

where $G(S, I) = \begin{bmatrix} \frac{\beta e S T_I}{N} - dT_L - k_1 T_L \\ k_1 T_L - (d + d_T)T_I - rT_I \\ rT_I - r_1 T_T - dT_T - d_T T_T \end{bmatrix}$ and $F(S, 0) = \begin{bmatrix} \Lambda - dS \\ 0 \end{bmatrix}$.

$G(S, I) = AI - \hat{G}(S, I)$ and $A = \begin{bmatrix} -d - k_1 & \beta e & 0 \\ k_1 & -d - d_T - r & 0 \\ 0 & r & -r_1 - d - d_T \end{bmatrix}$.

We get,

$$\hat{G}(S, I) = \begin{bmatrix} \hat{G}_1(S, I) \\ \hat{G}_2(S, I) \end{bmatrix} = \begin{bmatrix} \beta e T_I(1 - \frac{S}{N}) \\ 0 \\ 0 \end{bmatrix}.$$

Since S is always less than or equal to N, $\frac{S}{N} \leq 1$ and $\hat{G}_1(S, I) \geqslant 1$. Thus, $\hat{G}(S, I) \geq 0$ and this implies that E_0^T is globally asymptotically stable. □

3.2. **Existence, Stability and bifurcation analysis for endemic equilibrium point.** To find conditions for the existence of an equilibrium for which TB is endemic in the population, denoted by $E_1^T = (\tilde{S}, \tilde{T}_L, \tilde{T}_I, \tilde{T}_T)$, the equations in (3.1) are solved in terms of force of infection at steady state λ_T^*, given by

$$\lambda_T^* = \frac{\beta e T_I}{N}. \tag{3.7}$$

The system (3.1) reduces to the following:

$$\begin{bmatrix} -(\lambda_T^* + d) & 0 & 0 & r_1 \\ \lambda_T^* & -(d + k_1) & 0 & 0 \\ 0 & k_1 & -d - d_T - r & 0 \\ 0 & 0 & r & -(r_1 + d + d_T) \end{bmatrix} \begin{bmatrix} S \\ T_L \\ T_I \\ T_T \end{bmatrix} = \begin{bmatrix} -\Lambda \\ 0 \\ 0 \\ 0 \end{bmatrix}.$$

Solving this, we get

$$\tilde{S} = \frac{\Lambda(d+r+d_T)(d+k_1)(d+d_T+r_1)}{A},$$

$$\tilde{T}_L = \frac{\Lambda(\lambda_T^*(d+r+d_T))(d+d_T+r_1)}{A},$$

$$\tilde{T}_I = \frac{\Lambda\lambda_T^*k_1(d+d_T+r_1)}{A},$$

$$\tilde{T}_T = \frac{r\Lambda\lambda_T^*k_1}{A},$$

(3.8)

where $A = (d+r+d_T)(d+\lambda_T^*)(d+k_1)(d+d_T+r_1) - r\lambda_T^*k_1r_1$. Using (3.8) in (3.7), we get

$$\lambda_T^* = \frac{\beta e\Lambda k_1\lambda_T^*(d+d_T+r_1)}{N(d+r+d_T)(d+\lambda_T^*)(d+k_1)(d+d_T+r_1) - r\lambda_T^*k_1r_1},$$

which reduces to

$$\frac{\lambda_T^*\left[\frac{\beta e\Lambda k_1(d+r_1+d_T)}{N} - (d+r+d_T)(d+\lambda_T^*)(d+k_1)(d+d_T+r_1) + r\lambda_T^*k_1r_1\right]}{(d+r+d_T)(d+\lambda_T^*)(d+k_1)(d+d_T+r_1) - r\lambda_T^*k_1r_1} = 0,$$

where $\lambda_T^* = 0$ corresponds to the disease free equilibrium and

$$\lambda_T^* = \frac{\frac{\beta e\Lambda k_1(d+d_T+r_1)}{N} - d(d+r+d_T)(d+k_1)(d+d_T+r_1)}{(d+d_T+r)(d+k_1)(d+d_T+r_1) - rk_1r_1},$$

(3.9)

corresponds to the existence of endemic equilibrium. For a disease to spread, the force of infection (λ_T^*) should be positive. It can be seen clearly that denominator of (3.9) is always positive. So for λ_T^* to be positive, its numerator should be positive. Therefore,

$$\frac{\beta e\Lambda k_1}{N} - d(d+r+d_T)(d+k_1)(d+d_T+r_1) > 0,$$

$$\frac{\beta e\Lambda k_1}{Nd(d+r+d_T)(d+k_1)} > 1,$$

$$\Rightarrow \mathcal{R}_0^T > 1.$$

(3.10)

Thus, (3.9) reduces to $\mathcal{R}_0^T > 1$. We have just proved the following result.

Theorem 3.3. *The submodel system (3.1) has a unique endemic equilibrium whenever $\mathcal{R}_0^T > 1$.*

3.3. **Local stability of endemic equilibrium.** We prove the local asymptotic stability of the endemic equilibrium E_1^T, using the center manifold theory, as described in [5, Theorem 4.1], with $E_1^T = (\tilde{S}, \tilde{T}_L, \tilde{T}_I, \tilde{T}_T)$ and each of its components as given in (3.7). Firstly we simplify the system (3.1) to apply this method. Let $S = x_1, T_L = x_2, T_I = x_3$ and $T_T = x_4$, so that $N = x_1+x_2+x_3+x_4$,

then the system can be written in the form $\frac{dX}{dt} = (f_1, f_2, f_3, f_4)^T$ as follows:

$$
\begin{aligned}
\frac{dx_1}{dt} &= f_1 = \Lambda - \frac{\beta e x_1}{N} x_3 - dx_1 + r_1 x_4, \\
\frac{dx_2}{dt} &= f_2 = \frac{\beta e x_1}{N} x_3 - dx_2 - k_1 x_2, \\
\frac{dx_3}{dt} &= f_3 = k_1 x_2 - (d + d_T) x_3 - r x_3, \\
\frac{dx_4}{dt} &= f_4 = r x_3 - r_1 x_4 - dx_4 - d_T x_4.
\end{aligned}
\tag{3.11}
$$

The basic reproduction number of the system (3.1) is given by (3.2). We choose a bifurcation parameter β^*, by solving for βe from $\mathcal{R}_0^T = 1$:

$$
\beta^* = \frac{N d(d + r + d_T)(d + k_1)}{\Lambda k_1}.
$$

The system (3.1) has a disease free equilibrium given by

$$
E_0^T = (x_{1_0}, x_{2_0}, x_{3_0}, x_{4_0}) = \left(\frac{\Lambda}{d}, 0, 0, 0 \right).
$$

The Jacobian matrix of the linearized system of (3.11) evaluated at E_0^T, $J(E_0^T)$ is given as in (3.3). $J(E_0^T)|_{\beta^*}$ has a zero eigenvalue which is simple and all the other eigenvalues have negative real parts, therefore the center manifold theory can be applied.
The Jacobian matrix $J(E_0^T)|_{\beta^*}$ has a right eigenvector, associated with zero eigenvalue which is given by $w = (w_1, w_2, w_3, w_4)^T$, where

$$
\begin{aligned}
w_1 &= \frac{r_1}{d} - \frac{(d + r + d_T)(d + k_1)(d + d_T + r_1)}{drk_1}, \\
w_2 &= \frac{(d + r + d_T)(d + d_T + r_1)}{rk_1}, \\
w_3 &= \frac{(d + d_T + r_1)}{r}, \\
w_4 &= 1.
\end{aligned}
\tag{3.12}
$$

Since $x_{1_0} > 0$, there is no restriction on sign of w_1 [refer [5], Remark 1, pg. 375], while $w_i > 0 \; \forall \; i \neq 1$. Further, $J(E_0^T)|_{\beta^*}$ has a left eigenvector $v = (v_1, v_2, v_3, v_4)$, associated with the zero eigenvalue, where

$$
\begin{aligned}
v_1 &= 0, \\
v_2 &= \frac{k_1}{(d + k_1)}, \\
v_3 &= 1, \\
v_4 &= 0.
\end{aligned}
\tag{3.13}
$$

The local stability near the bifurcation point $\beta^* = \beta e$ is determined by the signs of the two associated constants, denoted by a and b which are defined by

$$a = \sum_{k,i,j=1}^{4} v_k w_i w_j \frac{\partial^2 f_k}{\partial x_i \partial x_j}(0,0),$$

$$b = \sum_{k,i,j=1}^{4} v_k w_i \frac{\partial^2 f_k}{\partial x_i \partial \phi}(0,0), \tag{3.14}$$

with $\phi = \beta e - \beta^*$ and for $\beta e = \beta^*, \phi = 0$.

For the system (3.11), the associated non-zero partial derivatives at E_0^T are

$$\frac{\partial^2 f_2}{\partial x_2 \partial x_3} = -\frac{\beta^* d}{\Lambda}, \qquad \frac{\partial^2 f_2}{\partial x_3^2} = -2\frac{\beta^* d}{\Lambda},$$

$$\frac{\partial^2 f_2}{\partial x_3 \partial x_4} = -\frac{\beta^* d}{\Lambda}, \qquad \frac{\partial^2 f_2}{\partial x_3 \partial \beta^*} = 1.$$

From the above expressions, we get

$$a = -\frac{(d+d_T+r)^2(d+r+d_T)^2 d}{\Lambda^2 r k_1} - \frac{2Nd^2(d+d_T+r_1)^2(d+r+d_T)}{r^2 \Lambda^2}$$

$$\quad -\frac{Nd^2(d+d_T+r_1)(d+d_T+r)}{r\Lambda^2},$$

$$b = \frac{k_1(d+d_T+r_1)}{r(d+k_1)}. \tag{3.15}$$

Since all the terms in the expressions in (3.15) are positive, therefore $a < 0$ and $b > 0$. Thus, [5, Theorem 4.1] implies that the unique equilibrium point of system (3.1), which exists when $\mathcal{R}_0^T > 1$ is locally asymptotically stable when $\beta^* < \beta e$ with βe close to β^*. Hence, the following result is established.

Theorem 3.4. *The endemic equilibrium E_1^T is locally asymptotically stable for the basic reproduction number $\mathcal{R}_0^T > 1$.*

4. HIV Submodel

We have HIV submodel when $T_L = T_I = T_T = C = C_1 = C_2 = C_1^T = C_2^T = 0$, which is given by the following system of equations:

$$\frac{dS}{dt} = \Lambda - dS - \frac{\lambda \sigma SH}{N},$$

$$\frac{dH}{dt} = \frac{\lambda \sigma SH}{N} - r_2 H - (d+d_H)H, \tag{4.1}$$

$$\frac{dH^T}{dt} = r_2 H - (d+d_H)H^T,$$

with initial conditions $S(0) = S_0 \geq 0, H(0) = H_0 \geq 0, H^T(0) = H_0^T \geq 0$ and the force of infection is given by

$$\lambda_H = \frac{\lambda \sigma H}{N},$$

and the total population for the system is $N = S + H + H^T$. Due to biological constraints, the system (4.1) is studied in the following region

$$D_2 = \left\{ (S,\ H,\ H^T) \in \mathbb{R}_+^3 : N(t) \leqslant \frac{\Lambda}{d} \right\}.$$

This is easy to prove that the solutions $S,\ H$ and H^T of the system (4.1) are bounded and positively invariant in D_2.

4.1. **Disease free equilibrium and stability analysis.** The disease free equilibrium for the system (4.1) is given by

$$E_0^H = (S_0,\ H_0,\ H_0^T) = \left(\frac{\Lambda}{d},\ 0,\ 0,\ 0 \right),$$

and the basic reproduction number is given by

$$\mathcal{R}_0^H = \frac{\Lambda \lambda \sigma}{Nd(r_2 + d + d_H)}. \tag{4.2}$$

Next we discuss the stability of disease free equilibrium.

Theorem 4.1. *The disease free equilibrium, E_0^H is locally asymptotically stable when $\mathcal{R}_0^H < 1$ and unstable when $\mathcal{R}_0^H > 1$.*

Proof. The Jacobian matrix of the system (4.1) at E_0^H is given by

$$J(E_0^H) = \begin{bmatrix} -d & -\frac{\Lambda \lambda \sigma}{Nd} & 0 \\ 0 & \frac{\Lambda \lambda \sigma}{Nd} - (r_2 + d + d_H) & 0 \\ 0 & r_2 & -(d + d_H) \end{bmatrix}, \tag{4.3}$$

which has characteristic polynomial

$$(d + x)(x + d + d_H) \left(\frac{\Lambda \lambda \sigma}{Nd} - x - d - d_H - r_2 \right). \tag{4.4}$$

Eigenvalues for (4.3) are $-d, -(d + d_H)$ and $(\frac{\Lambda \lambda \sigma}{Nd} - (d + d_H + r_2))$ which have negative real parts when $\frac{\Lambda \lambda \sigma}{Nd(d + d_H + r_2)} < 1$ i.e. $\mathcal{R}_0^H < 1$. Thus, E_0^H is locally asymptotically stable for $\mathcal{R}_0^H < 1$ and unstable for $\mathcal{R}_0^H > 1$. $\square$

We now discuss the global stability of disease free equilibrium E_0^H.

Theorem 4.2. *The fixed point $E_0^H = (S^*, 0)$ is a globally asymptotically stable equilibrium of system (4.1) provided that $\mathcal{R}_0^H < 1$ and the assumptions in (3.5) are satisfied.*

Proof. In theorem (4.1) we have proved that for $\mathcal{R}_0^H < 1$, E_0^H is locally asymptotically stable. Rewriting the system (4.1) as

$$
\begin{aligned}
\frac{dS}{dt} &= \Lambda - dS - \frac{\lambda\sigma H}{N} = F(S, I), \\
\frac{dI}{dt} &= G(S, I),
\end{aligned}
\tag{4.5}
$$

where

$$
G(S, I) = \begin{bmatrix} \frac{\lambda\sigma H}{N} - r_2 H - (d + d_H)H \\ r_2 H - (d + d_H)H^T \end{bmatrix},
$$

$$
I = \begin{bmatrix} H \\ H^T \end{bmatrix}, \quad F(S, 0) = \begin{bmatrix} \Lambda - dS \\ 0 \end{bmatrix},
$$

$$
G(S, I) = AI - \hat{G}(S, I), \quad A = \begin{bmatrix} \lambda\sigma - (r_2 + d + d_H) & 0 \\ r_2 & -(d + d_H) \end{bmatrix}.
$$

Then we get

$$
\hat{G}(S, I) = \begin{bmatrix} \hat{G}_1(S, I) \\ \hat{G}_2(S, I) \end{bmatrix} = \begin{bmatrix} \lambda\sigma H \left(1 - \frac{S}{N}\right) \\ 0 \end{bmatrix}.
$$

As S is always less than or equal to N, $\frac{S}{N} \leq 1$ and $\hat{G}_1(S, I) \geq 1$. Thus, $\hat{G}(S, I) \geq 0$ and E_0^H is globally asymptotically stable. $\qquad\square$

4.2. **Existence and Stability of Endemic Equilibrium point.** The endemic equilibrium is given by

$$
E_1^H = (\tilde{S}, \ \tilde{H}, \ \tilde{H}^T),
$$

where

$$
\begin{aligned}
\tilde{S} &= \frac{N(r_2 + d + d_H)}{\lambda\sigma}, \\
\tilde{H} &= \frac{\Lambda}{(r_2 + d + d_H)} - \frac{dN}{\lambda\sigma}, \\
\tilde{H}^T &= \frac{r_2}{(r_2 + d + d_H)} \left(\frac{\Lambda}{(r_2 + d + d_H)} - \frac{dN}{\lambda\sigma} \right).
\end{aligned}
\tag{4.6}
$$

The HIV endemic exists when λ_H^*, given by

$$
\lambda_H^* = \frac{\lambda\sigma\hat{H}}{N},
\tag{4.7}
$$

is positive. Using (4.6) in (4.7), if $\lambda_H^* > 0$, then

$$
\frac{\lambda\sigma}{N} \left(\frac{\Lambda}{(r_2 + d + d_H)} - \frac{dN}{\lambda\sigma} \right) > 0,
$$

$$
\frac{\lambda\sigma}{(r_2 + d + d_H)} > \frac{Nd}{\Lambda},
$$

Therefore, $\mathcal{R}_0^H > 1$. Thus, the endemic equilibrium exists when $\mathcal{R}_0^H > 1$. We have just proved the following result.

Theorem 4.3. *The endemic equilibrium, E_1^H exists whenever $\mathcal{R}_0^H > 1$.*

We now discuss the stability of the endemic equilibrium point E_1^H.

Theorem 4.4. *The endemic equilibrium E_1^H is locally asymptotically stable for the basic reproduction number $\mathcal{R}_0^H > 1$.*

Proof. The Jacobian matrix of the system (4.1) at E_1^H is given by

$$\begin{bmatrix} \frac{\Lambda\lambda\sigma}{N(r_2+d+d_H)} & -(r_2+d+d_H) & 0 \\ \frac{\Lambda\lambda\sigma}{N(r_2+d+d_H)} - d & 0 & 0 \\ 0 & r_2 & -(d+d_H) \end{bmatrix}. \tag{4.8}$$

The characteristic equation for (4.8) is given by

$$(x+d+d_H)\left(x^2 + \frac{\lambda\sigma x}{N(d+d_H+r_2)} - d(r_2+d+d_H) + \frac{\Lambda\lambda\sigma}{N}\right) = 0. \tag{4.9}$$

The factor $(x+d+d_H)$ gives an eigenvalue $-d-d_H$, which has negative real part. For the other quadratic factor we use Routh Hurwitz criterion of stability, by which all the coefficients in the quadratic factor should be positive. Comparing with standard quadratic form $a_2x^2 + a_1x + a_0$, we get

$$a_2 = 1,$$

$$a_1 = \frac{\lambda\sigma}{N(r_2+d+d_H)},$$

$$a_0 = -d(r_2+d+d_H) + \frac{\Lambda\lambda\sigma}{N}.$$

Now, $a_2 = 1 > 0$ and $a_1 = \frac{\lambda\sigma}{N(r_2+d+d_H)} > 0$ as all terms involved are positive. But $a_0 > 0$ if

$$-d(r_2+d+d_H) + \frac{\Lambda\lambda\sigma}{N} > 0,$$

$$\frac{\lambda\sigma\Lambda}{Nd(r_2+d+d_H)} > 1,$$

$$\Rightarrow \mathcal{R}_0^H > 1.$$

Therefore, in D_2 whenever $\mathcal{R}_0^H > 1$, E_1^H is locally asymptotically stable. $\qquad\square$

5. Analysis of the main model

In this section, we analyze the main model (2.3). Biologically, the full model can have four equilibria, namely, disease free equilibrium E_0, TB only endemic equilibrium E^T, HIV only endemic equilibrium E^H and the interior endemic equilibrium point E^{TH}.

5.1. **The disease free equilibrium and stability analysis.** The disease free equilibrium is given by

$$E_0 = \left(\frac{\Lambda}{d}, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0 \right).$$

First, we calculate the basic reproduction number by next generation operator method as in subsection (3.1). The transition matrix T and the transmission matrix Σ, are as follows:

$$T = \begin{bmatrix} 0 & \frac{\beta e \Lambda}{Nd} & 0 & 0 & \frac{\beta e \Lambda}{Nd} & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & \frac{\Lambda \lambda \sigma}{Nd} & \frac{\Lambda \lambda \sigma}{Nd} & \frac{\Lambda \lambda \sigma}{Nd} & \frac{\Lambda \lambda \sigma}{Nd} & \frac{\Lambda \lambda \sigma}{Nd} \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 \end{bmatrix}, \tag{5.1}$$

$$\Sigma = \begin{bmatrix} -d - k_1 & 0 & 0 & 0 & 0 & 0 & 0 \\ k_1 & -d - d_T - r & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & -r_2 - d - d_H & 0 & 0 & 0 & \rho_2 \\ 0 & 0 & 0 & k_2 - d - d_H & 0 & 0 & 0 \\ 0 & 0 & 0 & k_2 & C_1 & 0 & 0 \\ 0 & 0 & 0 & 0 & r_3 & C_2 & 0 \\ 0 & 0 & 0 & 0 & 0 & \rho_1 & C_3 \end{bmatrix}, \tag{5.2}$$

where
$C_1 = -d - d_T - d_H - r_3,$
$C_2 = -d - d_H - \rho_1 - \eta_1,$
$C_3 = -d - d_H - \rho_2 - \eta_2.$
The dominant eigenvalues of $-T\Sigma^{-1}$ are

$$\mathcal{R}_0^T = \frac{\beta e \Lambda k_1}{Nd(d^2 + dr + dd_T + dk_1 + rk_1 + d_T k_1)}, \quad \mathcal{R}_0^H = \frac{\Lambda \lambda \sigma}{Nd(r_2 + d + d_H)}.$$

Thus, the basic reproduction number of the model (2.3) is given by

$$\mathcal{R}_0 = \max\{\mathcal{R}_0^T, \mathcal{R}_0^H\}. \tag{5.3}$$

Theorem 5.1. *The disease free equilibrium, E_0 is locally asymptotically stable when $\mathcal{R}_0 < 1$ and unstable when $\mathcal{R}_0 > 1$.*

Proof. The Jacobian matrix $J(E_0)$ of the model system (2.3) at E_0 is given by

$$
\begin{bmatrix}
-d & 0 & -\frac{\beta e\Lambda}{Nd} & -\frac{\Lambda\lambda\sigma}{Nd} & -\frac{\Lambda\lambda\sigma}{Nd} & \frac{-\Lambda(\beta e+\lambda\sigma)}{Nd} & -\frac{\Lambda\lambda\sigma}{Nd} & -\frac{\Lambda\lambda\sigma}{Nd} & 0 & 0 & 0 & r_1 \\
0 & -d-k_1 & \frac{\beta e\Lambda}{Nd} & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & k_1 & C_0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & C_1 & \frac{\Lambda\lambda\sigma}{Nd} & \frac{\Lambda\lambda\sigma}{Nd} & \frac{\Lambda\lambda\sigma}{Nd} & \frac{\Lambda\lambda\sigma}{Nd}+\rho_2 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & C_2 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & k_2 & C_3 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & r_3 & C_4 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & \rho_1 & C_5 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & \eta_1 & 0 & C_6 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & \eta_2 & \rho_1 & C_7 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & \rho_2 & -d-d_H & 0 \\
0 & 0 & r & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & -d-d_T
\end{bmatrix},
$$

$$(5.4)$$

where,

$C_0 = -(d + r + d_T)$,
$C_1 = \frac{\Lambda\lambda\sigma}{Nd} - (d + d_H + r_2)$,
$C_2 = -(d + d_H + k_2)$,
$C_3 = -(d + d_H + d_T + r_3)$,
$C_4 = -(d + d_H + \eta_1 + \rho_1)$,
$C_5 = -(d + d_H + \eta_2 + \rho_2)$,
$C_6 = -(d + d_H + \alpha d_H^T + \rho_1)$,
$C_7 = -(d + d_H + \alpha d_H^T + \rho_2)$.

The characteristic equation of (5.4) is given by the following:

$$
(x + d + d_H + k_2)(x + d + d_T + r_1)(x + d + d_T + d_H + r_3)(x + d + d_H + \alpha d_H^T + \rho_1)
$$
$$
(x + d)(x + d + d_H)(x + d + d_H + \rho_1 + \eta_1)(x + d + d_H + \alpha d_H^T + \rho_2)(x + d + d_H + \rho_2 + \eta_2)
$$
$$
\left(x + d + d_H + r_2 - \frac{\Lambda\lambda\sigma}{Nd}\right)\left(x^2 + (2d + r + d_T + k_1)x + d^2 + dr + dd_T + dk_1 + rk_1\right) \quad (5.5)
$$
$$
+ d_T k_1 - \frac{\beta e\Lambda k_1}{Nd}\right) = 0.
$$

Clearly, the first nine factors in (5.5) give eigenvalues with negative real parts. Eigenvalue of factor $(x + d + d_H + r_2 - \frac{\Lambda\lambda\sigma}{Nd})$ would have negative real part if

$$
d + d_H + r_2 - \frac{\Lambda\lambda\sigma}{Nd} < 0,
$$
$$
\frac{\Lambda\lambda\sigma}{Nd(r_2 + d + d_H)} > 1,
$$
$$
\Rightarrow \mathcal{R}_0^H < 1.
$$

For the remaining quadratic factor in (5.5), we use Routh-Hurwitz Stability criterion, by which all the coefficients of the factor should be positive for the eigenvalues to have negative real parts.

Comparing this factor with general quadratic form $a_2 x^2 + a_1 x + a_0$, we get

$$
\begin{aligned}
a_2 &= 1, \\
a_1 &= 2d + r + d_T + k_1, \\
a_0 &= d^2 + dr + dd_T + dk_1 + rk_1 + d_T k_1 - \frac{\beta e \Lambda k_1}{Nd}.
\end{aligned}
$$

Clearly, a_2 and a_1 are positive. For a_0 to be positive, we need

$$
d^2 + dr + dd_T + dk_1 + rk_1 + d_T k_1 - \frac{\beta e \Lambda k_1}{Nd} > 0,
$$

$$
\frac{\beta e \Lambda k_1}{Nd(d^2 + dr + dd_T + dk_1 + rk_1 + d_T k_1)} < 1,
$$

$$
\Rightarrow \mathcal{R}_0^T < 1.
$$

Since all the coefficients of the quadratic factor are positive, by Routh-Hurwitz criterion the disease free equilibrium is locally asymptotically stable for $\mathcal{R}_0 < 1$ and unstable for $\mathcal{R}_0 > 1$. $\square$

Next we discuss the global stability of disease free equilibrium point.

5.1.1. *Global Stability of disease free equilibrium*. Rewriting the system (2.3) as in (3.5), we get

$$
\begin{aligned}
\frac{dS}{dt} &= \Lambda - \frac{\beta e S(T_I + C)}{N} - dS - \frac{\lambda \sigma S(H + H_L + C + C_1 + C_2)}{N}, \\
\frac{dI}{dt} &= G(S, I),
\end{aligned}
\tag{5.6}
$$

where $G(S, I) =$

$$
\begin{bmatrix}
\frac{\beta e S(T_I + C)}{N} - dT_L - \frac{\lambda \sigma T_L (H + H_L + C + C_1 + C_2)}{N} - k_1 T_L \\
-(d + d_T) T_I - \frac{\lambda \sigma T_I (H + H_L + C + C_1 + C_2)}{N} + k_1 T_L - r T_I \\
\frac{\lambda \sigma S(H + H_L + C + C_1 + C_2)}{N} - r_2 H - (d + d_H) H - \frac{\beta e H(T_I + C)}{N} + \rho_2 C_2 \\
\frac{\lambda \sigma T_L (H + H_L + C + C_1 + C_2)}{N} + \frac{\beta e H(T_I + C)}{N} - k_2 H_L - (d + d_H) H_L \\
k_2 H_L + \frac{\lambda \sigma T_I (H + H_L + C + C_1 + C_2)}{N} - (d + d_H + d_T) C - r_3 C \\
r_3 C - \rho_1 C_1 - (d + d_H) C_1 - \eta_1 C_1 \\
\rho_1 C_1 - \rho_2 C_2 - (d + d_H) C_2 - \eta_2 C_2 \\
\eta_1 C_1 - \rho_1 C_1^T - (d + d_H + \alpha d_H^T) C_1^T \\
\eta_2 C_2 + \rho_1 C_1^T - (d + d_H + \alpha d_H^T) C_2^T - \rho_2 C_2^T \\
\rho_2 C_2^T + r_2 H - (d + d_H) H^T \\
r T_I - r_1 T_T - dT_T - d_T T_T
\end{bmatrix},
$$

$$
F(S, 0) = \begin{bmatrix} \Lambda - dS \\ 0 \end{bmatrix},
$$

$$
G(S, I) = AI - \hat{G}(S, I),
$$

and the M-matrix A for (5.6) is given by the following:

$$
A = \begin{bmatrix}
-d-k_1 & \beta e & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
k_1 & A_1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & A_2 & \lambda\sigma & \lambda\sigma & \lambda\sigma & \lambda\sigma+\rho_2 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & A_3 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & k_2 & A_4 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & r_3 & A_5 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & \rho_1 & A_6 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & \eta_1 & 0 & A_7 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & \eta_2 & \rho_1 & A_8 & 0 & 0 \\
0 & 0 & r_2 & 0 & 0 & 0 & 0 & 0 & \rho_2 & -(d+d_H) & 0 \\
0 & r & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & -(r_1+d+d_T)
\end{bmatrix},
$$

where

$$
\begin{aligned}
A_1 &= -(d+d_T+r),\\
A_2 &= \lambda\sigma - (r_2+d+d_H),\\
A_3 &= -(k_2+d+d_H),\\
A_4 &= -(d+d_H+d_T+r_3),\\
A_5 &= -(d+d_H+\eta_1+\rho_1),\\
A_6 &= -(\rho_2+d+d_H+\eta_2),\\
A_7 &= -(d+d_H+\alpha d_H^T+\rho_1),\\
A_8 &= -(d+d_H+\alpha d_H^T+\rho_2).
\end{aligned}
$$

Thus, $\hat{G}(S,I) = \begin{bmatrix}
\beta e T_I \left(1-\frac{S}{N}\right) + \frac{\lambda\sigma T_L(H+H_L+C+C_1+C_2)}{N} \\
\frac{\lambda\sigma T_I(H+H_L+C+C_1+C_2)}{N} \\
\lambda\sigma(H+H_L+C+C_1+C_2)\left(1-\frac{S}{N}\right) \\
-\frac{\lambda\sigma T_L(H+H_L+C+C_1+C_2)}{N} - \frac{\beta e H(T_I+C)}{N} \\
-\frac{\lambda\sigma T_I(H+H_L+C+C_1+C_2)}{N} \\
0 \\
0 \\
0 \\
0 \\
0 \\
0
\end{bmatrix}.$

As $S \leq N$, $\left(1-\frac{S}{N}\right) \geq 0$. But not all entries in $\hat{G}(S,I)$ are non negative. $\hat{G}_3(S,I)$ and $\hat{G}_4(S,I)$ may be negative. Thus, disease free equilibrium of system (2.3) may not be globally stable.

5.2. **The endemic equilibria and their stability.** In this section, we discuss the various endemic equilibria and their stability. Biologically, there can be three endemic equilibria that are TB endemic, HIV endemic and an equilibrium point where both the diseases are endemic.

5.2.1. ***TB endemic equilibrium and stability.*** The TB endemic is given by

$$E_T = (\hat{S}, \ \hat{T}_L, \ \hat{T}_I, \ 0, \ 0, \ 0, \ 0, \ 0, \ 0, \ 0, \ 0, \ \hat{T}_T).$$

One condition for existence of TB endemic equilibrium can be shown as in (3.2) because for TB to be endemic $\lambda_T^* > 0$ which is given by (3.9) and results in $R_0^T > 1$ and the second condition will be proved by using center manifold theory. The $\hat{S}, \ \hat{T}_L, \ \hat{T}_I$ and $\hat{T}_T$ are given as in (3.8).

We prove the local stability of the endemic equilibrium E_T, using the center manifold theory, as described in [5, Theorem 4.1]. We simplify the system (2.3) to apply this method. Let $S = x_1$, $T_L = x_2$, $T_I = x_3$, $H = x_4$, $H_L = x_5$, $C = x_6$, $C_1 = x_7$, $C_2 = x_8$, $C_1^T = x_9$, $C_2^T = x_{10}$, $H^T = x_{11}$ and $T_T = x_{12}$, so that $N = x_1 + x_2 + x_3 + x_4 + x_5 + x_6 + x_7 + x_8 + x_9 + x_{10} + x_{11} + x_{12}$. The model system (2.3) can be written in the form $\frac{dX}{dt} = (f_1, \ f_2, \ f_3, \ f_4, \ f_5, \ f_6, \ f_7, \ f_8, \ f_9, \ f_{10}, \ f_{11}, \ f_{12})^T$ as following:

$$
\begin{aligned}
\frac{dx_1}{dt} &= f_1 = \Lambda - \frac{\beta e x_1 (x_3 + x_6)}{N} - d x_1 - \frac{\lambda \sigma x_1 (x_4 + x_5 + x_6 + x_7 + x_8) + r_1 x_{12}}{N}, \\
\frac{dx_2}{dt} &= f_2 = \frac{\beta e x_1 (x_3 + x_6)}{N} - d x_2 - \frac{\lambda \sigma x_2 (x_4 + x_5 + x_6 + x_7 + x_8)}{N} - k_1 x_2, \\
\frac{dx_3}{dt} &= f_3 = k_1 x_2 - (d + d_T) x_3 - \frac{\lambda \sigma x_3 (x_4 + x_5 + x_6 + x_7 + x_8)}{N} - r x_3, \\
\frac{dx_4}{dt} &= f_4 = \frac{\lambda \sigma x_1 (x_4 + x_5 + x_6 + x_7 + x_8)}{N} - r_2 x_4 - (d + d_H) x_4 - \frac{\beta e x_4 (x_3 + x_6)}{N} + \rho_2 x_8, \\
\frac{dx_5}{dt} &= f_5 = \frac{\lambda \sigma x_2 (x_4 + x_5 + x_6 + x_7 + x_8)}{N} + \frac{\beta e x_4 (x_3 + x_6)}{N} - k_2 x_5 - (d + d_H) x_5, \\
\frac{dx_6}{dt} &= f_6 = k_2 x_5 + \frac{\lambda \sigma x_3 (x_4 + x_5 + x_6 + x_7 + x_8)}{N} - (d + d_T + d_H) x_6 - r_3 x_6, \\
\frac{dx_7}{dt} &= f_7 = r_3 x_6 - \rho_1 x_7 - (d + d_H + \eta_1) x_7, \\
\frac{dx_8}{dt} &= f_8 = \rho_1 x_7 - \rho_2 x_8 - (d + d_H + \eta_2) x_8, \\
\frac{dx_9}{dt} &= f_9 = \eta_1 x_7 - \rho_1 x_9 - (d + d_H + \alpha d_H^T) x_9, \\
\frac{dx_{10}}{dt} &= f_{10} = \eta_2 x_8 + \rho_1 x_9 - (d + d_H + \alpha d_H^T + \rho_2) x_{10}, \\
\frac{dx_{11}}{dt} &= f_{11} = \rho_2 x_{10} + r_2 x_4 - (d + d_H) x_{11}, \\
\frac{dx_{12}}{dt} &= f_{12} = r x_3 - (r + d + d_T) x_{12}.
\end{aligned}
\tag{5.7}
$$

The basic reproduction number of the system (2.3) is given by (5.3). Now, we choose a bifurcation parameter β^*, by solving for $\mathcal{R}_0^T = 1$, we get,

$$\beta^* = \frac{Nd(d + r + d_T)(d + k_1)}{\Lambda k_1}.$$

The Jacobian matrix of the linearized system of (5.7) evaluated at disease free equilibrium point E_0 of system (2.3), is given by (5.4). The Jacobian matrix $J(E_0)$ evaluated at β^* i.e. $J(E_0)|_{\beta^*}$ has the following characteristic polynomial:

$$x(d + x)(d + x + d_H)(2d + r + x + d_T + k_1)(d + x + d_H + k_2)(d + x + d_T + r_1)$$

$$(d + x - \frac{\Lambda\lambda\sigma}{Nd} + d_H + r_2)(d + x + d_H + d_T + r_3)(d + x + d_H + \alpha d_H^T + \rho_1)(d + x + d_H + \eta_1 + \rho_1)$$

$$(d + x + d_H + \alpha d_H^T + \rho_2)(d + x + d_H + \eta_2 + \rho_2). \tag{5.8}$$

Clearly, (5.8) has a zero eigenvalue which is simple and all other eigenvalues have negative real parts when $\mathcal{R}_0^H < 1$. Therefore, we can apply center manifold theory here.

The Jacobian matrix $J(E_0)|_{\beta^*}$ has a right eigenvector, associated with zero eigenvalue given by $w = (w_1,\ w_2,\ w_3,\ w_4,\ w_5,\ w_6,\ w_7,\ w_8,\ w_9,\ w_{10},\ w_{11},\ w_{12})^T$, where $w_i = 0$ for all i except $i = 1, 2, 3$ and 12 which are as follows:

$$\begin{aligned}
w_1 &= \frac{r_1}{d} - \frac{(d + r + d_T)(d + k_1)(d + d_T + r_1)}{drk_1}, \\
w_2 &= \frac{(d + r + d_T)(d + d_T + r_1)}{rk_1}, \\
w_3 &= \frac{(d + d_T + r_1)}{r}, \\
w_{12} &= 1.
\end{aligned} \tag{5.9}$$

The $J(E_0)|_{\beta^*}$ has a left eigenvector $v = (v_1,\ v_2,\ v_3,\ v_4,\ v_5,\ v_6,\ v_7,\ v_8,\ v_9,\ v_{10},\ v_{11},\ v_{12})$ associated with the zero eigenvalue, where

$$\begin{aligned}
v_i &= 0 \ \forall\ i \neq 2, 3, \\
v_2 &= \frac{k_1}{(d + k_1)}, \\
v_3 &= 1.
\end{aligned} \tag{5.10}$$

For determining the local stability near the bifurcation point $\beta^* = \beta e$, we need to determine the signs of the two associated constants, a and b, defined by (3.14) with $\phi = \beta e - \beta^*$ and for $\beta e = \beta^*, \phi = 0$.

For the system (5.7), the associated non-zero partial derivatives at E_0 are

$$\begin{aligned}
\frac{\partial^2 f_2}{\partial x_2 \partial x_3} &= -\frac{\beta^* d}{\Lambda}, & \frac{\partial^2 f_2}{\partial x_3^2} &= -2\frac{\beta^* d}{\Lambda}, \\
\frac{\partial^2 f_2}{\partial x_3 \partial x_{12}} &= -\frac{\beta^* d}{\Lambda}, & \frac{\partial^2 f_2}{\partial x_3 \partial \beta^*} &= 1.
\end{aligned}$$

From the above calculations, we get

$$a = -\frac{(d + d_T + r)^2(d + r + d_T)^2 d}{\Lambda^2 r k_1} - \frac{2Nd^2(d + d_T + r_1)^2(d + r + d_T)}{r^2\Lambda^2}$$
$$- \frac{Nd^2(d + d_T + r_1)(d + d_T + r)}{r\Lambda^2},$$
$$b = \frac{k_1(d + d_T + r_1)}{r(d + k_1)}. \tag{5.11}$$

We conclude that $a < 0$ and $b > 0$. Thus, our calculations together with [5, Theorem 4.1] implies that there exists a TB endemic equilibrium point of system (2.3) when $\mathcal{R}_0^T > 1$ and $\mathcal{R}_0^H < 1$ and is locally asymptotically stable when $\beta^* < \beta e$ with βe close to β^*. Hence, we get the next result.

Theorem 5.2. *The endemic equilibrium point E_T exists for $\mathcal{R}_0^T > 1$ and $\mathcal{R}_0^H < 1$ and is locally asymptotically stable for $\mathcal{R}_0^T$ near 1.*

5.2.2. **HIV endemic and it's stability.** The HIV endemic is given by

$$E_H = (\tilde{S},\ 0,\ 0,\ \tilde{H},\ \tilde{H}_L,\ 0,\ 0,\ 0,\ 0,\ 0,\ \tilde{H}^T,\ 0).$$

One existence condition of HIV endemic equilibrium can be shown as in (4.3) and the other condition will be proved by using center manifold theory. The $\tilde{S}, \tilde{H}, \tilde{H}_L$ and $\tilde{H}^T$ are given as in (4.6). Again we use the center manifold theory, as described in [refer [5, Theorem 4.1]. Using (5.7) as linearized system for (2.3), we choose a bifurcation parameter λ^*. By solving for $\mathcal{R}_0^T = 1$, we get,

$$\lambda^* = \lambda\sigma = \frac{Nd(d + d_H + r_2)}{\Lambda}.$$

The Jacobian matrix of the system (5.7), evaluated at disease free equilibrium point E_0 of the system (2.3), is given by (5.4). The Jacobian matrix $J(E_0)$ evaluated at λ^* i.e. $J(E_0)|_{\lambda^*}$ has the following characteristic polynomial:

$$x(d + x)(d + x + d_H)(d + x + d_H + k_2)(d + x + d_T + r_1)(d + x + d_H + d_T + r_3)$$
$$(d + x + d_H + \alpha d_H^T + \rho_1)(d + x + d_H + \eta_1 + \rho_1)(d + x + d_H + \rho_2)(d + x + d_H + \eta_2 + \rho_2)$$
$$(d^2 + dr + 2dx + rx + x^2 + dd_T + xd_T + dk_1 + rk_1 + xk_1 - \frac{e\beta\Lambda k_1}{dN} + d_T k_1). \tag{5.12}$$

All the factors except last one are linear and have negative real parts. For the last quadratic factor, we use Routh Hurwitz criterion. Comparing with the general quadratic form $a_2 x^2 + a_1 x_1 + a_0$, we get

$$a_2 = 1,$$
$$a_1 = 2d + r + d_T + k_1,$$
$$a_0 = d^2 + dr + dd_T + dk_1 + rk_1 - \frac{e\beta\Lambda k_1}{dN} + d_T k_1.$$

Clearly, $a_2 > 0, a_1 > 0$ and $a_0 > 0$ if

$$d^2 + dr + dd_T + dk_1 + rk_1 - \frac{e\beta\Lambda k_1}{Nd} + d_T k_1 > 0,$$

$$\frac{e\beta\Lambda k_1}{Nd(d^2 + dr + dd_T + dk_1 + d_T k_1)} < 1,$$
$$\Rightarrow \mathcal{R}_0^T < 1.$$

Since the equilibrium point is non-hyperbolic with simple zero eigenvalue, center manifold theory can be applied here.

The Jacobian matrix $J(E_0)|_{\lambda^*}$ has a right eigenvector, associated with the zero eigenvalue given by $\tilde{w} = (\tilde{w}_1, \ \tilde{w}_2, \ \tilde{w}_3, \ \tilde{w}_4, \ \tilde{w}_5, \ \tilde{w}_6, \ \tilde{w}_7, \ \tilde{w}_8, \ \tilde{w}_9, \ \tilde{w}_{10}, \ \tilde{w}_{11}, \ \tilde{w}_{12})^T$, where $\tilde{w}_i = 0 \ \forall \ i$ except $i = 1, 4$ and 11, which are as follows:

$$\begin{aligned}
\tilde{w}_1 &= -\frac{(d + d_H + r_2)(d + d_H)}{dr_2}, \\
\tilde{w}_4 &= \frac{d + d_H}{r_2}, \\
\tilde{w}_{11} &= 1.
\end{aligned} \tag{5.13}$$

All the $\tilde{w}_i$'s except $\tilde{w}_1$ are non negative. The left eigenvector associated with zero eigenvalue is given by $\tilde{v} = (\tilde{v}_1, \ \tilde{v}_2, \ \tilde{v}_3, \ \tilde{v}_4, \ \tilde{v}_5, \ \tilde{v}_6, \ \tilde{v}_7, \ \tilde{v}_8, \ \tilde{v}_9, \ \tilde{v}_{10}, \ \tilde{v}_{11}, \ \tilde{v}_{12})$, where $\tilde{v}_i = 0 \ \forall \ i$ except $i = 4, 5, 6, 7$ and 8, which are as follows:

$$\begin{aligned}
\tilde{v}_4 =& \frac{d + d_H + \eta_2 + \rho_2}{d + d_H + r_2 + \rho_2}, \\
\tilde{v}_5 =& -\frac{(d + d_H + d_T + k_2 + r_3)\rho_1}{(d + d_H + k_2)(d + d_H + d_T + r_3)} + \left(\frac{d + d_H + \eta_1 + \rho_1}{d + d_H + k_2} + k_2 \frac{d + d_H + r_3 + \eta_1 - \rho_1}{d + d_H + d_T + r_3}\right) \\
& \left(\frac{\rho_1(d + d_H + r_2 + \rho_2) + (d + d_H + r_2)(d + d_H + \eta_2 + \rho_2)}{(d + d_H + \eta_1 + \rho_1)(d + d_H + r_2 + \rho_2)}\right), \\
\tilde{v}_6 =& -\frac{\rho_1}{d + d_H + d_T + r_3} \\
& + \frac{(d + d_H + r_3 + \eta_1 + \rho_1)\{\rho_1(d + d_H + r_2 + \rho_2) + (d + d_H + r_2)(d + d_H + \eta_2 + \rho_2)\}}{(d + d_H + r_2 + \rho_2)(d + d_H + d_T + r_3)(d + d_H + \eta_1 + \rho_1)}, \\
\tilde{v}_7 =& \left(\frac{\rho_1(d + d_H + r_2 + \rho_2) + (d + d_H + r_2)(d + d_H + \eta_2 + \rho_2)}{(d + d_H + \eta_1 + \rho_1)(d + d_H + r_2 + \rho_2)}\right), \\
\tilde{v}_8 =& 1.
\end{aligned}$$
$$\tag{5.14}$$

For determining the local stability near the bifurcation point $\lambda^* = \lambda\sigma$, we calculate a and b given by (3.14). For the system (5.7), the associated non-zero partial derivatives at E_0 are

$$\frac{\partial^2 f_4}{\partial x_4^2} = -2\frac{\lambda\sigma d}{\Lambda}, \qquad\qquad \frac{\partial^2 f_4}{\partial x_{11}\partial x_4} = -\frac{\lambda\sigma d}{\Lambda},$$
$$\frac{\partial^2 f_4}{\partial\lambda^*\partial x_4} = 1.$$

Thus, we get

$$a = -\frac{(d + d_H + \eta_2 + \rho_2)\lambda\sigma d(d + d_H)}{r_2\Lambda(d + d_H + r_2 + \rho_2)}\left(\frac{2(d + d_H)}{r_2} + 1\right),$$

$$b = \frac{(d + d_H + \eta_2 + \rho_2)(d + d_H)}{(d + d_H + r_2 + \rho_2)r_2}. \tag{5.15}$$

From (5.15), we get $a < 0$ and $b > 0$. Thus, from our calculation and [5, Theorem 4.1], there exists an HIV endemic E_H of the model system (2.3), when $\mathcal{R}_0^T < 1$ and $\mathcal{R}_0^H > 1$ and is locally asymptotically stable when $\lambda^* < \lambda\sigma$ with $\lambda\sigma$ close to λ^*. Thus, we get the following result:

Theorem 5.3. *The endemic equilibrium point E_H exists for $\mathcal{R}_0^T < 1$ and $\mathcal{R}_0^H > 1$ which is locally asymptotically stable for $\mathcal{R}_0^H$ near 1.*

5.2.3. **Interior endemic equilibrium.** The interior equilibrium point of system (2.3) exists when both the diseases are present in the population. For both the diseases to be endemic, force of infection λ_T and λ_H should be positive and given by (2.1) and (2.2) respectively. It is given by $E_T^H = (\dot{S}, \dot{T}_L, \dot{T}_I, \dot{H}, \dot{H}_L, \dot{C}, \dot{C}_1, \dot{C}_2, \dot{C}_1^T, \dot{C}_2^T, \dot{H}^T, \dot{T}_T)$.

6. Numerical results and discussion

In the present section, numerical simulations are carried out using various set of parameters. The numerical values of the parameters are given in Table (1) and time is set to 50 years. We use MATLAB for the numerical simulations of the system (2.3). For the numerical analysis, we use $N(0) = 20,000$, $S(0) = 11000$, $T_L(0) = 6600$, $T(I) = 832$, $H(0) = 340$, $H_L(0) = 113$, $C(0) = 92$, $C_1(0) = 64$, $C_2(0) = 64$, $C_1^T(0) = 32$, $C_2^T(0) = 32$, $H^T(0) = 265$, $T_T(0) = 566$ as the initial conditions. For initial conditions, it is assumed that more than half of the total population belong to the susceptible. One third of the total population is infected with TB [25]. The population infected with HIV is assumed to be 1.7% and 78% of HIV only infected individuals get proper treatment [20] and 11% of TB active people get co-infected with HIV. The remaining values are estimated assuming we are in controlled situation.

The natural death rate d corresponds to the life expectancy of 71.4 years [24] and $k_2 > k_1$ implies that progression of TB is faster in co-infected individuals. It can be seen that β and e always appear together and βe determines the TB reproduction number $\mathcal{R}_0^T$. Similarly, λ and σ always appear together and the product $\lambda\sigma$ determines the HIV reproduction number $\mathcal{R}_0^H$. In our calculations, we have fixed $\eta_1 = 0.03$ and $\eta_2 = 0.02$ from the given range in Table (1) and for the Figure 4, we variate the values within range. We choose different values of βe and $\lambda\sigma$ for our numerical simulations which are $\beta e = 0.5$ for $\mathcal{R}_0^T < 1$, $\beta e = 2$ for $\mathcal{R}_0^T > 1$, $\lambda\sigma = 0.3$ for $\mathcal{R}_0^H < 1$ and $\lambda\sigma = 1$ for $\mathcal{R}_0^H > 1$ resulting $\mathcal{R}_0^T = 0.73$, $\mathcal{R}_0^T = 2.93$, $\mathcal{R}_0^H = 0.5515$ and $\mathcal{R}_0^H = 1.84$, respectively.

Figure 2 represents the effect of change in total infected population with change in basic reproduction number. We have plotted total infected population by TB, that is, $T_L + T_I + C + C_1 + C_2 + C_1^T + C_2^T + T_T$ and total infected population by HIV, that is, given by $H + H_L + C + C_1 + C_2 + C_1^T + C_2^T + H^T$ verses time. Figure 2 (A) shows that if basic reproduction number $\mathcal{R}_0 < 1$ i.e. $\mathcal{R}_0^T < 1$ and $\mathcal{R}_0^H < 1$, then the infection dies out with time and approaches the disease free equilibrium point E_0. This implies that for $\mathcal{R}_0 < 1$, diseases can not persist for longer duration of time. Figure 2 (B) shows that if $\mathcal{R}_0^T < 1$ and $\mathcal{R}_0^H > 1$, then the TB infection dies out with time more rapidly than in Figure 2

TABLE 1. Model Parameters

Parameter	Symbol	Estimate	Source
Recruitment Rate	Λ	280	assumed
Natural death rate	d	0.01401	estimated
TB induced death rate	d_T	0.1	[3, 17]
HIV induced death rate	d_H	0.2	[17]
IRIS induced death rate	d_H^T	0.33	estimated
Progression rate from latent to active TB with no HIV	k_1	0.5	[3, 17]
Progression rate from latent to active TB with HIV	k_2	$1.3k_1$	[19]
Transition rate of TB treatment from early to late phase	ρ_1	5.56×10^{-3}	[14]
Transition rate of TB treatment from late to completion phase	ρ_2	1.11×10^{-2}	[14]
Recovery rate from TB with no HIV	r_1	0.82	estimated
Per capita HIV treatment rate with no TB	r_2	0.33	[1]
Per capita TB treatment rate in co-infected individuals	r_3	0.1	[14]
Per-capita TB treatment rate with no HIV	r	0.55	[1]
HIV early treatment rate	η_1	$0 - 0.05$	[14]
HIV late treatment rate	η_2	$0 - 0.05$	[14]
Rate of occurrence of IRIS	γ	1×10^{-3}	[14]

(A) and HIV infection first increases to a maximum value after that decreases to attain a constant value which corresponds to the HIV endemic equilibrium point E_H. Thus, increased HIV infection in population slightly decreases the TB infection and its time of persistence. Figure 2 (C) shows that for $\mathcal{R}_0^T > 1$ and $\mathcal{R}_0^H < 1$, TB infection increases very rapidly to attain a maximum value and then decreases slowly to retain a constant value. Also, HIV infection decreases with time but very slowly and approaching towards zero corresponding to the TB endemic E_T. This graph shows that highly increased TB infected population affects the HIV infected population. Therefore, it persists for a larger duration of time though small in number. It can be seen that HIV infected population is continuously decreasing with time but does not vanish even in a span of 50 years. Figure 2 (D) shows that if $\mathcal{R}_0^T > 1$ and $\mathcal{R}_0^H > 1$, then both the diseases become endemic and increase simultaneously to a peak value and then decrease to attain constant values corresponding to the interior equilibrium point E_T^H. This represents that in favourable conditions, that is, $\mathcal{R}_0^T > 1$ and $\mathcal{R}_0^H > 1$, both the diseases favour each other and continue increasing rapidly and after reaching a maximum value, they again decrease to attain a constant value. This shows that no epidemic can last forever.

Figure 3 depicts graphical representations of the change in population infected with single disease only, with change in reproduction number by plotting $T_L + T_I$, H and C verses time. For $\mathcal{R}_0^T < 1$ and $\mathcal{R}_0^H < 1$, Figure 3 (A) shows that the diseases die out with time. Figure 3 (B) shows that for $\mathcal{R}_0^T < 1$ and $\mathcal{R}_0^H > 1$, TB infection decreases rapidly with time and finally vanishes, while HIV infected population first increases rapidly and then decreases before attaining a constant value which is $\tilde{H}$ of equilibrium point E_H. Co-infected population also increases very rapidly even when $\mathcal{R}_0^T < 1$ and then decreases to become constant. Figure 3 (C) shows that for $\mathcal{R}_0^T > 1$ and $\mathcal{R}_0^H < 1$, TB infected population first increases very rapidly and then slowly decreases to a constant value which
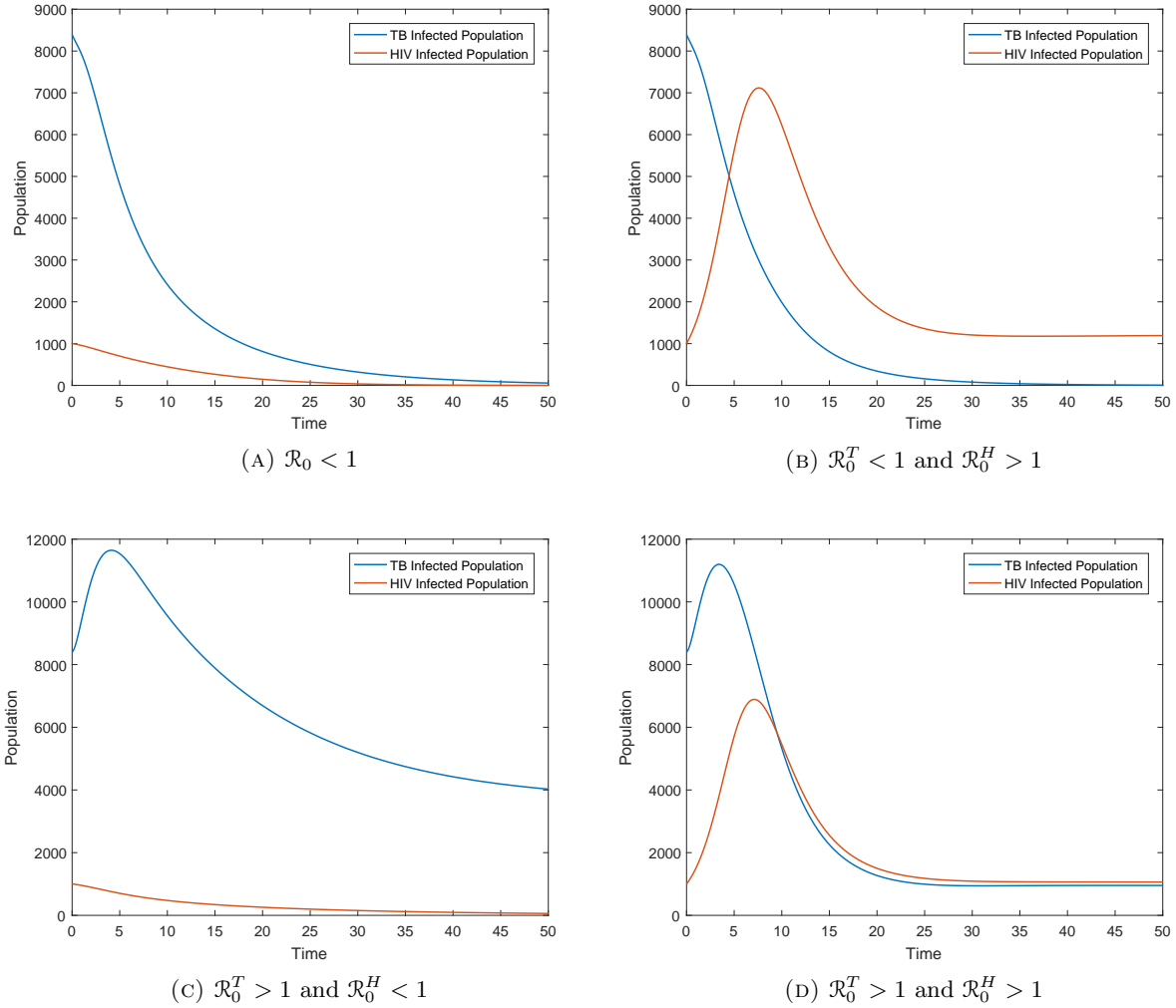
FIGURE 2. Effect of Reproduction Number on Infected population

is $\hat{T}_L + \hat{T}_I$, while HIV infected population vanishes very soon. Thus, the co-infected population also decreases with time and then vanishes. This corresponds to the equilibrium point E_T. Figure 3 (D) shows that for $\mathcal{R}_0^T > 1$ and $\mathcal{R}_0^H > 1$, both the infections in population first increase to a maximum value and after that decrease rapidly to attain constant values and these constant values correspond to the interior equilibrium point.

Figure 4 shows the effect of reproduction number with early or late initiation of ART during TB treatment on disease induced death. We have plotted the time verses disease induced death in compartments C_1^T and C_2^T. We have plotted the graphs for four different set of values $\eta_1 = 0$,

(A) $\mathcal{R}_0 < 1$

(B) $\mathcal{R}_0^T < 1$ and $\mathcal{R}_0^H > 1$

(C) $\mathcal{R}_0^T > 1$ and $\mathcal{R}_0^H < 1$

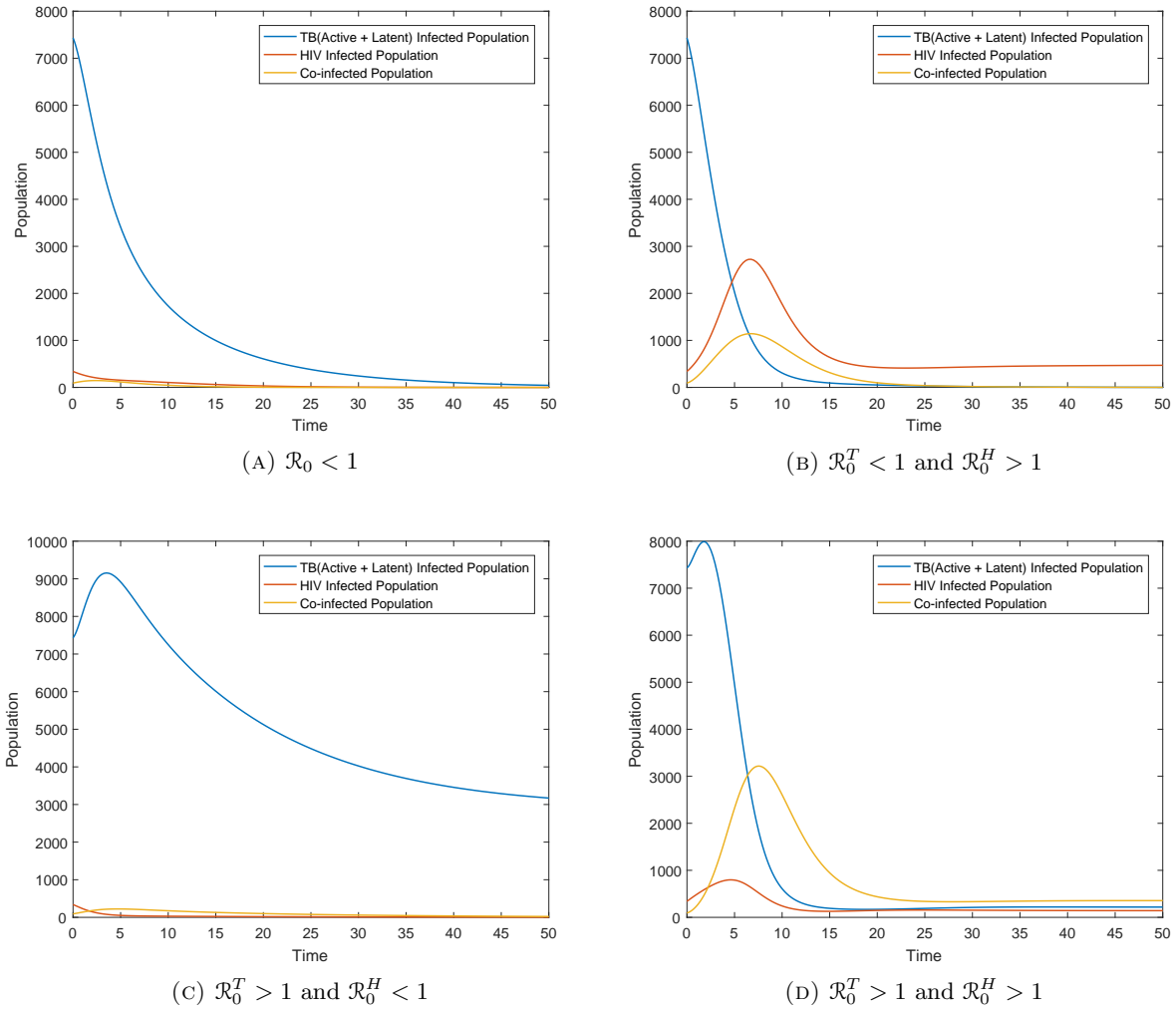(D) $\mathcal{R}_0^T > 1$ and $\mathcal{R}_0^H > 1$

FIGURE 3. Effect of Reproduction Number on TB only infected population ($T_L + T_I$), HIV only infected population (H) and Co-infected population undergoing no treatment (C).

$\eta_2 = 0$; $\eta_1 = 0.03$, $\eta_2 = 0.02$; $\eta_1 = 0.04$, $\eta_2 = 0.02$ and $\eta_1 = 0.02$, $\eta_2 = 0.04$. Figure 4 shows that higher the rate of early phase HIV treatment during TB treatment, lower is the disease induced death. Figure shows that for $\mathcal{R}_0 < 1$ disease induced death decreases with time and vanishes after some time. For $\mathcal{R}_0^T < 1$ and $\mathcal{R}_0^H > 1$, the disease induced death decreases to vanish after attaining a maximum value. For $\mathcal{R}_0^T > 1$ and $\mathcal{R}_0^H < 1$ the disease induced death increases after a slight decrease and then keep on decreasing. For $\mathcal{R}_0 > 1$, the disease induced death increases to a maximum value
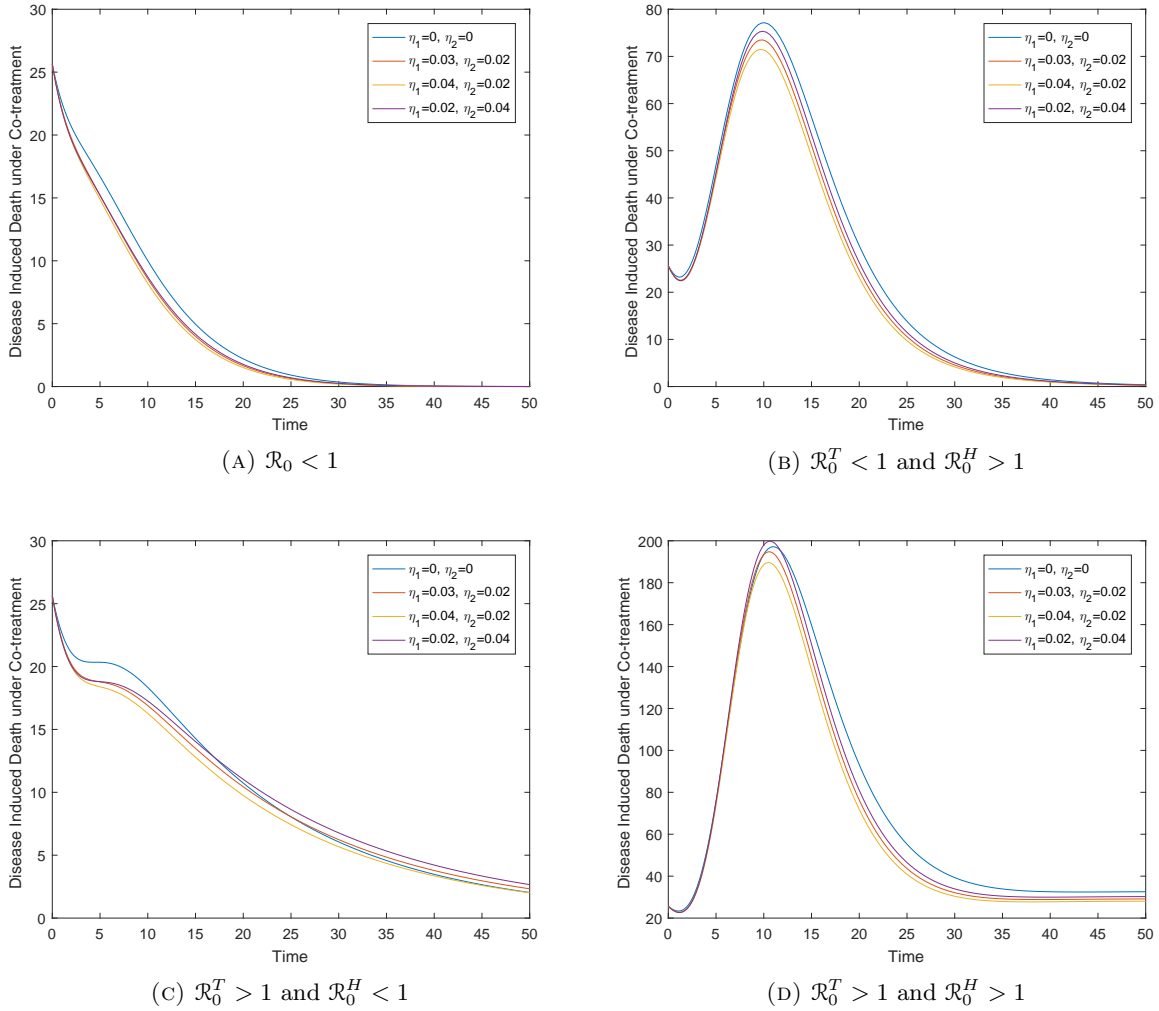
FIGURE 4. Effect of early or late Initiation of ART during TB treatment on disease induced death of population under Co-treatment

and then decreases to attain a constant value. Figure 4 shows that higher the rate of HIV early treatment during TB treatment, lower is the disease induced death, while increased rate of HIV late treatment does not have very remarkable impact on disease induced death.

Figure 5 shows the effect of treatment for single disease infection, that is, effect of r, r_2 and r_1 on the total infected population $(T_L + T_I + H + H_L + C + C_1 + C_2 + C_1^T + C_2^T)$. We plot the graph of the time verses infected population for different reproduction numbers. For population without treatment, we assume $r = r_1 = r_2 = 0$, that is, there is no treatment for TB for T_I class, so no

(A) $\mathcal{R}_0 < 1$

(B) $\mathcal{R}_0^T < 1$ and $\mathcal{R}_0^H > 1$

(C) $\mathcal{R}_0^T > 1$ and $\mathcal{R}_0^H < 1$

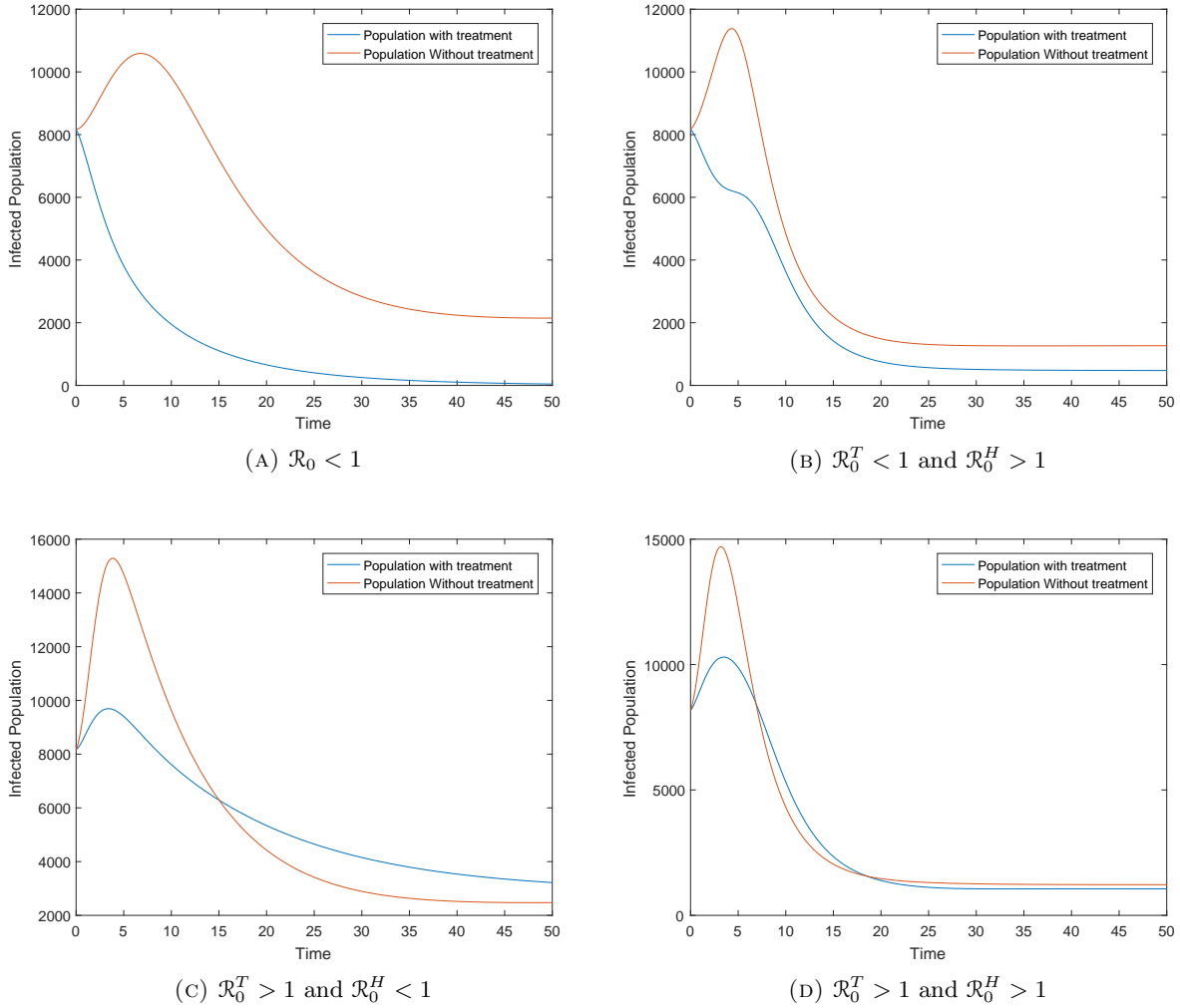(D) $\mathcal{R}_0^T > 1$ and $\mathcal{R}_0^H > 1$

FIGURE 5. Effect of single disease infection treatment on the infected population $(T_L + T_I + H + C + C_1 + C_2 + C_1^T + C_2^T)$.

recovery by treatment i.e. $r_1 = 0$ and there is no treatment for H compartment. Figure 5 (A) shows that for basic reproduction number $\mathcal{R}_0 < 1$ i.e. $\mathcal{R}_0^T < 1$ and $\mathcal{R}_0^H < 1$, the infection dies out with time when treatment is considered while for no single disease treatment infected population does not vanish even in a span of 50 years. Figure 5 (B) shows that when $\mathcal{R}_0^T < 1$ and $\mathcal{R}_0^H > 1$, for no treatment of single disease infected population, the infected population first increases rapidly and then decreases to become constant at a higher value than with the treatment. In our discussion henceforth, term treatment signifies the treatments for single disease infected population. Figure
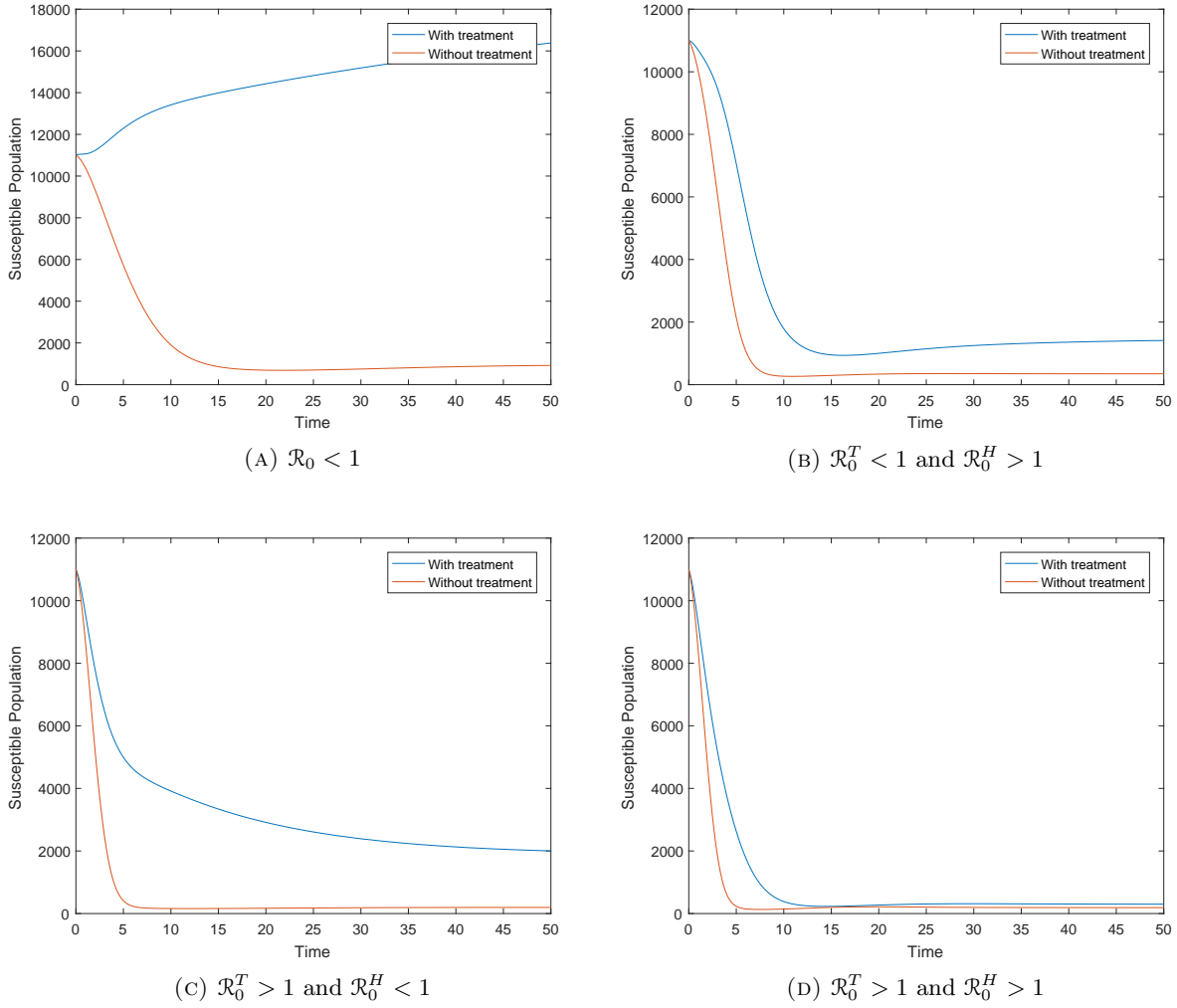
FIGURE 6. Effect of single disease infection treatment on susceptible population.

5 (C) shows that for $\mathcal{R}_0^T > 1$ and $\mathcal{R}_0^H < 1$, infected population first increases in both cases and then decreases, but for no treatment infection increases rapidly than for the treatment and then decreases to attain a constant value less than the value attained by the curve with treatment. Figure 5 (D) shows that for $\mathcal{R}_0^T > 1$ and $\mathcal{R}_0^H > 1$, infected population without treatment increases more rapidly and then decreases to attain a constant value a little larger than for the population with treatment.

Figure 6 shows the effect of single disease infection treatments on the susceptible population. Figure 6 (A) shows that for $\mathcal{R}_0 < 1$, the susceptible tend to increase with treatments while for

the other case susceptible decrease to attain a constant value which is very small. Figure 6 (B) shows that for $\mathcal{R}_0^T < 1$ and $\mathcal{R}_0^H > 1$, susceptible population undergoing treatment for single disease infection as well as co-infection treatment is always greater than the susceptible population with only co-infection treatment and with passage of time treatment increases the susceptible population while with no treatment, susceptible population decreases to a very small value. Figure 6 (C) shows that for $\mathcal{R}_0^T > 1$ and $\mathcal{R}_0^H < 1$, the susceptible in both cases decrease to attain a constant value but susceptible population without treatment decrease very rapidly to attain an extremely low value as compared to susceptible with treatment. Figure 6 (D) shows that for $\mathcal{R}_0^T > 1$ and $\mathcal{R}_0^H > 1$, the susceptible population decreases rapidly with time so that population without treatment is always less than the population with treatment.

From Figures 5 and 6, we conclude that in absence of treatment for single disease infection, the disease induced death increases and infection persists even when $\mathcal{R}_0 < 1$, disease induced death increases independent of the reproduction number and the susceptible population decreases to a very small quantity.

7. Conclusion

The main model (2.3) is a 12 dimensional system for which only limited analytical results are obtained. The TB only and HIV only models have globally stable disease free equilibria when their corresponding reproduction number is less than unity. For reproduction number greater than unity, the endemic equilibria also exist and are locally asymptotically stable. The full HIV-TB co-infection model is shown to have a locally asymptotically stable disease free equilibrium when $\mathcal{R}_0 < 1$. The HIV only and TB only equilibrium exist and are locally asymptotically stable when $\mathcal{R}_0^H > 1$, $\mathcal{R}_0^T < 1$ and $\mathcal{R}_0^H < 1$, $\mathcal{R}_0^T > 1$, respectively.

The simulation results provided many interesting insights into the effect of the dynamics of HIV-TB co-infection. Figure 2 and 3 show that the presence of TB may have a significant influence on HIV dynamics. For endemic TB, prevalence of HIV increases. When HIV is endemic that is $\mathcal{R}_0^H > 1$ then even for $\mathcal{R}_0^T < 1$, the co-infected population increases dramatically. Figure 4 shows that early initiation of ART during TB treatment is more effective to reduce disease induced death. Figures 5 and 6 show that co-infection treatment alone is not sufficient to eradicate the diseases, treatment for TB only and HIV only patients separately is also necessary. In the absence of that disease induced death becomes very high and infection prevails even when reproduction number is less than unity. Numerical results show that investing more in single disease infection treatments is more effective to reduce the infection and disease induced death.

Our model has limited implications as results are based on local mathematical analysis and the model does not consider the common forms of HIV transmission other than sexual transmission, the TB drug resistance and exogenous reinfection, the effect of age, effect of population density at a place etc. Thus, enhanced and more complex studies in this field are required to understand the infection dynamics in a further better way.

Acknowledgments

References

[1] C. P. Bhunu, W. Garira and Z. Mukandavire, Modeling HIV/AIDS and tuberculosis coinfection, Bull. Math. Biol. **71** (2009), no. 7, 1745–1780.

[2] M. M. Bosma-den Boer, M. L. van Wetten and L. Pruimboom, Chronic inflammatory diseases are stimulated by current lifestyle: how diet, stress levels and medication prevent our body from recovering, Nutr. Metab. (Lond.) (2012), no. 9.

[3] C. Castillo-Chavez and Z. Feng, To treat or not to treat: the case of tuberculosis, J. Math. Biol. **35** (1997), no. 6, 629–656.

[4] C. Castillo-Chavez, Z. Feng and W. Huang, On the computation of $\mathscr{R}_0$ and its role on global stability, in *Mathematical approaches for emerging and reemerging infectious diseases: an introduction (Minneapolis, MN, 1999)*, 229–250, IMA Vol. Math. Appl., 125, Springer, New York.

[5] C. Castillo-Chavez and B. Song, Dynamical models of tuberculosis and their applications, Math. Biosci. Eng. **1** (2004), no. 2, 361–404.

[6] De Cock, Kevin M., and R. E. Chaisson. Will DOTS do it? A reappraisal of tuberculosis control in countries with high rates of HIV infection, The International Journal of Tuberculosis and Lung Disease **3**, no. 6 (1999): 457–465.

[7] O. Diekmann, J. A. P. Heesterbeek and J. A. J. Metz, On the definition and the computation of the basic reproduction ratio $\mathcal{R}_0$ in models for infectious diseases in heterogeneous populations, J. Math. Biol. **28** (1990), no. 4, 365–382.

[8] O. Diekmann, J. A. P. Heesterbeek and M. G. Roberts. "The construction of next-generation matrices for compartmental epidemic models." Journal of the Royal Society Interface (2009): rsif20090386.

[9] S. Gakkhar and N. Chavda, A dynamical model for HIV-TB co-infection, Appl. Math. Comput. **218** (2012), no. 18, 9261–9270.

[10] G. Guzzetta et al., Modeling socio-demography to capture tuberculosis transmission dynamics in a low burden setting, J. Theoret. Biol. **289** (2011), 197–205.

[11] J. H. Jones, Notes on $\mathcal{R}_0$. http://web.stanford.edu/~jhj1/teachingdocs/Jones-on-R0.pdf

[12] N. Kaur, M. Ghosh and S. S. Bhatia, HIV-TB co-infection: a simple mathematical model, J. Adv. Res. Dyn. Control Syst. **7** (2015), no. 1, 66–81.

[13] E. F. Long, N. K. Vaidya and M. L. Brandeau, Controlling co-epidemics: analysis of HIV and tuberculosis infection dynamics, Oper. Res. **56** (2008), no. 6, 1366–1381.

[14] A. Mallela, S. Lenhart and N. K. Vaidya, HIV-TB co-infection treatment: modeling and optimal control theory perspectives, J. Comput. Appl. Math. **307** (2016), 143–161.

[15] R. Naresh, D. Sharma and A. Tripathi, Modelling the effect of tuberculosis on the spread of HIV infection in a population with density-dependent birth and death rate, Math. Comput. Modelling **50** (2009), no. 7-8, 1154–1166.

[16] L. Perko, *Differential equations and dynamical systems*, third edition, Texts in Applied Mathematics, 7, Springer-Verlag, New York, 2001.

[17] L.-I. W. Roeger, Z. Feng and C. Castillo-Chavez, Modeling TB and HIV co-infections, Math. Biosci. Eng. **6** (2009), no. 4, 815–837.

[18] K. A. Sepkowitz, How contagious is tuberculosis?, Clinical Infectious Diseases **23** (1996), no 6, 954–962.

[19] C. J. Silva and D. F. M. Torres, A TB-HIV/AIDS coinfection model and optimal control treatment, Discrete Contin. Dyn. Syst. **35** (2015), no. 9, 4639–4663.

[20] TBFACTS.ORG. https://www.tbfacts.org/tb-hiv/.

[21] TBFACTS.ORG. https://www.tbfacts.org/tb-treatment/.

[22] TBFACTS.ORG. https://www.tbfacts.org/tb-statistics/

[23] J. M. Trauer, J. T. Denholm and E. S. McBryde, Construction of a mathematical model for tuberculosis transmission in highly endemic regions of the Asia-pacific, J. Theoret. Biol. **358** (2014), 74–84.

[24] World Health Organisation. http://www.who.int/gho/mortality_burden_disease/life_tables/situation_trends/en/.

[25] World Health Organisation. http://www.who.int/mediacentre/factsheets/fs104/en/.

[26] World Health Organisation. http://www.who.int/mediacentre/factsheets/fs360/en/.

Sachin Kumar, Assistant Professor, Department of Mathematics, University of Delhi, New Delhi-110007, India.
  E-mail address: sachinambariya@gmail.com

Shikha Jain, Department of Mathematics, University of Delhi, Delhi, India.
  E-mail address: shikhajain01051990@gmail.com