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Mathematical Analysis of Optimal Control of Human Immunodeficiency Virus (HIV) Co-infection with Tuberculosis (TB)

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

The co-occurrence of Human Immunodeficiency Virus (HIV) and Tuberculosis (TB) poses a significant global health challenge, affecting an estimated 1.4 million individuals worldwide. The synergistic progression of these diseases contributes to elevated morbidity and mortality rates. Recognizing the substantial public health burden they impose, this study introduces fifteen (15) compartmental models to discern optimal control strategies for treating HIV-TB co-infection. Initial consideration is given to sub-models for HIV and TB individually, followed by the comprehensive HIV-TB co-infection model. The research quantitatively analyzes the existence and uniqueness of HIV and TB models, examining the stability of equilibrium points for disease-free and endemic states. The Basic Reproduction Number (R_0) is computed using the Next Generation Matrix method. Optimal control strategies are evaluated to determine the preferred sequence for treating co-infection. Employing MAPLE software with the differential transformation method, numerical simulations underscore the importance of epidemiological features in the dynamic spread of HIV-TB co-infection. The results emphasize the efficacy of simultaneous treatment for both diseases, coupled with immune system support, compared to sequential treatment of one disease.

Keywords: HIV; TB; reproduction number; equilibrium points; stability; optimal.

1. INTRODUCTION

HIV remains a substantial health challenge, causing both loss of lives and considerable economic burdens on governments and individuals. The disease has claimed over 39 million lives, and despite ongoing intervention efforts, its impact continues to affect numerous individuals. ([3], [7], [23], [36]). HIV is a virus that can be transmitted through specific body fluids, and it primarily targets the body's immune system, particularly the CD4 cells. These cells are crucial for maintaining immune function, and their levels are commonly used to measure the health of the immune system. As HIV progressively damages CD4 cells, the body's ability to defend itself against infections and diseases weakens, leading to an increased vulnerability to various opportunistic infections and illnesses ([22], [32]). Indeed, tuberculosis (TB) is one of the opportunistic diseases that can affect individuals with weakened immune systems, such as those living with HIV ([1], [35]). TB is caused by the bacterium Mycobacterium tuberculosis, and it is highly contagious. The bacteria primarily target the lungs, leading to pulmonary TB, but they can also spread to other organs and tissues in the body, causing extrapulmonary TB ([13], [27], [38]). Tuberculosis (TB) ranks second as a global killer caused by a single infectious agent, with a considerable number of infections and deaths ([15], [16]). The burden of TB disproportionately falls on low- and middle-income countries, where over 95% of TB-related deaths occur ([7], [37]). To effectively implement existing intervention strategies, an estimated $2 billion is needed to bridge the resource gap [8]. HIV and TB have a well-established synergistic relationship, where each disease increases the susceptibility to contracting the other. This co-infection can lead to more severe health consequences and challenges in treatment, making it crucial to address both diseases comprehensively in healthcare strategies ([8], [14], [20], [28]). Individuals living with HIV have a significantly higher risk of developing tuberculosis (TB) compared to those who are HIV-negative. Studies have shown that people with HIV are approximately 12 to 20 times more likely to contract TB, highlighting the increased vulnerability of this population to the disease ([8], [12]). In the case of HIV and TB co-infection, both diseases interact in a way that worsens their effects on the immune system and overall health, making it more challenging to manage and increasing the risk of severe health outcomes. Addressing these diseases as a syndemic requires comprehensive and integrated approaches to effectively control their spread and improve patient outcomes ([7], [18], [19], [29], [31]).

Indeed, mathematical modeling has been extensively utilized in researching HIV-TB co-infection. These models help in studying the complex dynamics between HIV and TB, and how the co-infection affects disease progression and transmission. [35] Developed a comprehensive mathematical model to analyze the transmission of HIV and curable TB co-infection in a population of varying size. Their model considers essential factors such as population size, transmission rates, treatment

effectiveness, and other relevant variables, making it a valuable tool for understanding the dynamics of these diseases and devising effective strategies for control.

The co-infection of Human Immunodeficiency Virus (HIV) and Tuberculosis (TB) stands as one of the deadliest diseases globally. Despite significant efforts through public health campaigns, seminars, drug administration, and the isolation of infected individuals, there remains a need for alternative strategies. The focus of this research is to explore optimal control strategies to address the longstanding debate on whether HIV or TB should be treated first, a dilemma that has impeded the effectiveness of co-infection control measures. The study aims to investigate and propose appropriate control measures for this complex health challenge.
The paper is structured as follows:

Section 2 outlines the formulation of the model. In Section 3, the complete model is divided into two fundamental sub-models, namely the HIV-only model and the TB only sub-model. The qualitative analysis of each sub-model is presented in this section. Then, in Section 4, the main model is extended to an optimal control problem, and its qualitative analysis using Pontryagin's maximum principle is discussed. In Section 5, numerical experimentation of the resulting optimal control is conducted, and the outcomes are analyzed. Finally, in Section 6, the main discussion and conclusions of the research are presented.

2. MATHEMATICAL MODEL FORMULATION

In modeling the dynamics of HIV- TB co-infection, the total homogeneously mixing population at time t, denoted by N(t), is divided into fifteen (15) compartments of Susceptible (S(t)) individuals, Latently HIV $(L_H(t))$ individuals, HIV Undetected $(H_U(t))$ individuals, HIV Detected $(H_D(t))$ individuals, Treated HIV $(H_W(t))$ individuals, Latently TB and HIV $(L_{TH}(t))$ individuals, Active TB and HIV $(A_{TH}(t))$ individuals, Latently HIV and TB $(L_{HT}(t))$ individuals, Active HIV and TB $(A_{HT}(t))$ individuals, Latent TB $(L_T(t))$ individuals, TB Undetected $(T_U(t))$ individuals, TB Detected $(T_D(t))$ individuals, Failed Treatment TB $(F_T(t))$ individuals, Recovered TB $(R_T(t))$ individuals, Recovered TB and HIV $(R_{TH}(t))$ individuals. Table 1 gives a description of these. So that:

$$N(t) = S + L_H + H_U + H_D + H_W + L_{TH} + A_{TH} + L_{HT} + A_{HT} + L_T + T_U + T_D + F_T + R_T + R_{TH} \quad (1.1)$$

The susceptible population expands through the recruitment of individuals at a rate π , while natural death μ and transmission from both singly and dually-infected individuals contribute to its decrease. Singly and dually-infected individuals play distinct roles in transmitting either HIV or TB infection, a concept elaborated in the subsequent sections. This separation facilitates a clearer formulation of the disease transmission process.

Susceptible individuals acquire HIV infection, following effective contact with people infected with HIV only (i.e. those in the $(L_H, \eta_U H_U, \eta_{dH} H_D and \eta_W H_W)$classes at a rate λ_H , given by:

$$\lambda_H = \beta_H \frac{(L_H + \eta_U H_U + \eta_{dH} H_D + \eta_W H_W)}{N} \quad (1.2)$$

Where, β_H is the effective contact rate for HIV transmission.

Similarly, susceptible individuals acquire TB infection from individuals with TB only i.e. $(L_T, \eta_U T_U, \eta_{dT} T_D, \eta_{RT} R_T and F_T)$ classes at a rate λ_T , given by

$$\lambda_T = \beta_T \frac{(L_T + \eta_U T_U + \eta_{dT} T_D + \eta_{RT} R_T + F_T)}{N} \quad (1.3)$$

Where, β_T is the effective contact rate for the TB infection.

Dually-infected individuals are assumed capable of transmitting either HIV or TB, but not the mixed infection.

The Transmission rate of HIV and TB is given as:

$$\lambda_{HT} = \beta_{HT}\frac{(L_{HT}+\eta_H A_{HT})}{N} \quad (1.4)$$

Also, the Transmission rate of TB and HIV is given as:

$$\lambda_{TH} = \beta_{TH}\frac{(L_{TH}+\eta_T A_{TH}+\eta_{RT} R_{TH})}{N} \quad (1.5)$$

Then:

$$\frac{dS}{dt} = \pi - \lambda_H S - \lambda_T S - \mu S - \lambda_{TH} S - \lambda_{HT} S \quad (1.6)$$

A fraction ε_1 of the newly infected individuals are assumed to show no disease symptoms initially. These individuals (known as "slow progressors") are moved to the latently HIV class(L_H). The remaining fraction, $(1-\varepsilon_1)$ of the newly infected individuals are assumed to immediately display disease symptoms (fast progressors) and are moved to the undetected infectious class H_U. The population of latent class is decreased by the progression of latent HIV individual to active undetected HIV H_U (at a rate κ_H) and also reduced by natural death rate (μ) and finally increased by the fraction of Treated HIV at the rate (φ) that moves from treated class to latently HIV compartment. Thus:

$$\frac{dL_H}{dt} = \varepsilon_1\lambda_H S - (\kappa_H + \mu)L_H + \varphi H_W \quad (1.7)$$

The population of undetected infected individuals is increased by the infection of fast progressors at the rate $(1-\varepsilon_1)\lambda$ and the development of symptoms by latently individual at the rate, $(1-\omega_1)\kappa_H$ where ω_1 is the endogenous reactivation rate. This population is decreased by natural death rate (μ) and disease induced death (at a rateδ_{UH}) and further decreased by detection rate (γ_{UH}) of HIV undetected infected individuals. Hence:

$$\frac{dH_U}{dt} = (1-\varepsilon_1)\lambda_H S + (1-\omega_1)\kappa_H L_H - (\gamma_{UH} + \mu + \delta_{UH})H_U \quad (1.8)$$

The population of detected infected HIV individual increases by the fraction of latently HIV individuals who develop disease symptoms (at the rate$\omega_1\kappa_H$), where $\omega_1$is the endogenous reactivation rate and the detection of undetected individual at the rateγ_{UH}. The population is later decreased by treatment rate (τ_1) for HIV detected individual and finally reduced by the natural death rate, induced mortality death rate at μ and δ_{UH} respectively. Hence:

$$\frac{dH_D}{dt} = \omega_1\kappa_H L_H + \gamma_{UH}H_U - (\tau_1 + \mu + \delta_{U_H})H_D \quad (1.9)$$

The population of treated HIV individuals is increased by those that have received treatment from HIV detected infected individual at the rate (τ_1), this population reduces by the fraction of treated individuals that moved back to latently HIV individuals at the rate, (ϕ) since treatment does not completely clears the virus and finally reduced by natural death rate (μ).
Hence,

$$\frac{dH_W}{dt} = \tau_1 H_D - (\varphi + \mu)H_W \quad (2.0)$$

The population of latent TB and HIV is increased by infection, which can be acquired following effective contact with infectious individuals in the latent TB and HIV (L_{TH}), Active TB induced HIV ($\eta_T A_{TH}$) or Recovered TB induced HIV ($\eta_{RT}R_{TH}$) categories at a rate λ given by

$$\lambda_{TH} = \beta_{TH}\frac{(L_{TH}+\eta_T A_{TH}+\eta_{RT} R_{TH})}{N} \quad (2.1)$$

Whereβ_{TH} represents the effective contact rate.

The population is reduced by progression from latent stage to active stage at the rate (κ_{TH}), and by natural death at the rate (μ). The population later is increased by the fraction of those that have been treated that moved from treated compartment at the rate (α_T). Then the rate of change of latent TB induced HIV population is given by:

$$\frac{dL_{TH}}{dt} = \lambda_{TH} S - (\kappa_{TH} + \mu)L_{TH} + \alpha_T R_{TH} \quad (2.2)$$

The population of active TB and HIV is increased by the progression from latent stage to active stage at the rate (κ_{TH}), the population is decreased by natural death, induced mortality due to disease at the rate (μ) and (δ) respectively, individuals who recovered also moved to recovered TB induced HIV at the rate (σ_1).

Hence,

$$\frac{dA_{T_H}}{dt} = \kappa_{TH}L_{TH} - (\mu + \sigma_1 + \delta A_{TH})A_{TH} \quad (2.3)$$

The population of latent HIV and TB is increased by infection, which can be acquired following effective contact with infectious individuals in the latent HIV and TB (L_{HT}), or active HIV induced TB ($\eta_H A_{HT}$) categories at a rate λ given by:

$$\lambda_{HT} = \beta_{HT}\frac{(L_{HT}+\eta_H A_{HT})}{N} \quad (2.4)$$

Where β_{HT} represents the effective contact rate. The population is reduced by progression from latent stage to active stage at the rate (κ_{HT}) and by natural death rate. Hence, latent HIV and TB population is given by:

$$\frac{dL_{HT}}{dt} = \lambda_{HT}S - (\kappa_{HT} + \mu)L_{HT} \quad (2.5)$$

Active HIV and TB (A_{HT}) population is increased by the progression from latent stage to active stage at the rate (κ_{HT}). The population decreased by natural death rate (μ) and disease induced mortality at the rate (δ). Hence the system of equation of Active HIV induced TB is given by:

$$\frac{dA_{HT}}{dt} = \kappa_{HT} - (\mu + \delta A_{HT})A_{HT} \quad (2.6)$$

A fraction ε_2 of the newly–infected individuals are assumed to show no disease symptoms initially. These individuals (known as slow progressors for TB) moved to the latently TB class (L_T). The remaining fraction $(1-\varepsilon_2)$ of the newly infected individuals are assumed to immediately display disease symptoms (fast progressor for TB) and are moved to the undetected infected compartment (T_U). The population is decreased by progression rate (κ_T) from latent TB class to infected undetected class, natural death rate (μ) and exogenous re-infective (at a rate$\phi\lambda_T$), where $\phi < 1$ accounts for the assumption that latent individuals have reduced infection rate, this is to account for the fact that individuals with latent TB infection have partial immunity against exogenous re-infection. The population is increased by natural recovery at the rate (υ), number of unsuccessful treated individuals who move to the latent TB individuals at the rate ($\theta_1\rho$)and rate ($r\alpha$) respectively at which treated TB individuals wane the treatment. Then the population is given by:

$$\frac{dL_T}{dt} = \varepsilon_2\lambda_T S - (\kappa_T + \phi\lambda_T + \mu)L_T + \upsilon T_U + \theta_1\rho F_T + r\alpha R_T \quad (2.7)$$

The population of undetected infectious individuals is increased by the infection of fast progressors at the rate $(1-\varepsilon_2)\lambda_T$ and the development of symptoms by latent individuals at the rate, $(1-\omega_2)\kappa_T$, where ω_2 is the fraction of exposed individuals who develop symptoms and are detected. It is further increased by the exogenous re-infection of expressed individuals at the rate, $(1-\omega_3)\phi\lambda_T$, where $\omega_3$is the fraction of re-infected exposed individuals who are detected, and fraction of unsuccessful treated individuals that move from detected individuals to undetected individuals at the rate, $(\theta_2\rho)$. The population is decreased by natural recovery at a rate, (υ), detection of undetected individuals at a rate, (γ_{UH}), natural death at the rate (μ) and disease induced death at a rate (δ_{UT}). Hence:

$$\frac{dT_U}{dt} = (1-\varepsilon_2)\lambda_H S + (1-\omega_2)\kappa_T L_T + (1+\omega_3)\phi\lambda_T L_T + \theta_2\rho F_T - (\upsilon + \gamma_{UT} + \mu + \delta_{UT})T_U \quad (2.8)$$

The population of detected infectious individuals increases by the fraction of latent individuals who develop diseases symptoms at a rate $\omega_2\kappa_T$, exogenous re-infection of latent individuals, detection rate for undetected individuals at the rates $\omega_3\phi, \gamma_{UT}$ respectively and numbers of unsuccessful treated individuals who move to latent and undetected individuals at the rates θ_1 andθ_2 respectively. The population is decreased by those that are treated and recovered who later moved to recovered

compartment at the rate (σ_2), treatment rate (τ_2), natural death rate (μ) and disease induced death at a rate (δ_{dT})This gives:

$$\frac{dT_D}{dt} = \omega_2\kappa_T L_T + \omega_3\phi L_T + \gamma_{UT}T_U + [1-(\theta_1+\theta_2)]\rho F_T - (\sigma_2+\tau_2+\mu+\delta_{dT})T_D \quad (2.9)$$

The population of failed treatment compartment is generated by the failure of treated infected detected individuals at the rate, $(1-q_1)\tau_2$. The treatment failure could be due to a number of reasons, such as incomplete compliance to the specified treatment or drug resistance among others. The population is decreased by the fraction of treated individuals who lose their treatment; the population is decreased by the rate at which TB individuals who fail treatment move to other classes, natural death and induced death at the rate ($\ell + \mu + \delta_F$). Thus:

$$\frac{dF_T}{dt} = (1-q_1)\tau_2 T_D + (1-r)\alpha R_T - (\rho+\mu+\delta_F)F_T \quad (3.0)$$

The population of TB recovered individuals is increased by the treatment of detected individuals at the rate $q_1\tau_2$ and treated detected individuals at the rate σ_2, successfully– recovered individuals eventually move to the latent class at the rate, α. This population is further decreased by natural death and disease induced death at the rate μ and δ_{RT} respectively.

Hence:

$$\frac{dR_T}{dt} = q_1\tau_2 T_D - (\alpha+\mu+\delta_{RT})R_T + \sigma_2 T_D \quad (3.1)$$

The population of TB and HIV recovered individual is increased by the treatment of active TB at the σ_1 and later reduced by natural death rate μ and the rate (α_T), at which treated individuals lose their treatment induced immunity. Thus we have:

$$\frac{dR_{TH}}{dt} = \sigma_1 A_{TH} - (\alpha_T+\mu)R_{TH} \quad (3.2)$$

Mathematical Model of HIV-TB:

$$\left.\begin{aligned}
&\frac{dS}{dt} = \pi - \lambda_H S - \lambda_T S - \mu S - \lambda_{TH} S - \lambda_{HT} S\\
&\frac{dL_H}{dt} = \varepsilon_1\lambda_H S - K_1 L_H + \varphi H_W\\
&\frac{dH_U}{dt} = (1-\varepsilon_1)\lambda_H S + (1-\omega_1)\kappa_H L_H - K_2 H_U\\
&\frac{dH_D}{dt} = \omega_1\kappa_H L_H + \gamma_{UH}H_U - K_3 H_D\\
&\frac{dH_W}{dt} = \tau_1 H_D - K_4 H_W\\
&\frac{dL_{TH}}{dt} = \lambda_{TH} S - K_5 L_{TH} + \alpha_T R_{TH}\\
&\frac{dA_{TH}}{dt} = \kappa_{TH} L_{TH} - K_6 A_{TH}\\
&\frac{dL_{HT}}{dt} = \lambda_{HT} S - K_7 L_{HT}\\
&\frac{dA_{HT}}{dt} = \kappa_{HT} L_{HT} - K_8 A_{HT}\\
&\frac{dL_T}{dt} = \varepsilon_2\lambda_T S - K_9 L_T + \upsilon T_U + \theta_1\rho F_T + r\alpha R_T\\
&\frac{dT_U}{dt} = (1-\varepsilon_2)\lambda_H S + (1-\omega_2)\kappa_T L_T + (1+\omega_3)\phi L_T + \theta_2\rho F_T - K_{10}T_U\\
&\frac{dT_D}{dt} = \omega_2\kappa_T L_T + \omega_3\phi L_T + \gamma_{UT}T_U + [1-(\theta_1+\theta_2)]\rho F_T - K_{11}T_D\\
&\frac{dF_T}{dt} = (1-q_1)\tau_2 T_D + (1-r)\alpha R_T - K_{12}F_T\\
&\frac{dR_T}{dt} = q_1\tau_2 T_D - K_{13}R_T + \sigma_2 T_D\\
&\frac{dR_{TH}}{dt} = \sigma_1 A_{TH} - K_{14}R_{TH}
\end{aligned}\right\} \quad (3.3)$$

Where

$$K_1 = (\kappa_H + \mu), K_2 = (\gamma_{UH} + \mu + \delta_{UH}), K_3 = (\tau_1 + \mu + \delta_{dH}), K_4 = (\varphi + \mu), K_5 = (\kappa_{TH} + \mu),$$
$$K_6 = (\mu + \sigma_1 + \delta_{TH}), K_7 = (\kappa_{HT} + \mu), K_8 = (\mu + \delta_{TH}), K_9 = (\kappa_T + \mu), K_{10} = (\upsilon + \gamma_{UT} + \mu + \delta_{UT}),$$
$$K_{11} = (\sigma_2 + \tau_2 + \mu + \delta_{dT}), K_{12} = (\rho + \mu + \delta_{FT}), K_{13} = (\alpha + \mu + \delta_{RT}), K_{14} = -(\alpha_T + \mu)$$

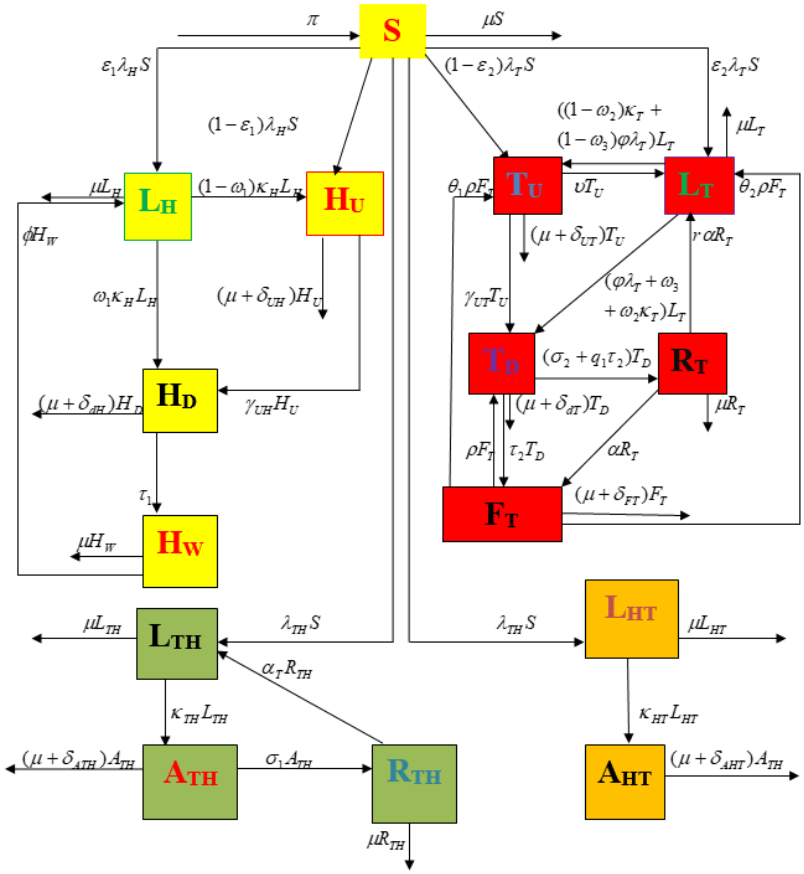

Fig. 1. Schematic diagram of the HIV-TB model

3. POSITIVITY OF SOLUTIONS

For the model of Human Immunodeficiency Virus co-infection with tuberculosis to be epidemiologically meaningful and mathematically well posed, it is necessary to prove that all state variables are non-negative for all $t > 0$.

Theorem 1.

Let:

$$\{S(0) \geq 0, L_H(0) \geq 0, H_U(0) \geq 0, H_D(0) \geq 0, H_W(0) \geq 0 H_W(0) \geq 0, L_{TH}(0) \geq 0, A_{TH}(0) \geq 0,$$
$$L_{HT}(0) \geq 0, A_{HT}(0) \geq 0, L_T(0) \geq 0, T_U(0) \geq 0, T_D(0) \geq 0, F_T(0) \geq 0, R_T(0) \geq 0, R_{TH}(0) \geq 0\} \in \Gamma$$

Then, the solution:

$$\{S(t), L_H(t), H_U(t), H_D(t), H_W(t) L_{TH}(t), A_{TH}(t), L_{HT}(t), A_{HT}(t), L_T(t), T_U(t), T_D(t), F_T(t),$$
$R_T(t), R_{TH}(t)\}$ Of the model system equation (3.3) are positive $\forall t \geq 0$.

Proof:

In order to prove the theorem (1.1), the equations of the system (3.1) were used. From the first equation of the model (3.3):

$$\frac{dS}{dt} = \pi - \lambda_H S - \mu S \quad (3.4)$$

From which it follows that:

$$\frac{dS}{dt} =\geq -\mu S \quad (3.5)$$

Consequently:

$\frac{dS}{dt} + \mu S \geq 0$ is the first order homogeneous differential equation.

$$\text{I.F.}= \quad \ell^{\int \mu dt} = \ell^{\mu t} \quad (3.6)$$

Multiplying by the Integrating factor on both sides will give:

$$\ell^{\mu t}\frac{dS}{dt} + \mu S\ell^{\mu t} \geq 0 \quad (3.7)$$

It then follows that:

$$d(S\ell^{\mu t}) \geq 0dt$$

Integrating on both sides gives:

$S\ell^{\mu t} \geq C$ where C is a constant of the integration, it follows that:

$$S(t) \geq C\ell^{-\mu t} \quad (3.8)$$

3.1.1HIV model only

$$\left.\begin{aligned}
\frac{dS}{dt} &= \pi - \lambda_H S - \mu S \\
\frac{dL_H}{dt} &= \varepsilon_1\lambda_H S - K_1 L_H + \varphi H_W \\
\frac{dH_U}{dt} &= (1-\varepsilon_1)\lambda_H S + (1-\omega_1)\kappa_H L_H - K_2 H_U \\
\frac{dH_D}{dt} &= \omega_1\kappa_H L_H + \gamma_{UH} H_U - K_3 H_D \\
\frac{dH_W}{dt} &= \tau_1 H_D - K_4 H_W
\end{aligned}\right\} \quad (3.9)$$

For critical points, we set:

$$\frac{dS}{dt}=\frac{dL_H}{dt}=\frac{dH_U}{dt}=\frac{dH_D}{dt}=\frac{dH_W}{dt}=0 \quad (4.0)$$

At this free equilibrium, it is assumed that there is no infection, then we set λ_H =0

Applying the initial condition that, when $t = 0, S(t) = S(0)$,we have:

$S(0) \geq C$

Hence:

$S(t) \geq S(0)\ell^{-\mu t}$

Since $\mu > 0 and S(0) \geq 0$,then:

$S(t) \geq 0$, if $t = 0 and t \to \infty$

Therefore:

$S(t) \geq 0 \forall t \geq 0$.

Similarly, it can be shown that $L_H \geq 0, H_U \geq 0, H_D \geq 0, H_W \geq 0, L_{TH} \geq 0, A_{TH} \geq 0, L_{HT} \geq 0, A_{HT} \geq 0, L_T \geq 0, T_U \geq 0, T_D \geq 0, F_T \geq 0, R_T \geq 0, R_{TH} \geq 0 \ ^{\forall t \geq 0}$.

Therefore, HIV-TB model formulated is mathematically and epidemiologically well posed.

3.1Analysis of Sub Models

Before analyzing the full model (3.3), it is instructive to gain insights into the dynamics of the models for HIV only and TB only.

Disease free equilibrium is:

$$\varepsilon_0 = \left\{\frac{\pi}{\mu}, 0,0,0,0\right\}$$

Existence of Endemic Equilibrium (EE)

Where $\varepsilon_0^* = (S^*, L_H^*, H_U^*, H_D^*, H_W^*)$are the endemic equilibrium points.

$$S^{**} = \frac{\pi}{(\lambda_H+\mu)} \tag{4.1a}$$

$$L_{H^{**}} = \frac{\varepsilon_1\lambda_H S^{**}+\varphi H_{W^{**}}}{K_1} \tag{4.1b}$$

$$H_{U^{**}} = \frac{(1-\varepsilon_1)\lambda_H S^{**}+(1-\omega_1)\kappa_H L_H}{K_2} \tag{4.1c}$$

$$H_{D^{**}} = \frac{\omega_1 K_H {L_H}^{**}+\gamma_{UH} H_{U^{**}}}{K_3} \tag{4.1d}$$

$$H_{W^{**}} = \frac{\tau_1 H_{D^{**}}}{K_4} \tag{4.1e}$$

After the substitution, we have the results (4.1b*-4.1e*) in terms ofS^{**};

$$L_{H^{**}} = \frac{\varepsilon_1\lambda_{H^{**}}S^{**}}{K_1 A} + \frac{\varphi\tau_1\gamma_{UH}(1-\varepsilon_1)\lambda_H^{**}S^{**}}{K_1K_3K_4K_2A} L_{H^{**}} = \rho_1\lambda_H^{**}S^{**} \tag{4.1b*}$$

$$H_{U^{**}} = \frac{(1-\varepsilon_1)\lambda_H^{**}S^{**}}{K_2} + \frac{K_2\kappa_H P_1\lambda_H^{**}S^{**}}{K_2} = P_2\lambda_H^{**}S^{**} \tag{4.1c*}$$

$$H_{D^{**}} = \frac{\omega_1\kappa_H P_1\lambda_H^{**}S^{**}}{K_3} + \frac{\gamma_{UH}P_2\lambda_H^{**}S^{**}}{K_3} = P_3\lambda_H^{**}S^{**} \tag{4.1d*}$$

$$H_W = \frac{\tau_1 P_3\lambda_H^{**}S^{**}}{K_4} = P_4\lambda_H^{**}S^{**} \tag{4.1e*}$$

Where:

$$A = \left(1 - \frac{\varphi\tau_1\omega_1\kappa_H}{K_1K_3K_4} - \frac{\varphi\tau_1\gamma_{UH}(1-\omega_1)\kappa_H}{K_1K_3K_4K_2}\right)$$

$$P_1 = \frac{\varepsilon_1}{K_1A} + \frac{\varphi\tau_1\gamma_{UH}(1-\varepsilon_1)}{K_1K_3K_4K_2A}$$

$$P_2 = \frac{(1-\varepsilon_1)}{K_2} + \frac{(1-\omega_1)\kappa_H}{K_2}\left[\frac{\varepsilon_1}{K_1A} + \frac{\varphi\tau_1\gamma_{UH}(1-\varepsilon_1)}{K_1K_3K_4K_2A}\right]$$

$$P_3 = \frac{\omega_1 K_H}{K_4}\left[\frac{\varepsilon_1}{K_1 A} + \frac{\varphi\tau_1\gamma_{UH}(1-\varepsilon_1)}{K_1K_3K_4K_2A}\right] + \frac{\gamma_{UH}}{K_3}\left[\frac{(1-\varepsilon_1)}{(1-\omega_1)} + \frac{(1-\omega_1)\kappa_H}{K_2}\left[\frac{\varepsilon_1}{K_1A} + \frac{\varphi\tau_1\gamma_{UH}(1-\varepsilon_1)}{K_1K_3K_4K_2A}\right]\right]$$

$$P_4 = \frac{\tau_1}{K_4}.\frac{\omega_1\kappa_H}{K_3}\left[\frac{\varepsilon_1}{K_1 A} + \frac{\varphi\tau_1\gamma_{UH}(1-\varepsilon_1)}{K_1K_3K_4K_2A}\right] + \frac{\gamma_{UH}}{K_3}\left[\frac{(1-\varepsilon_1)}{(1-\omega_1)} + \frac{(1-\omega_1)\kappa_H}{K_2}\left[\frac{\varepsilon_1}{K_1A} + \frac{\varphi\tau_1\gamma_{uH}(1-\varepsilon_1)}{K_1K_3K_4K_2A}\right]\right]$$

Where:

$$\lambda_H^{**} = \frac{\beta_H[L_H^{**} + \eta_U H_U^{**} + \eta_{dH} H_D^{**} + \eta_W H_W^{**}]}{N} \tag{4.2}$$

Substituting the expressions in (4.1b*-4.1e*) into (4.2) we have

$$\lambda_H^{**}[S^{**} + P_1\lambda_H^{**}S^{**} + P_2\lambda_H^{**}S^{**} + P_3\lambda_H^{**}S^{**} + P_4\lambda_H^{**}S^{**}] = \beta\lambda_H^{**}S^{**}[P_1 + \eta_U P_2 + \eta_{dH}P_3 + \eta_W P_4] \tag{4.3}$$

Divide each term in (4.3) by $\lambda_H{}^{**}S^{**}$

$$1 + P_5\lambda^{**} = \beta[P_1 + \eta_U P_2 + \eta_{dH}P_3 + \eta_W P_4]$$

Where $P_5 = P_1 + P_2 + P_3 + P_4 \geq 0$

So that:

$$1 + P_5\lambda_H^{**} = \frac{\beta}{K_1K_2K_3K_4}\left[\frac{\varepsilon_1(K_2K_3K_4)}{K_1A} + \frac{\varphi\tau_1\gamma_{UH}(1-\varepsilon_1)}{(A)} + (1-\varepsilon_1)K_1K_3K_4\right.$$
$$+\frac{K_2\kappa_H\varepsilon_1K_3K_4}{A} + \frac{\varphi\tau_1\gamma_{UH}(1-\varepsilon_1)}{A} + \frac{\omega_1\kappa_H\varepsilon_1K_2K_4}{A} + \frac{\varphi\tau_1\gamma_{UH}(1-\varepsilon_1)}{A} + \gamma_{UH}(1-\varepsilon_1)K_1K_4$$
$$+\frac{\gamma_{UH}K_2\varepsilon_1\kappa_HK_4}{A} + \frac{\gamma_{UH}K_2\kappa_H\varphi\tau_1\gamma_{UH}(1-\varepsilon_1)}{K_3K_2A} + \frac{\tau_1\omega_1\kappa_H\varepsilon_1K_2}{A} + \frac{\tau_1\omega_1\kappa_H\varphi\tau_1\gamma_{UH}(1-\varepsilon_1)}{K_4K_1+A} + \gamma_{UH}(1-\varepsilon_1)K_1K_4$$
$$+\frac{\gamma_{UH}K_2\kappa_H\varepsilon_1K_4}{A} + \frac{\gamma_{UH}K_2\kappa_H\varphi\tau_1\gamma_{UH}(1-\varepsilon_1)}{K_3K_2A} = R_H + Q \quad where$$
$$Q = \frac{\beta}{K_1K_2K_3K_4}\left[\frac{\varepsilon_1K_2K_5}{A}(K_5 + \omega_1\kappa_H) + \frac{\varepsilon_1K_2K_4\kappa_H}{A}(K_3 + 2\gamma_{UH}) + \frac{\varepsilon_1\tau_1\omega_1\kappa_HK_2}{A}\right.$$
$$\left.+3\frac{\varphi\tau_1\gamma_{UH}(1-\varepsilon)}{A} + \frac{(1-\varepsilon_1)2\gamma_{UH}\kappa_H}{AK_3K_2}(K_2\varphi\tau_1 + K_2\varphi\tau_1) + (1-\varepsilon_1)\gamma_{UH}\left(\frac{2\tau_1\omega_1\kappa_H\varphi}{K_4K_3A} + 2K_1K_4 + K_1K_3K_4\right)\right]$$

Therefore: $1 + P_5\lambda^{**} = R_H + Q$

$\lambda^{**} = \frac{R_H+Q-1}{P_5} > 0$Whenever, $R_H > 1$

3.1.2 Stability of the HIV model

The basic reproduction number of the model (3.3)is calculated by using the next generation matrix ([2], [6], [24], [25], [26]). Using this approach, we have:

$$F = \begin{pmatrix} \varepsilon_1\beta_H & \varepsilon_1\beta_H\eta_U & \varepsilon_1\beta_H\eta_{dH} & \varepsilon_1\beta_H\eta_W \\ (1-\varepsilon_1)\beta_H & (1-\varepsilon_1)\beta_H\eta_U & (1-\varepsilon_1)\beta_H\eta_{dH} & (1-\varepsilon_1)\beta_H\eta_W \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{pmatrix} \tag{4.4}$$

$$V = \begin{pmatrix} K_1 & 0 & 0 & -\varphi \\ -(1-\omega_1)\kappa_H & K_2 & 0 & 0 \\ -\omega_1 K_H & -\gamma_{UH} & K_3 & 0 \\ 0 & 0 & -\tau_1 & K_4 \end{pmatrix} \tag{4.5}$$

The reproduction number is the dominant eigenvalue of $F \times V^{-1}$. Thus,

$$R_H = \left\{ \begin{pmatrix} \left(\frac{1}{\varphi\tau_1(1-\omega_1)\kappa_H\gamma_{UH}+\varphi\tau_1\omega_1 K_H K_2 - K_3 K_4 K_1 K_2}\right) \\ \beta_H(-(1-\varepsilon_1)\gamma_{UH}\varphi\tau_1 + (1-\varepsilon_1)\eta_U\varphi\tau_1\omega_1\kappa_H \\ -(1-\varepsilon_1)\eta_U K_4 K_3 K_1 - (1-\varepsilon_1)\gamma_{UH}\eta_{dH}K_4 K_1 \\ -(1-\varepsilon_1)\gamma_{UH}\eta_W\tau_1 K_1 - \varepsilon_1 K_3 K_4 K_2 - \varepsilon_1 K_3 K_4(1-\omega_1)\kappa_H\eta_U \\ -\eta_{dH}\omega_1\kappa_H\varepsilon_1 K_4 K_2 - \eta_{dH}\gamma_{UH}\varepsilon_1 K_4(1-\omega_1)K_H - \tau_1\omega_1\kappa_H\varepsilon_1\eta_W K_2 \\ -\eta_W\gamma_{UH}\varepsilon_1\tau_1(1-\omega_1)\kappa_H \end{pmatrix} \right\} \tag{4.6}$$

"The threshold quantity R_H is the basic reproduction number of the normalized model system (3.3) for HIV infection in a population. It measures the average number of new secondary infections generated by a single infected individual in his or her infectious period in a susceptible population" [5].

3.1.3 Global stability of disease-free equilibrium (HIV)

We study the global stability of equilibrium without disease and we implement the approach of [5], then the equations of the model may be rewritten in the form;

$$\frac{dM}{dt} = F(M, I)$$

$$\frac{dI}{dt} = G(M, I) \tag{4.7}$$

With $G(P, 0) = 0$, where $P \in R^1$ represents the uninfected classes (S) and $I \in R^4$ represents the infected classes (L_H, I_U, I_D, H_W). Also, $E_o = (M^*, 0)$ denotes the disease-free equilibrium of the model.

The two conditions (H1) and (H2) stated below must be satisfied for the model to be globally stable

(H1): For $\frac{dM}{dt} = F(M, 0), M^*$ is globally asymptotically stable

(H2): $G(M, I) = AI - \hat{G}(M, I), \hat{G}(M, I) \geq 0$ for $(M, I) \in D$

Where $A = D_I G(M^*, 0)$ is an M-matrix (the off-diagonal elements of A are non-negative) and D is the region is the feasible region where the model is biologically meaningful. If (H1) and (H2) are satisfied, then the following theorem holds;

Theorem 2: The disease-free equilibrium $E_o = (M^*, 0)$ is a globally asymptotically stable equilibrium of the model if $R_0 < 1$ and that the conditions (H1) and (H2) are satisfied

Proof:

Now $M = (S, H_W)$ and $I = (L_H, H_U, H_D)$

$$F(M, 0) = (\pi - \mu S) \tag{4.8}$$

And

$$A = \begin{pmatrix} \varepsilon_1\beta_H & -K_1\varepsilon_1\beta_H\eta_U & \varepsilon_1\beta_H\eta_{dH} & \varepsilon_1\beta_H\eta_W - \varphi \\ (1-\varepsilon_1)\beta_H - (1-\omega_1)\kappa_H(1-\varepsilon_1)\beta_H\eta_U - K_2(1-\varepsilon_1)\beta_H\eta_{dH}(1-\varepsilon_1)\beta_H\eta_W & & & \\ \omega_1 & \kappa_H\gamma_{UH} & -K_3 & 0 \\ 0 & 0 & \tau_1 & -K_4 \end{pmatrix} \tag{4.9}$$

Then

$$\hat{G}(M,I)=\begin{pmatrix}\varepsilon_1\beta_H\left(1-\frac{S}{N}\right)\\(1-\varepsilon_1)\beta_H\left(1-\frac{S}{N}\right)\\0\\0\end{pmatrix} \tag{5.0}$$

Since $0 \le \varepsilon \le 1$, clearly $\hat{G}(M,I) \ge 0$, $E_o=\left(\frac{\pi}{\mu}\right)$ is a globally asymptotic stable equilibrium of the model equations. Hence, the two conditions above are satisfied. Therefore, the disease-free equilibrium is globally asymptotically stable. This implies biologically that the prevention of HIV leads to AIDS is independent of the initial sizes of the sub-populations whenever the basic production number is less than one.

3.1.4TB model only

$$\left.\begin{aligned}\frac{dS}{dt}&=\pi-\lambda_T S-\mu\\\frac{dL_T}{dt}&=\varepsilon_2\lambda_T S-K_9L_T+\upsilon T_U+\theta_1\rho F_T+r\alpha R_T\\\frac{dT_U}{dt}&=(1-\varepsilon_2)\lambda_H S+(1-\omega_2)\kappa_T L_T+(1+\omega_3)\phi\lambda_T L_T+\theta_2\rho F_T-K_{10}T_U\\\frac{dT_D}{dt}&=\omega_2\kappa_T L_T+\omega_3\phi\lambda_T L_T+\gamma_{UT}T_U+[1-(\theta_1+\theta_2)]\rho F_T-K_{11}T_D\\\frac{dF_T}{dt}&=(1-q_1)\tau_2T_D+(1-r)\alpha R_T-K_{12}F_T\\\frac{dR_T}{dt}&=q_1\tau_2T_D-K_{13}R_T+\sigma_2T_D\end{aligned}\right\} \tag{5.1}$$

Where

$$\lambda_T=\beta_T\frac{(L_T+\eta_U T_U+\eta_{dT}T_D+\eta_{RT}R_T+F_T)}{N} \tag{5.2}$$

Disease-free equilibrium is:

$$\varepsilon_0=\left(\frac{\pi}{\mu},0,0,0,0,0\right)$$

Existence of Endemic Equilibrium for TB Model Only

Where $\varepsilon_0^*=(S^*,\ L_T^*,\ T_U^*,T_D^*,F_T^*,R_T^*)$ are the endemic equilibrium points.

For a special case of TB-only model, when $q_1=1$ and $\upsilon_1,\theta_1,\theta_2\ and\ \alpha$ are very small (negligible).

Therefore, equations (5.1) become:

$$\left.\begin{aligned}\frac{dS}{dt}&=\pi-\lambda_T S-\mu S\\\frac{dL_T}{dt}&=\varepsilon_2\lambda_T S-K_9L_T\\\frac{dT_U}{dt}&=(1-\varepsilon_2)\lambda_T S+(1-\omega_2)\kappa_T L_T-K_{10}T_U\\\frac{dT_D}{dt}&=\omega_2\kappa_T L_T+\gamma_{UT}T_U-K_{11}T_D\\\frac{dR_T}{dt}&=\tau_2T_D-\mu R_T+\sigma_2T_D\end{aligned}\right\} \tag{5.2}$$

$$S^{**} = \frac{\pi}{(\lambda_T+\mu)} \tag{5.2a}$$

$$L_{T**} = \frac{\varepsilon_2\lambda_T S^{**}}{K_9} \tag{5.2b}$$

$$T_{U^{**}} = \frac{(1-\varepsilon_2)\lambda_T S^{**}+(1-\omega_2)\kappa_T L_H}{K_{10}} \tag{5.2c}$$

$$T_{D^{**}} = \frac{\omega_2 K_T L_T{}^{**}+\gamma_{UT} T_{U^{**}}}{K_{11}} \tag{5.2d}$$

$$R_{T^{**}} = \frac{(\sigma_2+\tau_2)T_{D^{**}}}{\mu} \tag{5.2e}$$

The expression for λ_T at the endemic steady-state, denoted by λ^{**} is given by

$$\lambda_T^{**} = \beta_T \frac{(L_T^{**}+\eta_U T_U^{**}+\eta_{dT} T_D^{**}+\eta_{RT} R_T^{**}+\eta_{FT} F_T)}{N^{**}} \tag{5.3}$$

$$L_{T**} = \frac{\varepsilon_2\lambda_T S^{**}}{K_9} \tag{5.2b*}$$

$$T_{U^{**}} = \frac{(1-\varepsilon_2)\lambda_T S^{**}}{K_{10}} + \frac{(1-\omega_2)\kappa_T\varepsilon_2\lambda_T S^{**}}{K_{10}K_9} = P_1\lambda_T^{**}S^{**} \tag{5.2c*}$$

$$T_{D^{**}} = \frac{\omega_2\kappa_T\varepsilon_2\lambda_T S^{**}}{K_{11}K_9} + \frac{\gamma_{UT}P_1\lambda_T S^{**}}{K_{11}} = P_2\lambda_T^{**}S^{**} \tag{5.2d*}$$

$$R_{T^{**}} = \frac{(\sigma_2+\tau_2)}{\mu}\left[\frac{\omega_2\kappa_T\varepsilon_2\lambda_T^{**}S^{**}}{K_{11}K_9} + \frac{\gamma_{UT}P_1\lambda_T^{**}S^{**}}{K_{11}}\right] = P_3\lambda_T^{**}S^{**} \tag{5.2e*}$$

Substituting the expression in (5.2b*)-(5.2e*) into (5.3)

$$\lambda_T^{**}\left[S^{**} + \frac{\varepsilon_2\lambda_T S^{**}}{K_9} + P_1\lambda_T^{**}S^{**} + P_2\lambda_T^{**}S^{**}P_3\lambda_T^{**}S^{**}\right] = \beta_T\lambda_T^{**}S^{**}[\eta_U P_1 + \eta_{dT}P_2 + \eta_{RT}P_3] \tag{5.3}$$

Divide each term in (5.3) by $\lambda_T{}^{**}S^{**}$

$$1 + P_4\lambda_T^{**} = \beta_T[\eta_U P_1 + \eta_{dT}P_2 + \eta_{RT}P_3]$$

Where

$$P_4 = \beta_T\left[\frac{\varepsilon_2}{K_9} + P_1 + P_2 + P_3\right] \geq 0$$

So that:

$$1+P_4\lambda^{**} = \frac{\beta_T}{K_9\ K_{10}K_{11}}\Big[\eta_U(1-\varepsilon_2)K_{11}K_9\ + \eta_U(1-\omega_2)\kappa_T\varepsilon_2K_{10} + \eta_{dT}\omega_2\kappa_T\varepsilon_2K_{10}$$
$$+\eta_{dT}\gamma_{UT}\Big[(1-\varepsilon_2)K_9\ + (1-\omega_2)\kappa_T\varepsilon_2\Big] + \eta_{RT}\frac{(\sigma_2+\tau_2)}{\mu}\omega_2\kappa_T\varepsilon_2K_{10} + \eta_{RT}\frac{(\sigma_2+\tau_2)}{\mu}\gamma_{UT}$$
$$\Big[(1-\varepsilon_2)K_9\ + (1-\omega_2)\kappa_T\varepsilon_2\Big] = R_T + Q$$

$$Q = \frac{\beta_T}{K_9\ K_{10}K_{11}}\left[(1-\varepsilon_2)K_9\left[\eta_U K_{11} + \eta_{dT}\gamma_{UT} + \eta_{RT}\frac{(\sigma_2+\tau_2)}{\mu}\right] + (1-\omega_2)\kappa_T\varepsilon_2\left[\eta_U K_{10} + \eta_{dT}\gamma_{UT} + \eta_{RT}\gamma_{UT}\frac{(\sigma_2+\tau_2)}{\mu}\right] + w_2\kappa_T\varepsilon_2 K_{12}\left[\eta_{dT} + \eta_{RT}\frac{(\sigma_2+\tau_2)}{\mu}\right]\right]$$

Therefore $1 + P_4\lambda_T^{**} = R_T + Q$

$$\lambda_T^{**} = \frac{R_T + Q - 1}{P_4} > 0$$

whenever $R_T > 1$

3.15 Derivation of Basic Reproduction Number (R_o) for TB Only

The basic reproduction number of the model (5.1) R_T is calculated by using the next generation matrix([17], [27]). Using this approach we have:

$$F = \begin{pmatrix} \varepsilon_2\beta_T & \varepsilon_2\beta_T\eta_U & \varepsilon_2\beta_T\eta_{dT} & \varepsilon_2\beta_T\eta_{RT} & \varepsilon_2\beta_T\eta_{FT} \\ (1-\varepsilon_2)\beta_T & (1-\varepsilon_2)\beta_T\eta_U & (1-\varepsilon_2)\beta_T\eta_{dT} & (1-\varepsilon_2)\beta_T\eta_{RT} & (1-\varepsilon_2)\beta_T\eta_{FT} \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \end{pmatrix} \quad (5.4)$$

$$V = \begin{pmatrix} K_9 & -\upsilon & 0 & -\theta_1\rho & -r\alpha \\ -a & K_{10} & 0 & -\theta_2\rho & 0 \\ -\omega_2 & \kappa_T - \gamma_{UT} & K_{11} & b & 0 \\ 0 & 0 & -c & K_{12} & d \\ 0 & 0 & -e & 0 & K_{13} \end{pmatrix} \quad (5.5)$$

Hence;

$$R_T = \frac{B_1+B_2+B_3}{M} \quad (5.6)$$

Where: $M = \begin{bmatrix} \upsilon K_{13}K_{12}K_{11}a + \gamma_{UT}\alpha rea K_{12} - \gamma_{UT}\theta_1\rho eda + \gamma_{UT}\theta_1\rho c K_{13}K_9 - \upsilon abde \\ +\gamma_{UT}\theta_2\rho K_9 de + \upsilon\omega_2\theta_2\kappa_T\rho K_9 de + K_{13}K_{10}K_9 bc - K_{10}K_9K_{11}K_{12}K_{13} \\ +\omega_2\theta_1\kappa_T\rho deK_{10} - \gamma_{UT}\theta_2\rho c K_{13}K_9 + \upsilon abcK_{13} - \omega_2\kappa_T r\alpha eK_{10}K_{12} \\ -\upsilon\omega_2\theta_2\kappa_T\rho c K_{13} - \omega_2\theta_1\kappa_T\rho c K_{10}K_{13} - K_9K_{10}bde \end{bmatrix}$

$$\begin{aligned} B_1 = (&\beta_T(r\alpha eK_{12}\gamma_{UT} + K_{13}K_{12}K_{11}\upsilon + K_{13}bc\upsilon - bde\upsilon + \gamma_{UT}\theta_1\rho de - \gamma_{UT}\theta_1\rho cK_{13} \\ &-\varepsilon_2\eta_U abde + \varepsilon_2\eta_{dT}K_{12}K_{13}\gamma_{UT} + \varepsilon_2\eta_{RT}acK_{13}\gamma_{UT} - \varepsilon_2\eta_{RT}ade\gamma_{UT} + \varepsilon_2\eta_{FT}aeK_{12}\gamma_{UT} \\ &-\varepsilon_2 r\alpha eK_{12}\gamma_{UT} - \varepsilon_2\eta_U bcK_9K_{13} + \varepsilon_2\eta_U bdeK_9 - \varepsilon_2\eta_U eK_9K_{11}K_{13} - \varepsilon_2\eta_{dT}K_9K_{12}K_{13}\gamma_{UT})) \end{aligned}$$

$$\begin{aligned} B_2 = (&\beta_T(\varepsilon_2\eta_{RT}deK_9\gamma_{UT} - \varepsilon_2\eta_{RT}cK_9K_{13}\gamma_{UT} - \varepsilon_2\rho cK_{13}\theta_2\gamma_{UT} + \varepsilon_2\rho de\theta_2\gamma_{UT} + \varepsilon_2\eta_U aK_{11}K_{12}K_{13} \\ &+\varepsilon_2\eta_U abcK_{13} + \omega_2\eta_U\kappa_T\theta_1 cK_{13} - \omega_2\eta_U\kappa_T\theta_1 de + \omega_2\eta_{RT}\kappa_T\upsilon cK_{13} - \omega_2\eta_{RT}\kappa_T\upsilon de \\ &+\omega_2\eta_{dT}\kappa_T\upsilon K_{12}K_{13} + \omega_2\eta_{FT}\kappa_T\upsilon eK_{12} - \varepsilon_2\omega_2\eta_U\kappa_T\theta_1 cK_{13} + \varepsilon_2\omega_2\eta_U\kappa_T\theta_1 de - \varepsilon_2\omega_2\eta_{dT}\kappa_T\upsilon K_{12}K_{13} \\ &-\varepsilon_2\omega_2\eta_{RT}\kappa_T\upsilon cK_{13} + \varepsilon_2\omega_2\eta_{RT}\kappa_T\upsilon de - \varepsilon_2\omega_2\eta_{FT}\kappa_T\upsilon eK_{12} + \varepsilon_2\omega_2\eta_{dT}\kappa_T K_{13}K_{12}K_{10})) \end{aligned}$$

$$\begin{aligned} B_3 = (&\beta_T(\varepsilon_2\omega_2\eta_{RT}\kappa_T cK_{13}K_{10} - \varepsilon_2\omega_2\eta_{RT}\kappa_T ceK_{10} + \varepsilon_2\omega_2\eta_{FT}\kappa_T eK_{10}K_{12} - r\alpha\omega_2\eta_U\kappa_T eK_{12} - \varepsilon_2\upsilon K_{11}K_{12}K_{13} \\ &-\varepsilon_2\upsilon bcK_{13} + \varepsilon_2\upsilon bde + \varepsilon_2K_{13}c\theta_1\gamma_{UT} - \varepsilon_2de\theta_1\gamma_{UT} + \varepsilon_2bcK_{10}K_{13} - \varepsilon_2bdeK_{10} \\ &+\varepsilon_2K_{10}K_{11}K_{12}K_{13} + \eta_U bcK_9K_{13} - \eta_U bceK_9 + \eta_U K_9K_{11}K_{12}K_{13} + \eta_{RT}cK_9K_{13}\gamma_{UT} - \eta_{RT}deK_9\gamma_{UT} \\ &+\eta_{dT}K_9K_{12}K_{13}\gamma_{UT} + \eta_{FT}eK_{12}K_9\gamma_{UT} + \varepsilon_2 r\alpha\omega_2\eta_U\kappa_T eK_{12} + \eta_U\varepsilon_2\rho cK_{13}\theta_2\omega_2\kappa_T - \eta_U\varepsilon_2\rho de\theta_2\omega_2\kappa_T)) \end{aligned}$$

$a = (1-\omega_2)\kappa_T$, $b = [1-(\theta_1+\theta_2)]\rho$, $c = (1-q_1)\tau_2$, $d = (1-r)\alpha$, $e = (q_1\tau_2 + \sigma_2)$

"The threshold quantity R_T is the basic reproduction number of the normalized model system (5.1) for TB infection in a population. It measures the average number of new secondary infections generated by a single infected individual in his or her infectious period in a susceptible population" [13].

3.1.6 Global stability of disease free equilibrium (TB)

We study the global stability of equilibrium without disease for a special case For a special case of TB-only model, when $q_1 = 1$ and $\upsilon_1, \theta_1, \theta_2 \ and \ \alpha$ are very small (negligible)and we implement the approach of [5], then the equations of the model may be rewritten in the form;

$$\frac{dM}{dt} = F(M, I)$$

$$\frac{dI}{dt} = G(M, I) \tag{5.7}$$

With $G(P, 0) = 0$, where $P \in R^2$ represents the uninfected classes (S, R_T) and $I \in R^3$ represents the infected classes(L_T, T_U, T_D). Also, $E_o = (M^*, 0)$ denotes the disease-free equilibrium of the model.

The two conditions (H1) and (H2) stated below must be satisfied for the model to be globally stable

(H1): For $\frac{dM}{dt} = F(M, 0), M^*$ is globally asymptotically stable

(H2): $G(M, I) = AI - \hat{G}(M, I), \hat{G}(M, I) \geq 0$ for $(M, I) \in D$

Where $A = D_I G(M^*, 0)$is an M-matrix (the off-diagonal elements of A are non-negative) and D is the region is the feasible region where the model is biologically meaningful. If (H1) and (H2) are satisfied, then the following theorem holds;

Theorem 2: The disease-free equilibrium $E_o = (M^*, 0)$ is a globally asymptotically stable equilibrium of the model if $R_0 < 1$ and that the conditions (H1) and (H2) are satisfied:

Proof:

Now $M = (S, R_T)$ and $I = (L_T, T_U, T_D)$

$$F(M, 0) = \begin{pmatrix} \pi - \mu S \\ 0 \end{pmatrix} \tag{5.8}$$

And

$$A = \begin{pmatrix} \varepsilon_2\beta_T & -K_9 & \varepsilon_2\beta_T\eta_U & \varepsilon_2\beta_T\eta_{dT} \\ (1-\varepsilon_2)\beta_T & -(1-\omega_2)\kappa_T(1-\varepsilon_2)\beta_T\eta_U - K_{10} & (1-\varepsilon_2)\beta_T\eta_{dT} \\ \omega_2 & \kappa_T & \gamma_{UT} & -K_{11} \end{pmatrix} \tag{5.9}$$

$$\hat{G}(M, I) = \begin{pmatrix} \varepsilon_2\beta_T\left(1 - \frac{S}{N}\right) \\ (1-\varepsilon_2)\beta_T\left(1 - \frac{S}{N}\right) \\ 0 \end{pmatrix} \tag{6.0}$$

Since $0 \leq \varepsilon \leq 1,$ clearly $\hat{G}(M, I) \geq 0$, $E_o = \left(\frac{\pi}{\mu}\right)$ is a globally asymptotic stable equilibrium of the model equations. Hence, the two conditions above are satisfied. Therefore, the disease-free equilibrium is globally asymptotically stable. This implies biologically that the prevention of TB is independent of the initial sizes of the sub-populations whenever the basic production number is less than one.

4. MATHEMATICAL ANALYSIS OF OPTIMALITY OF THE FULL MODEL

In this section, we analyze the mathematical analysis of the possible control strategy that will be useful to the public health practitioners achieve the best control strategy in the spread of HIV-TB co-infection in the environment. In order to derive the necessary conditions for these optimal control variables, we introduce Boosting immune system (u_1), campaign/education (u_2), HIV treatment $(u_3)$and TB treatment(u_4) as control strategy for the spread of HIV-TB co-infection. So the model equation (3.3) becomes:

$$\frac{dS(t)}{dt} = \pi - \big((1-u_1)+(1-u_2)\big)(\lambda_H - \lambda_T - \lambda_{TH} - \lambda_{HT})S(t) - \mu S(t)$$

$$\frac{dL_H(t)}{dt} = ((1-u_1)+(1-u_2))\varepsilon_1\lambda_H S(t) - (\kappa_H + \mu)L_H + (1-u_3)\varphi H_W(t)$$

$$\frac{dH_U(t)}{dt} = ((1-u_1)+(1-u_2))(1-\varepsilon_1)\lambda_H S(t) + (1-\omega_1)\kappa_H L_H(t) - (\gamma_{UH}(1-u_2) + \mu + \delta_{UH})H_U(t)$$

$$\frac{dH_D(t)}{dt} = \omega_1\kappa_H L_H(t) + (1-u_2)\gamma_{UH}H_U(t) - \big(\tau_1(1-u_3) + \mu + \delta_{d_H}\big)H_D(t)$$

$$\frac{dH_W(t)}{dt} = \tau_1(1-u_3)H_D(t) - ((1-u_3)\varphi + \mu)H_W(t)$$

$$\frac{dL_{T_H}(t)}{dt} = \big((1-u_1)+(1-u_2)\big)\lambda_{TH}S(t) - \Big(\big((1-u_3)+(1-u_4)\big)\kappa_{TH} + \mu\Big)L_{TH}(t) + \alpha_T R_{TH}(t) \quad (6.1)$$

$$\frac{dA_{T_H}(t)}{dt} = ((1-u_3)+(1-u_4))\kappa_{TH}L_{TH}(t) - (\mu + \sigma_1 + \delta A_{TH})A_{TH}(t)$$

$$\frac{dL_{HT}(t)}{dt} = ((1-u_1)+(1-u_2))\lambda_{HT}S(t) - (((1-u_3)+(1-u_4))\kappa_{HT} + \mu)L_{HT}(t)$$

$$\frac{dA_{HT}(t)}{dt} = ((1-u_3)+(1-u_4))\kappa_{HT}L_{HT}(t) - (\mu + \delta A_{HT})A_{HT}(t)$$

$$\frac{dL_T(t)}{dt} = ((1-u_1)+(1-u_2))\varepsilon_{\ 2}\lambda_T S(t) - (\kappa_T + \mu)L_T(t) + \upsilon T_U(t) + \theta_1\rho F_T(t) + r\alpha R_T(t)$$

$$\frac{dT_U(t)}{dt} = ((1-u_1)+(1-u_2))(1-\varepsilon_2)\lambda_H S(t) + (1-\omega_2)\kappa_T L_T(t) + \theta_2\rho F_T(t) - (\upsilon + (1-u_2)\gamma_{UT} + \mu + \delta_{UT})T_U(t)$$

$$\frac{dT_D(t)}{dt} = \omega_2\kappa_T L_T(t) + (1-u_2)\gamma_{UT}T_U(t) + [1-(\theta_1+\theta_2)]\rho F_T(t) - (\sigma_2 + (1-u_4)\tau_2 + \mu + \delta_{dT})T_D(t)$$

$$\frac{dF_T(t)}{dt} = (1-u_4)(1-q_1)\tau_2 T_D(t) + (1-r)\alpha R_T(t) - (\rho + \mu + \delta_F)F_T(t)$$

$$\frac{dR_T(t)}{dt} = (1-u_4)q_1\tau_2 T_D(t) - (\alpha + \mu + \delta_{RT})R_T(t) + \sigma_2 T_D(t)$$

$$\frac{dR_{T_H}}{dt} = \sigma_1 A_{TH}(t) - (\alpha_T + \mu)R_{TH}(t)$$

Let the function $0 \le u_1 \le 1$ denote the boosting effect immune system of HIV-TB susceptible individuals, while $0 \le u_2 \le 1$ represents the effectiveness of educating the society of the menace of HIV-TB. Again, let$0 \le u_3 \le g_1$, $(0 \le g_1 \le 1)$and$0 \le u_4 \le g_2$, $(0 \le g_2 \le 1)$represent the controls on

treatment of HIV and TB respectively, where g_1 and g_2 is the drug efficacy used for the treatment. Since treatments cannot be continued infinitely, because of the negative side which is known as poison, so for our control classes we choose measurable functions which is defined on a fixed interval that satisfy $0 \leq a_i \leq u_i(t) \leq b_i < 1$ for i=1,2,3,4.

4.1Existence of an Optimal Control Pair.

Following the results of [22], the existence of an optimal control pair for the model (6.1) is obtained.

Optimality System:

The Objective functional to be minimized is given as:

$J(u_1, u_2, u_3, u_4) = \int_0^{t_f} (aH_U + bH_D + cA_{TH} + dA_{HT} + eT_U + fT_D + A_1{u_1}^2 + A_2{u_2}^2 + A_3{u_3}^2 + A_4{u_4}^2)d$ (6.2)
Here the constants $a, b, \rightleftarrows c, d, e, f, A_1, A_2, A_3, \rightleftarrows\rightleftarrows\rightleftarrows A_4$ are all positive weights to balance the size of the terms. $t_f$is the final time of interest while zero is the initial time. The objective here is to minimize the number of infectious individuals$H_U, H_D, A_{TH}, A_{HT}, T_U and T_D$, while minimizing the cost of control $u_1(t), u_2t), u_3(t), u_4(t)$. therefore, the optimal control pair ${u_1}^*, {u_2}^*, {u_3}^*, {u_4}^*$ is sought such that:
$J({u_1}^*, {u_2}^*, {u_3}^*, {u_4}^*) = \underset{{u_1}^*, {u_2}^*, {u_3}^*, \rightleftarrows {u_4}^*}{Min} \{J(u_1, u_2, u_3, u_4)/(u_1, u_2, u_3, u_4) \in U\}$ (6.3)

Where$U = \{(u_1, u_2, u_3, u_4)$

Such that$u_1, u_2, u_3, u_4$are measurable with:
$0 \leq u_1 \leq 1, 0 \leq u_2 \leq 1, 0 \leq u_3 \leq g_1, 0 \leq u_4 \leq g_2$for $t \in [0, t_f] \rightarrow [0,1]$is the control set.

The terms $aH_D + bT_D + cH_U + dT_U + eA_{HT} + fA_{TH}$ are the cost of infection while ${A_1u_1}^2, {A_2u_2}^2, {A_3u_3}^2, A_4u_4$ are the costs of Boosting immune system, campaign/education, HIV treatment and TB treatment efforts respectively. Now, we obtained the optimal control pair using Pontryagin's maximum principle. This principle converts equations (6.2) and (6.3) into a problem of minimizing point-wise a Hamiltonian, H with respect tou_1, u_2, u_3andu_4. Then

$$
\begin{aligned}
H &= aH_U + bH_D + cA_{TH} + dA_{HT} + eT_U + fT_D + A_1{u_1}^2 + A_2{u_2}^2 + A_3{u_3}^2 + A_4{u_4}^2 \\
&+M_S[\pi - ((1-u_1) + (1-u_2))(\lambda_H - \lambda_T - \lambda_{TH} - \lambda_{HT})S(t) - \mu S(t)] \\
&+M_{L_H}[((1-u_1) + (1-u_2))\varepsilon_1\lambda_H S(t) - (\kappa_H + \mu)L_H(t) + (1-u_3)\varphi H_W(t)] \\
&+M_{H_U}[((1-u_1) + (1-u_2))(1-\varepsilon_1)\lambda_H S(t) + (1-\omega_1)\kappa_H L_H(t) - (\gamma_{UH}(1-u_2) + \mu + \delta_{UH})H_U(t)] \\
&+M_{H_D}[\omega_1\kappa_H L_H(t) + (1-u_2)\gamma_{UH}H_U(t) - (\tau_1(1-u_3) + \mu + \delta_{d_H})H_D(t)] \\
&+M_{H_W}[\tau_1(1-u_3)H_D(t) - ((1-u_3)\varphi + \mu)H_W(t)] \\
&+M_{L_{TH}}\left[\left((1-u_1) + (1-u_2)\right)\lambda_{TH}S(t) - \left(\left((1-u_3) + (1-u_4)\right)\kappa_{TH} + \mu\right)L_{TH}(t) + \alpha_T R_{TH}(t)\right] \qquad (6.4) \\
&+M_{A_{TH}}[((1-u_3) + (1-u_4))\kappa_{TH}L_{TH}(t) - (\mu + \sigma_1 + \delta A_{TH})A_{TH}(t)] \\
&+M_{L_{HT}}[(1-u_1) + (1-u_2)]\lambda_{HT}S(t) - (((1-u_3) + (1-u_4))\kappa_{HT} + \mu)L_{HT}(t)] \\
&+M_{A_{HT}}[((1-u_3) + (1-u_4))\kappa_{HT}L_{HT}(t) - (\mu + \delta A_{HT})A_{HT}(t)] \\
&+M_{L_T}[((1-u_1) + (1-u_2))\varepsilon\ {}_2\lambda_T S(t) - (\kappa_T + \mu)L_T(t) + \upsilon T_U(t) + \theta_1\rho F_T(t) + r\alpha R_T(t)] \\
&+M_{T_U}[((1-u_1) + (1-u_2))(1-\varepsilon_2)\lambda_T S(t) + (1-\omega_2)\kappa_T L_T(t) + \theta_2\rho F_T(t) - (\upsilon + (1-u_2)\gamma_{UT} + \mu \\
&\qquad + \delta_{UT})T_U(t)] \\
&+M_{T_D}[\omega_2\kappa_T L_T(t) + (1-u_2)\gamma_{UT}T_U(t) + [1 - (\theta_1 + \theta_2)]\rho F_T(t) - (\sigma_2 + (1-u_4)\tau_2 + \mu + \delta_{dT})T_D(t)] \\
&+M_{F_T}[(1-u_4)(1-q_1)\tau_2 T_D(t) + (1-r)\alpha R_T(t) - (\rho + \mu + \delta_F)F_T(t)] \\
&+M_{R_T}[(1-u_4)q_1\tau_2 T_D(t) - (\alpha + \mu + \delta_{RT})R_T(t) + \sigma_2 T_D(t)] \\
&+M_{R_{TH}}[\sigma_1 A_{TH}(t) - (\alpha_T + \mu)R_{TH}(t)]
\end{aligned}
$$

Theorem 3: Given an optimal control ${u_1}^*, {u_2}^*, {u_3}^*, {u_4}^*$ and solutions

$S^*, {L_H}^*, {H_U}^*, {H_D}^*, {H_W}^*, {L_{TH}}^*, {A_{TH}}^*, {L_{HT}}^*, {A_{HT}}^*, {L_T}^*, {T_U}^*, {T_D}^*, F^*, {R_T}^*, {R_{TH}}^*$ of the corresponding state system (6.1) that minimizes the objective functional $J(u_1, u_2, u_3, u_4)$over U, there exist

Adjoint variables

$M_S, M_{L_H}, M_{H_U}, M_{H_D}, M_{H_W}, M_{L_{TH}}, M_{A_{TH}}, M_{L_{HT}}, M_{A_{HT}}, M_{L_T}, M_{T_U}, M_{T_D}, M_{F_T}, M_{R_T}, M_{R_{TH}}$ satisfying:

$$-\frac{dM_S}{dt} = -M_S[((1-u_1)+(1-u_2))(\lambda_H - \lambda_T - \lambda_{TH} - \lambda_{HT}) + \mu] + M_{L_H}((1-u_1)+(1-u_2))\varepsilon_1\lambda_H$$
$$+M_{H_U}((1-u_1)+(1-u_2))(1-\varepsilon_1)\lambda_H + M_{L_{TH}}((1-u_1)+(1-u_2))\lambda_{TH} + M_{L_{HT}}((1-u_1)+(1-u_2))\lambda_{HT}$$
$$-\frac{dM_{L_H}}{dt} = -M_S((1-u_1)+(1-u_2))S(t)\beta_H - (\kappa_H + \mu)M_{L_H} + M_{H_U}(1-\omega_1)\kappa_H + M_{H_D}\omega_1\kappa_H$$
$$-\frac{dM_{H_U}}{dt} = a - M_S((1-u_1)+(1-u_2))S(t)\beta_H\eta_U - M_{H_U}(\gamma_{UH}(1-u_2) + \mu + \delta_{UH}) + M_{H_D}(1-u_3)\gamma_{UH}$$
$$-\frac{dM_{H_D}}{dt} = b - M_S((1-u_1)+(1-u_2))S(t)\beta_H\eta_{dH} - M_{H_D}(\tau_1(1-u_3) + \mu + \delta_{d_H}) + M_{H_W}\tau_1(1-u_3)$$
$$-\frac{dM_{H_W}}{dt} = -M_S((1-u_1)+(1-u_2))S(t)\beta_H\eta_W - M_{H_W}((1-u_3)\varphi + \mu) + M_{L_H}(1-u_3)\varphi \quad (6.5)$$
$$-\frac{dM_{L_{TH}}}{dt} = -M_S((1-u_1)+(1-u_2))S(t)\beta_T - M_{L_{TH}}(((1-u_3)+(1-u_4))\kappa_{TH} + \mu) + M_{A_{TH}}((1-u_3)$$
$$+(1-u_4))\kappa_{TH}$$
$$-\frac{dM_{A_{TH}}}{dt} = c - M_S((1-u_1)+(1-u_2))S(t)\beta_T\eta_T - M_{A_{TH}}(\mu + \sigma_1 + \delta A_{TH}) + M_{R_{TH}}\sigma_1$$
$$-\frac{dM_{L_{HT}}}{dt} = -M_S((1-u_1)+(1-u_2))S(t)\beta_H - M_{L_{HT}}(((1-u_3)+(1-u_4))\kappa_{HT} + \mu) + M_{A_{HT}}((1-u_3)$$
$$+(1-u_4))\kappa_{HT}$$
$$-\frac{dM_{A_{HT}}}{dt} = d - M_S((1-u_1)+(1-u_2))S(t)\beta_H\eta_H - M_{A_{HT}}(\mu + \delta A_{HT})$$
$$-\frac{dM_{L_T}}{dt} = -M_S((1-u_1)+(1-u_2))S(t)\beta_T - M_{L_T}(\kappa_T + \mu) + M_{T_U}(1-\omega_2)\kappa_T + M_{T_D}\omega_2\kappa_T$$
$$-\frac{dM_{T_U}}{dt} = e - M_S((1-u_1)+(1-u_2))S(t)\beta_T\eta_U - M_{T_U}(\upsilon + (1-u_2)\gamma_{UT} + \mu + \delta_{UT}) + M_{T_D}(1-u_2)\gamma_{UT}$$
$$-\frac{dM_{T_D}}{dt} = f - M_S((1-u_1)+(1-u_2))S(t)\beta_T\eta_{dT} - M_{T_D}(\sigma_2 + (1-u_4)\tau_2 + \mu + \delta_{dT}) + M_{F_T}((1-u_4)(1$$
$$-q_1)\tau_2)$$
$$+M_{R_T}(1-u_4)q_1\tau_2$$
$$-\frac{dM_{F_T}}{dt} = -M_S((1-u_1)+(1-u_2))S(t)\beta_T - M_{F_T}(\rho + \mu + \delta_F) + M_{T_D}[1-(\theta_1+\theta_2)]\rho + M_{T_U}\theta_2\rho$$
$$+M_{L_T}\theta_1\rho$$
$$-\frac{dM_{R_T}}{dt} = -M_S((1-u_1)+(1-u_2))S(t)\beta_T\eta_{RT} - M_{R_T}(\alpha + \mu + \delta_{RT}) + r\alpha M_{L_T}$$
$$-\frac{dM_{R_{TH}}}{dt} = -M_S((1-u_1)+(1-u_2))S(t)\beta_T\eta_{RT} - M_{R_{TH}}(\alpha_T + \mu) + M_{l_{TH}}\alpha_T$$

$$M_S(t_f) = M_{L_H}(t_f) = M_{H_U}(t_f) = M_{H_D}(t_f) = M_{H_W}(t_f) = M_{L_{TH}}(t_f) = M_{A_{TH}}(t_f) = M_{L_{HT}}(t_f) =$$
$$M_{A_{HT}}(t_f) = M_{L_T}(t_f) = M_{T_U}(t_f) = M_{T_D}(t_f) = M_{F_T}(t_f) = M_{R_T}(t_f) = M_{R_{TH}}(t_f) = 0$$

tranversality conditions with the controls $u_1^*,\ u_2^*,\ u_3^*\ and\ \ u_4^*$ satisfying the optimality condition;

$$u_1^* = max\left\{0, min\left(1, \frac{\begin{matrix}[(-M_S)(\lambda_H - \lambda_T - \lambda_{TH} - \lambda_{HT}) + (\varepsilon_1 M_{L_H} + (1-\varepsilon_1)M_{H_U})\lambda_H \\ +\lambda_{TH}M_{L_{TH}} + \lambda_{HT}M_{L_{HT}} + (\varepsilon_2 M_{L_T} + (1-\varepsilon_2)M_{T_U})\lambda_T]S^*(t)\end{matrix}}{2A_1}\right)\right\}$$

$$u_2^* = max\left\{0, min\left(1, \frac{\begin{matrix}[(-M_S)(\lambda_H - \lambda_T - \lambda_{TH} - \lambda_{HT}) + (\varepsilon_1 M_{L_H} + (1-\varepsilon_1)M_{H_U})\lambda_H \\ +\lambda_{TH}M_{L_{TH}} + \lambda_{HT}M_{L_{HT}} + (\varepsilon_2 M_{L_T} + (1-\varepsilon_2)M_{T_U})\lambda_T]S^*(t) \\ +\gamma_{UH}(M_{H_D}H_D(t)^* - M_{H_U}H_U(t)^*) + \gamma_{UT}(M_{T_D}T_D(t)^* - M_{T_U}T_U(t)^*)\end{matrix}}{2A_2}\right)\right\} \quad (6.6)$$

$$u_3^* = max\left\{0, min\left(1, \frac{\varphi H_W{}^*(t)[M_{L_H} - M_{H_W}] + \kappa_{TH}L_{TH}{}^*(t)[M_{A_{TH}} - M_{L_{TH}}] + \kappa_{HT}L_{HT}{}^*(t)[M_{A_{HT}} - M_{L_{HT}}]}{2A_3}\right)\right\}$$

$$u_4^* = max\left\{0, min\left(1, \frac{\begin{matrix}\tau_2 T_D{}^*(t)\left[M_{T_D} - M_{F_T}(1-q_1) + q_1 M_{R_T}\right] + \kappa_{TH}L_{TH}{}^*(t)\left[M_{A_{TH}} - M_{L_{TH}}\right] \\ +\kappa_{HT}L_{HT}{}^*(t)\left[M_{A_{HT}} - M_{L_{HT}}\right]\end{matrix}}{2A_4}\right)\right\}$$

Proof:

Following Pontryagin's maximum principle, we obtained the standard form of the adjoint equations and tranversality conditions by differentiating the Hamiltonian function with respect to state $M_S, M_{L_H}, M_{H_U}, M_{H_D}, M_{H_W}, M_{L_{TH}}, M_{A_{TH}}, M_{L_{HT}}, M_{A_{HT}}, M_{L_T}, M_{T_U}, M_{T_D}, M_{F_T}, M_{R_T} and M_{R_{TH}}$ respectively which is evaluated at the optimal control function u_1, u_2, u_3, u_4

So we re-write the adjoint system as follows:

$$-\frac{dM_S}{dt} = \frac{\partial H}{\partial S} = -M_S[((1-u_1)+(1-u_2))(\lambda_H - \lambda_T - \lambda_{TH} - \lambda_{HT}) + \mu] + M_{L_H}((1-u_1)+(1-u_2))\varepsilon_1\lambda_H$$
$$+M_{H_U}((1-u_1)+(1-u_2))(1-\varepsilon_1)\lambda_H + M_{L_{TH}}((1-u_1)+(1-u_2))\lambda_{TH} + M_{L_{HT}}((1-u_1)+(1-u_2))\lambda_{HT}$$
$$-\frac{dM_{L_H}}{dt} = \frac{\partial H}{\partial L_H} = -M_S((1-u_1)+(1-u_2))S(t)\beta_H - (\kappa_H + \mu)M_{L_H} + M_{H_U}(1-\omega_1)\kappa_H + M_{H_D}\omega_1\kappa_H$$
$$-\frac{dM_{H_U}}{dt} = \frac{\partial H}{\partial H_U} = a - M_S((1-u_1)+(1-u_2))S(t)\beta_H\eta_U - M_{H_U}(\gamma_{UH}(1-u_2) + \mu + \delta_{UH}) + M_{H_D}(1$$
$$-u_3)\gamma_{UH}$$
$$-\frac{dM_{H_D}}{dt} = \frac{\partial H}{\partial H_D} = b - M_S((1-u_1)+(1-u_2))S(t)\beta_H\eta_{dH} - M_{H_D}(\tau_1(1-u_3) + \mu + \delta_{d_H}) + M_{H_W}\tau_1(1-u_3)$$
$$-\frac{dM_{H_W}}{dt} = \frac{\partial H}{\partial H_W} = -M_S((1-u_1)+(1-u_2))S(t)\beta_H\eta_W - M_{H_W}((1-u_3)\varphi + \mu) + M_{L_H}(1-u_3)\varphi$$
$$-\frac{dM_{L_{TH}}}{dt} = \frac{\partial H}{\partial L_{TH}} = -M_S((1-u_1)+(1-u_2))S(t)\beta_T - M_{L_{TH}}(((1-u_3)+(1-u_4))\kappa_{TH} + \mu) + M_{A_{TH}}((1$$
$$-u_3)+(1-u_4))\kappa_{TH}$$
$$-\frac{dM_{A_{TH}}}{dt} = \frac{\partial H}{\partial A_{TH}} = c - M_S((1-u_1)+(1-u_2))S(t)\beta_T\eta_T - M_{A_{TH}}(\mu + \sigma_1 + \delta A_{TH}) + M_{R_{TH}}\sigma_1$$
$$-\frac{dM_{L_{HT}}}{dt} = \frac{\partial H}{\partial L_{HT}} = -M_S((1-u_1)+(1-u_2))S(t)\beta_H - M_{L_{HT}}(((1-u_3)+(1-u_4))\kappa_{HT} + \mu) + M_{A_{HT}}((1$$
$$-u_3)+(1-u_4))\kappa_{HT}$$
$$-\frac{dM_{A_{HT}}}{dt} = \frac{\partial H}{\partial A_{HT}} = d - M_S((1-u_1)+(1-u_2))S(t)\beta_H\eta_H - M_{A_{HT}}(\mu + \delta A_{HT}) \quad (6.7)$$
$$-\frac{dM_{L_T}}{dt} = \frac{\partial H}{\partial L_T} = -M_S((1-u_1)+(1-u_2))S(t)\beta_T - M_{L_T}(\kappa_T + \mu) + M_{T_U}(1-\omega_2)\kappa_T + M_{T_D}\omega_2\kappa_T$$

$$-\frac{dM_{T_U}}{dt}=\frac{\partial H}{\partial T_U}=e-M_S((1-u_1)+(1-u_2))S(t)\beta_T\eta_U-M_{T_U}(\upsilon+(1-u_2)\gamma_{UT}+\mu+\delta_{UT})+M_{T_D}(1-u_2)\gamma_{UT}$$

$$-\frac{dM_{T_D}}{dt}=\frac{\partial H}{\partial T_D}=f-M_S((1-u_1)+(1-u_2))S(t)\beta_T\eta_{dT}-M_{T_D}(\sigma_2+(1-u_4)\tau_2+\mu+\delta_{dT})+M_{F_T}((1-u_4)(1-q_1)\tau_2)+M_{R_T}(1-u_4)q_1\tau_2$$

$$-\frac{dM_{F_T}}{dt}=\frac{\partial H}{\partial F_T}=-M_S((1-u_1)+(1-u_2))S(t)\beta_T-M_{F_T}(\rho+\mu+\delta_F)+M_{T_D}[1-(\theta_1+\theta_2)]\rho+M_{T_U}\theta_2\rho+M_{L_T}\theta_1\rho$$

$$-\frac{dM_{R_T}}{dt}=\frac{\partial H}{\partial R_T}=-M_S((1-u_1)+(1-u_2))S(t)\beta_T\eta_{RT}-M_{R_T}(\alpha+\mu+\delta_{RT})+r\alpha M_{L_T}$$

$$-\frac{dM_{R_{TH}}}{dt}=\frac{\partial H}{\partial R_{TH}}=-M_S((1-u_1)+(1-u_2))S(t)\beta_T\eta_{RT}-M_{R_{TH}}(\alpha_T+\mu)+M_{l_{TH}}\alpha_T$$

With transverlity conditions

$$M_S(t_f)=M_{L_H}(t_f)=M_{H_U}(t_f)=M_{H_D}(t_f)=M_{H_W}(t_f)=M_{L_{TH}}(t_f)=M_{A_{TH}}(t_f)=M_{L_{HT}}(t_f)=M_{A_{HT}}(t_f)=M_{L_T}(t_f)=M_{T_U}(t_f)=M_{T_D}(t_f)=M_{F_T}(t_f)=M_{R_T}(t_f)=M_{R_{TH}}(t_f)=0 \quad (6.8)$$

Solving $\frac{dH}{du_1}=0,\ \frac{dH}{du_2}=0,\ \frac{dH}{du_3}=0\ \ and\ \ \frac{dH}{du_4}=0,$ and evaluating at the optimal control on the interior of the control set, where $0\le u_i\le 1$ for $i=1,2,3,4$ we obtain;

$$0=\frac{\partial H}{\partial u_1}=\begin{pmatrix}2A_1u_1+[(M_S)(\lambda_H-\lambda_T-\lambda_{TH}-\lambda_{HT})-(\varepsilon_1M_{L_H}+(1-\varepsilon_1)M_{H_U})\lambda_H\\-\lambda_{TH}M_{L_{TH}}-\lambda_{HT}M_{L_{HT}}-(\varepsilon_2M_{L_T}+(1-\varepsilon_2)M_{T_U})\lambda_T]S^*(t)\end{pmatrix}$$

$$\Rightarrow 2A_1u_1=\begin{pmatrix}[(-M_S)(\lambda_H-\lambda_T-\lambda_{TH}-\lambda_{HT})+(\varepsilon_1M_{L_H}+(1-\varepsilon_1)M_{H_U})\lambda_H\\+\lambda_{TH}M_{L_{TH}}+\lambda_{HT}M_{L_{HT}}+(\varepsilon_2M_{L_T}+(1-\varepsilon_2)M_{T_U})\lambda_T]S^*(t)\end{pmatrix}$$

$$0=\frac{\partial H}{\partial u_2}=\begin{pmatrix}2A_2u_2+[(M_S)(\lambda_H-\lambda_T-\lambda_{TH}-\lambda_{HT})-(\varepsilon_1M_{L_H}+(1-\varepsilon_1)M_{H_U})\lambda_H\\-\lambda_{TH}M_{L_{TH}}-\lambda_{HT}M_{L_{HT}}-(\varepsilon_2M_{L_T}+(1-\varepsilon_2)M_{T_U})\lambda_T]S^*(t)\\-\gamma_{UH}(M_{H_D}H_D(t)^*-M_{H_U}H_U(t)^*)-\gamma_{UT}(M_{T_D}T_D(t)^*-M_{T_U}T_U(t)^*)\end{pmatrix} \quad (6.9)$$

$$\Rightarrow 2A_2u_2=\begin{pmatrix}[(-M_S)(\lambda_H-\lambda_T-\lambda_{TH}-\lambda_{HT})+(\varepsilon_1M_{L_H}+(1-\varepsilon_1)M_{H_U})\lambda_H\\+\lambda_{TH}M_{L_{TH}}+\lambda_{HT}M_{L_{HT}}+(\varepsilon_2M_{L_T}+(1-\varepsilon_2)M_{T_U})\lambda_T]S^*(t)\\+\gamma_{UH}(M_{H_D}H_D(t)^*-M_{H_U}H_U(t)^*)+\gamma_{UT}(M_{T_D}T_D(t)^*-M_{T_U}T_U(t)^*)\end{pmatrix}$$

$$0=\frac{\partial H}{\partial u_3}=\begin{pmatrix}2A_3u_3-\varphi H_W{}^*(t)[M_{L_H}-M_{H_W}]-\kappa_{TH}L_{TH}{}^*(t)[M_{A_{TH}}-M_{L_{TH}}]\\-\kappa_{HT}L_{HT}{}^*(t)[M_{A_{HT}}-M_{L_{HT}}]\end{pmatrix}$$

$$\Rightarrow 2A_3u_3=\begin{pmatrix}\varphi H_W{}^*(t)[M_{L_H}-M_{H_W}]+\kappa_{TH}L_{TH}{}^*(t)[M_{A_{TH}}-M_{L_{TH}}]\\+\kappa_{HT}L_{HT}{}^*(t)[M_{A_{HT}}-M_{L_{HT}}]\end{pmatrix}$$

$$0=\frac{\partial H}{\partial u_4}=\begin{pmatrix}2A_4u_4-\tau_2T_D{}^*(t)[M_{T_D}-M_{F_T}(1-q_1)+q_1M_{R_T}]-\kappa_{TH}L_{TH}{}^*(t)[M_{A_{TH}}-M_{L_{TH}}]\\-\kappa_{HT}L_{HT}{}^*(t)[M_{A_{HT}}-M_{L_{HT}}]\end{pmatrix}$$

$$\Rightarrow 2A_4u_4=\begin{pmatrix}\tau_2T_D{}^*(t)[M_{T_D}-M_{F_T}(1-q_1)+q_1M_{R_T}]+\kappa_{TH}L_{TH}{}^*(t)[M_{A_{TH}}-M_{L_{TH}}]\\+\kappa_{HT}L_{HT}{}^*(t)[M_{A_{HT}}-M_{L_{HT}}]\end{pmatrix}$$

Therefore:

$$u_1{}^*=max\left\{0,min\left(1,\frac{\begin{matrix}[(-M_S)(\lambda_H-\lambda_T-\lambda_{TH}-\lambda_{HT})+(\varepsilon_1M_{L_H}+(1-\varepsilon_1)M_{H_U})\lambda_H\\+\lambda_{TH}M_{L_{TH}}+\lambda_{HT}M_{L_{HT}}+(\varepsilon_2M_{L_T}+(1-\varepsilon_2)M_{T_U})\lambda_T]S^*(t)\end{matrix}}{2A_1}\right)\right\}$$

$$u_2{}^* = max\left\{0, min\left(1, \frac{\begin{matrix}[(-M_S)(\lambda_H - \lambda_T - \lambda_{TH} - \lambda_{HT}) + (\varepsilon_1 M_{L_H} + (1-\varepsilon_1)M_{H_U})\lambda_H + \lambda_{TH}M_{L_{TH}} + \lambda_{HT}M_{L_{HT}} \\ +(\varepsilon_2 M_{L_T} + (1-\varepsilon_2)M_{T_U})\lambda_T]S^*(t) + \gamma_{UH}(M_{H_D}H_D(t)^* - M_{H_U}H_U(t)^*) + \gamma_{UT}(M_{T_D}T_D(t)^* - M_{T_U}T_U(t)^*)\end{matrix}}{2A_2}\right)\right\}u_3{}^*$$

$$= max\left\{0, min\left(1, \frac{\varphi H_W{}^*(t)[M_{L_H} - M_{H_W}] + \kappa_{TH}L_{TH}{}^*(t)[M_{A_{TH}} - M_{L_{TH}}] + \kappa_{HT}L_{HT}{}^*(t)[M_{A_{HT}} - M_{L_{HT}}]}{2A_3}\right)\right\}$$

$$u_4{}^* = max\left\{0, min\left(1, \frac{\tau_2 T_D{}^*(t)[M_{T_D} - M_{F_T}(1-q_1) + q_1 M_{R_T}] + \kappa_{TH}L_{TH}{}^*(t)[M_{A_{TH}} - M_{L_{TH}}] + \kappa_{HT}L_{HT}{}^*(t)[M_{A_{HT}} - M_{L_{HT}}]}{2A_4}\right)\right\}$$

By standard control arguments involving the bounds on the control variables, we have

$$u_1{}^* = \begin{cases} \dfrac{\begin{matrix}[(-M_S)(\lambda_H - \lambda_T - \lambda_{TH} - \lambda_{HT}) + (\varepsilon_1 M_{L_H} + (1-\varepsilon_1)M_{H_U})\lambda_H \\ +\lambda_{TH}M_{L_{TH}} + \lambda_{HT}M_{L_{HT}} + (\varepsilon_2 M_{L_T} + (1-\varepsilon_2)M_{T_U})\lambda_T]S^*(t)\end{matrix}}{2A_1}, if \\ 0 < \dfrac{\begin{matrix}[(-M_S)(\lambda_H - \lambda_T - \lambda_{TH} - \lambda_{HT}) + (\varepsilon_1 M_{L_H} + (1-\varepsilon_1)M_{H_U})\lambda_H \\ +\lambda_{TH}M_{L_{TH}} + \lambda_{HT}M_{L_{HT}} + (\varepsilon_2 M_{L_T} + (1-\varepsilon_2)M_{T_U})\lambda_T]S^*(t)\end{matrix}}{2A_1} < 1, \end{cases}$$

$$0 if \frac{\begin{matrix}[(-M_S)(\lambda_H - \lambda_T - \lambda_{TH} - \lambda_{HT}) + (\varepsilon_1 M_{L_H} + (1-\varepsilon_1)M_{H_U})\lambda_H \\ +\lambda_{TH}M_{L_{TH}} + \lambda_{HT}M_{L_{HT}} + (\varepsilon_2 M_{L_T} + (1-\varepsilon_2)M_{T_U})\lambda_T]S^*(t)\end{matrix}}{2A_1} \leq 0$$

$$1 if \frac{\begin{matrix}[(-M_S)(\lambda_H - \lambda_T - \lambda_{TH} - \lambda_{HT}) + (\varepsilon_1 M_{L_H} + (1-\varepsilon_1)M_{H_U})\lambda_H \\ +\lambda_{TH}M_{L_{TH}} + \lambda_{HT}M_{L_{HT}} + (\varepsilon_2 M_{L_T} + (1-\varepsilon_2)M_{T_U})\lambda_T]S^*(t)\end{matrix}}{2A_1} \geq 1$$

Similarly:

$$u_2{}^* = \begin{cases} \dfrac{\begin{matrix}[(-M_S)(\lambda_H - \lambda_T - \lambda_{TH} - \lambda_{HT}) + (\varepsilon_1 M_{L_H} + (1-\varepsilon_1)M_{H_U})\lambda_H \\ +\lambda_{TH}M_{L_{TH}} + \lambda_{HT}M_{L_{HT}} + (\varepsilon_2 M_{L_T} + (1-\varepsilon_2)M_{T_U})\lambda_T]S^*(t) \\ +\gamma_{UH}(M_{H_D}H_D(t)^* - M_{H_U}H_U(t)^*) + \gamma_{UT}(M_{T_D}T_D(t)^* - M_{T_U}T_U(t)^*)\end{matrix}}{2A_2}, if \\ 0 < \dfrac{\begin{matrix}[(-M_S)(\lambda_H - \lambda_T - \lambda_{TH} - \lambda_{HT}) + (\varepsilon_1 M_{L_H} + (1-\varepsilon_1)M_{H_U})\lambda_H \\ +\lambda_{TH}M_{L_{TH}} + \lambda_{HT}M_{L_{HT}} + (\varepsilon_2 M_{L_T} + (1-\varepsilon_2)M_{T_U})\lambda_T]S^*(t) \\ +\gamma_{UH}(M_{H_D}H_D(t)^* - M_{H_U}H_U(t)^*) + \gamma_{UT}(M_{T_D}T_D(t)^* - M_{T_U}T_U(t)^*)\end{matrix}}{2A_2} < 1, \end{cases}$$

$$0 if \frac{\begin{matrix}[(-M_S)(\lambda_H - \lambda_T - \lambda_{TH} - \lambda_{HT}) + (\varepsilon_1 M_{L_H} + (1-\varepsilon_1)M_{H_U})\lambda_H \\ +\lambda_{TH}M_{L_{TH}} + \lambda_{HT}M_{L_{HT}} + (\varepsilon_2 M_{L_T} + (1-\varepsilon_2)M_{T_U})\lambda_T]S^*(t) \\ +\gamma_{UH}(M_{H_D}H_D(t)^* - M_{H_U}H_U(t)^*) + \gamma_{UT}(M_{T_D}T_D(t)^* - M_{T_U}T_U(t)^*)\end{matrix}}{2A_2} \leq 0$$

$$1 if \frac{\begin{matrix}[(-M_S)(\lambda_H - \lambda_T - \lambda_{TH} - \lambda_{HT}) + (\varepsilon_1 M_{L_H} + (1-\varepsilon_1)M_{H_U})\lambda_H \\ +\lambda_{TH}M_{L_{TH}} + \lambda_{HT}M_{L_{HT}} + (\varepsilon_2 M_{L_T} + (1-\varepsilon_2)M_{T_U})\lambda_T]S^*(t) \\ +\gamma_{UH}(M_{H_D}H_D(t)^* - M_{H_U}H_U(t)^*) + \gamma_{UT}(M_{T_D}T_D(t)^* - M_{T_U}T_U(t)^*)\end{matrix}}{2A_2} \geq 1$$

$$u_3{}^* = \begin{cases} \dfrac{\varphi H_W{}^*(t)[M_{L_H} - M_{H_W}] + \kappa_{TH}L_{TH}{}^*(t)[M_{A_{TH}} - M_{L_{TH}}] + \kappa_{HT}L_{HT}{}^*(t)[M_{A_{HT}} - M_{L_{HT}}]}{2A_3}, if \\ 0 < \dfrac{\varphi H_W{}^*(t)[M_{L_H} - M_{H_W}] + \kappa_{TH}L_{TH}{}^*(t)[M_{A_{TH}} - M_{L_{TH}}] + \kappa_{HT}L_{HT}{}^*(t)[M_{A_{HT}} - M_{L_{HT}}]}{2A_3} < 1, \end{cases}$$

$$0 if \frac{\varphi H_W{}^*(t)[M_{L_H} - M_{H_W}] + \kappa_{TH}L_{TH}{}^*(t)[M_{A_{TH}} - M_{L_{TH}}] + \kappa_{HT}L_{HT}{}^*(t)[M_{A_{HT}} - M_{L_{HT}}]}{2A_3} \leq 0$$

$$1 if \frac{\varphi H_W{}^*(t)[M_{L_H} - M_{H_W}] + \kappa_{TH}L_{TH}{}^*(t)[M_{A_{TH}} - M_{L_{TH}}] + \kappa_{HT}L_{HT}{}^*(t)[M_{A_{HT}} - M_{L_{HT}}]}{2A_3} \geq 1$$

Also:

$$u_4^* = \begin{cases} \dfrac{\tau_2 T_D^*(t)[M_{T_D} - M_{F_T}(1-q_1) + q_1 M_{R_T}] + \kappa_{TH} L_{TH}^*(t)[M_{A_{TH}} - M_{L_{TH}}] + \kappa_{HT} L_{HT}^*(t)[M_{A_{HT}} - M_{L_{HT}}]}{2A_4}, & if \\ 0 < \dfrac{\tau_2 T_D^*(t)[M_{T_D} - M_{F_T}(1-q_1) + q_1 M_{R_T}] + \kappa_{TH} L_{TH}^*(t)[M_{A_{TH}} - M_{L_{TH}}] + \kappa_{HT} L_{HT}^*(t)[M_{A_{HT}} - M_{L_{HT}}]}{2A_4} < 1, & \\ 0 \quad if \ \dfrac{\tau_2 T_D^*(t)[M_{T_D} - M_{F_T}(1-q_1) + q_1 M_{R_T}] + \kappa_{TH} L_{TH}^*(t)[M_{A_{TH}} - M_{L_{TH}}] + \kappa_{HT} L_{HT}^*(t)[M_{A_{HT}} - M_{L_{HT}}]}{2A_4} \le 0 & \\ 1 \quad if \ \dfrac{\tau_2 T_D^*(t)[M_{T_D} - M_{F_T}(1-q_1) + q_1 M_{R_T}] + \kappa_{TH} L_{TH}^*(t)[M_{A_{TH}} - M_{L_{TH}}] + \kappa_{HT} L_{HT}^*(t)[M_{A_{HT}} - M_{L_{HT}}]}{2A_4} \ge 1 & \end{cases}$$

This completes the proof.
The optimality system consists of the state system coupled with the adjoint system with the initial and tranversality conditions together with the characterization of the optimal control pair.

Substituting (6.6) into (6.1) we obtained the following optimality system;

$$\frac{dS(t)}{dt} = \pi - \left(\left(1 - max\left\{0, min\left(1, \frac{[(-M_S)(\lambda_H - \lambda_T - \lambda_{TH} - \lambda_{HT}) + (\varepsilon_1 M_{L_H} + (1-\varepsilon_1)M_{H_U})\lambda_H + \lambda_{TH} M_{L_{TH}} + \lambda_{HT} M_{L_{HT}} + (\varepsilon_2 M_{L_T} + (1-\varepsilon_2)M_{T_U})\lambda_T]S^*(t)}{2A_1}\right)\right\}\right)\right.$$
$$+\left(\left(1 - max\left\{0, min\left(1, \frac{[(-M_S)(\lambda_H - \lambda_T - \lambda_{TH} - \lambda_{HT}) + (\varepsilon_1 M_{L_H} + (1-\varepsilon_1)M_{H_U})\lambda_H + \lambda_{TH} M_{L_{TH}} + \lambda_{HT} M_{L_{HT}} + (\varepsilon_2 M_{L_T} + (1-\varepsilon_2)M_{T_U})\lambda_T]S^*(t) + \gamma_{UH}(M_{H_D} H_D(t)^* - M_{H_U} H_U(t)^*) + \gamma_{UT}(M_{T_D} T_D(t)^* - M_{T_U} T_U(t)^*)}{2A_2}\right)\right\}\right)(\lambda_H - \lambda_T$$
$$- \lambda_{TH} - \lambda_{HT})S(t)$$
$$-\mu S(t)$$

$$\frac{dL_H(t)}{dt} = \left(\left(1 - max\left\{0, min\left(1, \frac{[(-M_S)(\lambda_H - \lambda_T - \lambda_{TH} - \lambda_{HT}) + (\varepsilon_1 M_{L_H} + (1-\varepsilon_1)M_{H_U})\lambda_H + \lambda_{TH} M_{L_{TH}} + \lambda_{HT} M_{L_{HT}} + (\varepsilon_2 M_{L_T} + (1-\varepsilon_2)M_{T_U})\lambda_T]S^*(t)}{2A_1}\right)\right\}\right)\right.$$
$$+\left(\left(1 - max\left\{0, min\left(1, \frac{[(-M_S)(\lambda_H - \lambda_T - \lambda_{TH} - \lambda_{HT}) + (\varepsilon_1 M_{L_H} + (1-\varepsilon_1)M_{H_U})\lambda_H + \lambda_{TH} M_{L_{TH}} + \lambda_{HT} M_{L_{HT}} + (\varepsilon_2 M_{L_T} + (1-\varepsilon_2)M_{T_U})\lambda_T]S^*(t) + \gamma_{UH}(M_{H_D} H_D(t)^* - M_{H_U} H_U(t)^*) + \gamma_{UT}(M_{T_D} T_D(t)^* - M_{T_U} T_U(t)^*)}{2A_2}\right)\right\}\right)\varepsilon_1 \lambda_H S(t)$$
$$- (\kappa_H + \mu)L_H$$
$$+\left(1\right.$$
$$\left. - max\left\{0, min\left(1, \frac{\varphi H_W^*(t)[M_{L_H} - M_{H_W}] + \kappa_{TH} L_{TH}^*(t)[M_{A_{TH}} - M_{L_{TH}}] + \kappa_{HT} L_{HT}^*(t)[M_{A_{HT}} - M_{L_{HT}}]}{2A_3}\right)\right\}\right)\varphi H_W(t)$$

$$\frac{dH_U(t)}{dt}=\left(\left(1-\max\left\{0,\min\left(1,\frac{\begin{array}{l}[(-M_S)(\lambda_H-\lambda_T-\lambda_{TH}-\lambda_{HT})+(\varepsilon_1 M_{L_H}+(1-\varepsilon_1)M_{H_U})\lambda_H\\+\lambda_{TH}M_{L_{TH}}+\lambda_{HT}M_{L_{HT}}+(\varepsilon_2 M_{L_T}+(1-\varepsilon_2)M_{T_U})\lambda_T]S^*(t)\end{array}}{2A_1}\right)\right\}\right)\right.$$

$$+\left(1-\max\left\{0,\min\left(1,\frac{\begin{array}{l}[(-M_S)(\lambda_H-\lambda_T-\lambda_{TH}-\lambda_{HT})+(\varepsilon_1 M_{L_H}+(1-\varepsilon_1)M_{H_U})\lambda_H\\+\lambda_{TH}M_{L_{TH}}+\lambda_{HT}M_{L_{HT}}+(\varepsilon_2 M_{L_T}+(1-\varepsilon_2)M_{T_U})\lambda_T]S^*(t)\\+\gamma_{UH}(M_{H_D}H_D(t)^*-M_{H_U}H_U(t)^*)+\gamma_{UT}(M_{T_D}T_D(t)^*-M_{T_U}T_U(t)^*)\end{array}}{2A_2}\right)\right\}\right)(1-\varepsilon_1)\lambda_H S(t)+$$

$$(1-\omega_1)\kappa_H L_H(t)-(\gamma_{UH}\left(1-\max\left\{0,\min\left(1,\frac{\begin{array}{l}[(-M_S)(\lambda_H-\lambda_T-\lambda_{TH}-\lambda_{HT})+(\varepsilon_1 M_{L_H}+(1-\varepsilon_1)M_{H_U})\lambda_H\\+\lambda_{TH}M_{L_{TH}}+\lambda_{HT}M_{L_{HT}}+(\varepsilon_2 M_{L_T}+(1-\varepsilon_2)M_{T_U})\lambda_T]S^*(t)\\+\gamma_{UH}(M_{H_D}H_D(t)^*-M_{H_U}H_U(t)^*)+\gamma_{UT}(M_{T_D}T_D(t)^*-M_{T_U}T_U(t)^*)\end{array}}{2A_2}\right)\right\}\right)$$

$$+\mu+\delta_{UH})H_U(t)$$

$$\frac{dH_D(t)}{dt}=\omega_1\kappa_H L_H(t)+\left(1-\max\left\{0,\min\left(1,\frac{\begin{array}{l}[(-M_S)(\lambda_H-\lambda_T-\lambda_{TH}-\lambda_{HT})+(\varepsilon_1 M_{L_H}+(1-\varepsilon_1)M_{H_U})\lambda_H\\+\lambda_{TH}M_{L_{TH}}+\lambda_{HT}M_{L_{HT}}+(\varepsilon_2 M_{L_T}+(1-\varepsilon_2)M_{T_U})\lambda_T]S^*(t)\\+\gamma_{UH}(M_{H_D}H_D(t)^*-M_{H_U}H_U(t)^*)+\gamma_{UT}(M_{T_D}T_D(t)^*-M_{T_U}T_U(t)^*)\end{array}}{2A_2}\right)\right\}\right)\gamma_{UH}H_U(t)$$

$$-(\tau_1\left(1-\max\left\{0,\min\left(1,\frac{\phi H_W{}^*(t)[M_{L_H}-M_{H_W}]+\kappa_{TH}L_{TH}{}^*(t)[M_{A_{TH}}-M_{L_{TH}}]+\kappa_{HT}L_{HT}{}^*(t)[M_{A_{HT}}-M_{L_{HT}}]}{2A_3}\right)\right\}\right)+\mu+\delta_{dH})H_D(t)$$

$$\frac{dH_W(t)}{dt}=\tau_1\left(1-\max\left\{0,\min\left(1,\frac{\phi H_W{}^*(t)[M_{L_H}-M_{H_W}]+\kappa_{TH}L_{TH}{}^*(t)[M_{A_{TH}}-M_{L_{TH}}]+\kappa_{HT}L_{HT}{}^*(t)[M_{A_{HT}}-M_{L_{HT}}]}{2A_3}\right)\right\}\right)H_D(t)$$

$$-\left(\left(1-\max\left\{0,\min\left(1,\frac{\phi H_W{}^*(t)[M_{L_H}-M_{H_W}]+\kappa_{TH}L_{TH}{}^*(t)[M_{A_{TH}}-M_{L_{TH}}]+\kappa_{HT}L_{HT}{}^*(t)[M_{A_{HT}}-M_{L_{HT}}]}{2A_3}\right)\right\}\right)\phi+\mu\right)H_W(t)$$

$$\frac{dL_{TH}(t)}{dt}=\left(\left(1-\max\left\{0,\min\left(1,\frac{\begin{array}{l}[(-M_S)(\lambda_H-\lambda_T-\lambda_{TH}-\lambda_{HT})+(\varepsilon_1 M_{L_H}+(1-\varepsilon_1)M_{H_U})\lambda_H\\+\lambda_{TH}M_{L_{TH}}+\lambda_{HT}M_{L_{HT}}+(\varepsilon_2 M_{L_T}+(1-\varepsilon_2)M_{T_U})\lambda_T]S^*(t)\end{array}}{2A_1}\right)\right\}\right)+\right.$$

$$\left(1-\max\left\{0,\min\left(1,\frac{\begin{array}{l}[(-M_S)(\lambda_H-\lambda_T-\lambda_{TH}-\lambda_{HT})+(\varepsilon_1 M_{L_H}+(1-\varepsilon_1)M_{H_U})\lambda_H\\+\lambda_{TH}M_{L_{TH}}+\lambda_{HT}M_{L_{HT}}+(\varepsilon_2 M_{L_T}+(1-\varepsilon_2)M_{T_U})\lambda_T]S^*(t)\\+\gamma_{UH}(M_{H_D}H_D(t)^*-M_{H_U}H_U(t)^*)+\gamma_{UT}(M_{T_D}T_D(t)^*-M_{T_U}T_U(t)^*)\end{array}}{2A_2}\right)\right\}\right)\lambda_{TH}S(t)$$

$$-((\left(1-\max\left\{0,\min\left(1,\frac{\phi H_W{}^*(t)[M_{L_H}-M_{H_W}]+\kappa_{TH}L_{TH}{}^*(t)[M_{A_{TH}}-M_{L_{TH}}]+\kappa_{HT}L_{HT}{}^*(t)[M_{A_{HT}}-M_{L_{HT}}]}{2A_3}\right)\right\}\right)$$

$$+\left(1-\max\left\{0,\min\left(1,\frac{\tau_2 T_D{}^*(t)[M_{T_D}-M_{F_T}(1-q_1)+q_1M_{R_T}]+\kappa_{TH}L_{TH}{}^*(t)[M_{A_{TH}}-M_{L_{TH}}]}{+\kappa_{HT}L_{HT}{}^*(t)[M_{A_{HT}}-M_{L_{HT}}]}{2A_4}\right)\right\}\right)\kappa_{TH}+\mu)L_{TH}(t)$$

$$+\alpha_T R_{TH}(t)$$

$$\frac{dA_{TH}(t)}{dt}=(\left(1-\max\left\{0,\min\left(1,\frac{\phi H_W{}^*(t)[M_{L_H}-M_{H_W}]+\kappa_{TH}L_{TH}{}^*(t)[M_{A_{TH}}-M_{L_{TH}}]+\kappa_{HT}L_{HT}{}^*(t)[M_{A_{HT}}-M_{L_{HT}}]}{2A_3}\right)\right\}\right)$$

$$+\left(1-\max\left\{0,\min\left(1,\frac{\tau_2 T_D{}^*(t)[M_{T_D}-M_{F_T}(1-q_1)+q_1M_{R_T}]+\kappa_{TH}L_{TH}{}^*(t)[M_{A_{TH}}-M_{L_{TH}}]}{+\kappa_{HT}L_{HT}{}^*(t)[M_{A_{HT}}-M_{L_{HT}}]}{2A_4}\right)\right\}\right)\kappa_{TH}L_{TH}(t)$$

$$-(\mu+\sigma_1+\delta A_{TH})A_{TH}(t)$$

$$\frac{dL_{HT}(t)}{dt}=(\left(1-\max\left\{0,\min\left(1,\frac{[(-M_S)(\lambda_H-\lambda_T-\lambda_{TH}-\lambda_{HT})+(\varepsilon_1M_{L_H}+(1-\varepsilon_1)M_{H_U})\lambda_H}{+\lambda_{TH}M_{L_{TH}}+\lambda_{HT}M_{L_{HT}}+(\varepsilon_2M_{L_T}+(1-\varepsilon_2)M_{T_U})\lambda_T]S^*(t)}{2A_1}\right)\right\}\right)+$$

$$\left(1-\max\left\{0,\min\left(1,\frac{\begin{array}{l}[(-M_S)(\lambda_H-\lambda_T-\lambda_{TH}-\lambda_{HT})+(\varepsilon_1M_{L_H}+(1-\varepsilon_1)M_{H_U})\lambda_H\\+\lambda_{TH}M_{L_{TH}}+\lambda_{HT}M_{L_{HT}}+(\varepsilon_2M_{L_T}+(1-\varepsilon_2)M_{T_U})\lambda_T]S^*(t)\\+\gamma_{UH}(M_{H_D}H_D(t)^*-M_{H_U}H_U(t)^*)+\gamma_{UT}(M_{T_D}T_D(t)^*-M_{T_U}T_U(t)^*)\end{array}}{2A_2}\right)\right\}\right)\lambda_{HT}S(t)$$

$$-(\left(1-\max\left\{0,\min\left(1,\frac{\phi H_W{}^*(t)[M_{L_H}-M_{H_W}]+\kappa_{TH}L_{TH}{}^*(t)[M_{A_{TH}}-M_{L_{TH}}]+\kappa_{HT}L_{HT}{}^*(t)[M_{A_{HT}}-M_{L_{HT}}]}{2A_3}\right)\right\}\right)$$

$$+\left(1-\max\left\{0,\min\left(1,\frac{\tau_2 T_D{}^*(t)[M_{T_D}-M_{F_T}(1-q_1)+q_1M_{R_T}]+\kappa_{TH}L_{TH}{}^*(t)[M_{A_{TH}}-M_{L_{TH}}]}{+\kappa_{HT}L_{HT}{}^*(t)[M_{A_{HT}}-M_{L_{HT}}]}{2A_4}\right)\right\}\right)\kappa_{HT}+\mu)L_{HT}(t) \quad (4.10)$$

$$\frac{dA_{HT}(t)}{dt}=(\left(1-\max\left\{0,\min\left(1,\frac{\phi H_W{}^*(t)[M_{L_H}-M_{H_W}]+\kappa_{TH}L_{TH}{}^*(t)[M_{A_{TH}}-M_{L_{TH}}]+\kappa_{HT}L_{HT}{}^*(t)[M_{A_{HT}}-M_{L_{HT}}]}{2A_3}\right)\right\}\right)$$

$$+\left(1-\max\left\{0,\min\left(1,\frac{\tau_2 T_D{}^*(t)[M_{T_D}-M_{F_T}(1-q_1)+q_1M_{R_T}]+\kappa_{TH}L_{TH}{}^*(t)[M_{A_{TH}}-M_{L_{TH}}]}{+\kappa_{HT}L_{HT}{}^*(t)[M_{A_{HT}}-M_{L_{HT}}]}{2A_4}\right)\right\}\right)\kappa_{HT}L_{HT}(t)$$

$$-(\mu+\delta A_{HT})A_{HT}(t)$$

$$\frac{dL_T(t)}{dt} = \left(\left(1-\max\left\{0,\min\left(1,\frac{\begin{array}{l}[(-M_S)(\lambda_H-\lambda_T-\lambda_{TH}-\lambda_{HT})+(\varepsilon_1 M_{L_H}+(1-\varepsilon_1)M_{H_U})\lambda_H\\ +\lambda_{TH}M_{L_{TH}}+\lambda_{HT}M_{L_{HT}}+(\varepsilon_2 M_{L_T}+(1-\varepsilon_2)M_{T_U})\lambda_T]S^*(t)\end{array}}{2A_1}\right)\right\}\right)\right.$$

$$\left.+\left(1-\max\left\{0,\min\left(1,\frac{\begin{array}{l}[(-M_S)(\lambda_H-\lambda_T-\lambda_{TH}-\lambda_{HT})+(\varepsilon_1 M_{L_H}+(1-\varepsilon_1)M_{H_U})\lambda_H\\ +\lambda_{TH}M_{L_{TH}}+\lambda_{HT}M_{L_{HT}}+(\varepsilon_2 M_{L_T}+(1-\varepsilon_2)M_{T_U})\lambda_T]S^*(t)\\ +\gamma_{UH}(M_{H_D}H_D(t)^*-M_{H_U}H_U(t)^*)+\gamma_{UT}(M_{T_D}T_D(t)^*-M_{T_U}T_U(t)^*)\end{array}}{2A_2}\right)\right\}\right)\varepsilon_2\lambda_T S(t)$$

$$-(\kappa_T+\mu)L_T(t)+\upsilon T_U(t)+\theta_1\rho F_T(t)+r\alpha R_T(t)$$

$$\frac{dT_U(t)}{dt} = \left(\left(1-\max\left\{0,\min\left(1,\frac{\begin{array}{l}[(-M_S)(\lambda_H-\lambda_T-\lambda_{TH}-\lambda_{HT})+(\varepsilon_1 M_{L_H}+(1-\varepsilon_1)M_{H_U})\lambda_H\\ +\lambda_{TH}M_{L_{TH}}+\lambda_{HT}M_{L_{HT}}+(\varepsilon_2 M_{L_T}+(1-\varepsilon_2)M_{T_U})\lambda_T]S^*(t)\end{array}}{2A_1}\right)\right\}\right)\right.$$

$$\left.+\left(1-\max\left\{0,\min\left(1,\frac{\begin{array}{l}[(-M_S)(\lambda_H-\lambda_T-\lambda_{TH}-\lambda_{HT})+(\varepsilon_1 M_{L_H}+(1-\varepsilon_1)M_{H_U})\lambda_H\\ +\lambda_{TH}M_{L_{TH}}+\lambda_{HT}M_{L_{HT}}+(\varepsilon_2 M_{L_T}+(1-\varepsilon_2)M_{T_U})\lambda_T]S^*(t)\\ +\gamma_{UH}(M_{H_D}H_D(t)^*-M_{H_U}H_U(t)^*)+\gamma_{UT}(M_{T_D}T_D(t)^*-M_{T_U}T_U(t)^*)\end{array}}{2A_2}\right)\right\}\right)(1-\varepsilon_2)\lambda_H S(t)$$

$$+(1-\omega_2)\kappa_T L_T(t)+\theta_2\rho F_T(t)-(\upsilon+\left(1-\max\left\{0,\min\left(1,\frac{\begin{array}{l}[(-M_S)(\lambda_H-\lambda_T-\lambda_{TH}-\lambda_{HT})+(\varepsilon_1 M_{L_H}+(1-\varepsilon_1)M_{H_U})\lambda_H\\ +\lambda_{TH}M_{L_{TH}}+\lambda_{HT}M_{L_{HT}}+(\varepsilon_2 M_{L_T}+(1-\varepsilon_2)M_{T_U})\lambda_T]S^*(t)\\ +\gamma_{UH}(M_{H_D}H_D(t)^*-M_{H_U}H_U(t)^*)+\gamma_{UT}(M_{T_D}T_D(t)^*-M_{T_U}T_U(t)^*)\end{array}}{2A_2}\right)\right\}\right)\gamma_{UT}$$

$$+\mu+\delta_{UT})T_U(t)$$

$$\frac{dT_D(t)}{dt} = \omega_2\kappa_T L_T(t)+\left(1-\max\left\{0,\min\left(1,\frac{\begin{array}{l}[(-M_S)(\lambda_H-\lambda_T-\lambda_{TH}-\lambda_{HT})+(\varepsilon_1 M_{L_H}+(1-\varepsilon_1)M_{H_U})\lambda_H\\ +\lambda_{TH}M_{L_{TH}}+\lambda_{HT}M_{L_{HT}}+(\varepsilon_2 M_{L_T}+(1-\varepsilon_2)M_{T_U})\lambda_T]S^*(t)\\ +\gamma_{UH}(M_{H_D}H_D(t)^*-M_{H_U}H_U(t)^*)+\gamma_{UT}(M_{T_D}T_D(t)^*-M_{T_U}T_U(t)^*)\end{array}}{2A_2}\right)\right\}\right)\gamma_{UT}T_U(t)$$

$$+\left[1-(\theta_1+\theta_2)\right]\rho F_T(t)-$$

$$\left(1-\max\left\{0,\min\left(1,\frac{\begin{array}{l}\tau_2 T_D{}^*(t)[M_{T_D}-M_{F_T}(1-q_1)+q_1M_{R_T}]+\kappa_{TH}L_{TH}{}^*(t)[M_{A_{TH}}-M_{L_{TH}}]\\ +\kappa_{HT}L_{HT}{}^*(t)[M_{A_{HT}}-M_{L_{HT}}]\end{array}}{2A_4}\right)\right\}\tau_2+\mu+\delta_{dT}\right)T_D(t)$$

$$\frac{dF_T(t)}{dt} = \left(1 - \max\left\{0, \min\left(1, \frac{\tau_2 T_D^{*}(t)[M_{T_D} - M_{F_T}(1-q_1) + q_1 M_{R_T}] + \kappa_{TH} L_{TH}^{*}(t)[M_{A_{TH}} - M_{L_{TH}}] + \kappa_{HT} L_{HT}^{*}(t)[M_{A_{HT}} - M_{L_{HT}}]}{2A_4}\right)\right\}\right)(1-q_1)\tau_2 T_D(t)$$

$$+ (1-r)\alpha R_T(t) - (\rho + \mu + \delta_F)F_T(t)$$

$$\frac{dR_T(t)}{dt} = \left(1 - \max\left\{0, \min\left(1, \frac{\tau_2 T_D^{*}(t)[M_{T_D} - M_{F_T}(1-q_1) + q_1 M_{R_T}] + \kappa_{TH} L_{TH}^{*}(t)[M_{A_{TH}} - M_{L_{TH}}] + \kappa_{HT} L_{HT}^{*}(t)[M_{A_{HT}} - M_{L_{HT}}]}{2A_4}\right)\right\}\right) q_1 \tau_2 T_D(t)$$

$$-(\alpha + \mu + \delta_{RT})R_T(t) + \sigma_2 T_D(t)$$

$$\frac{dR_{TH}(t)}{dt} = \sigma_1 A_{TH}(t) - (\alpha_T + \mu)R_{TH}(t)$$

5. NUMERICAL SIMULATION

In order to authenticate the theoretical calculations of the model, the numerical simulations of the model (3.3) are carried out by differential transformation method, using a set of estimated parameter values given in Table 1.

Table 1. Parameter Values used in Numerical Simulations

Parameters	Value	Sources
π	2000	Assumed
τ_1, τ_2	0.20619, 0.20619	Assumed
μ	0.02	[9]
$\varepsilon_1, \varepsilon_2$	0.7,0.7	[30]
κ_H, κ_T	0.2522,0.2522	[30]
ω_1, ω_2	0.2,0.3	[30]
γ_{UH}, γ_{UT}	0.2,0.2	Assumed
ϕ	0.7	[34]
β_H, β_T	0.1,0.1	[30]
δ_{UH}, δ_{dH}	0.3,0.1	[30]
$\eta_U, \eta_{dH,} \eta_W$	0.001, 0.001, 0.001	[30]
θ_1, θ_2	0.1,0.1	[30]
φ	0.85	[10]
κ_{HT}, κ_{TH}	0.2522, 0.2522	Assumed
ω_2, ω_3	0.7, 0.7	[11]
υ	0.2	Assumed
α	0.5	[30]
R	0.8	[11]
ρ	0.1	Assumed
$\delta_{UT}, \delta_{dT}, \delta_F, \delta_{RT}$	0.3, 0.1, 0.1, 0.3	[11]
σ_1, σ_2	0.2	[17]

Parameters	Value	Sources
q_1	0.7	[34]
$\eta_U, \eta_{dT}, \eta_{FT}, \eta_{RT}$	0.001, 0.001, 0.001, 0.001	[30]

6. RESULTS AND DISCUSSION

From this research, fifteen (15) new non linear differential equations for gaining more insight on the effect of epidemiological features on the dynamical spread of HIV-TB co-infection have been obtained. Numerical simulation of the model was carried out by MAPLE software, using differential transformation method in order to determine the dynamical spread pattern of the disease in the community and to determine which of the diseases should be treated first or the two simultaneously.

The results obtained from numerical simulations using differential transformation method are presented in the figures.

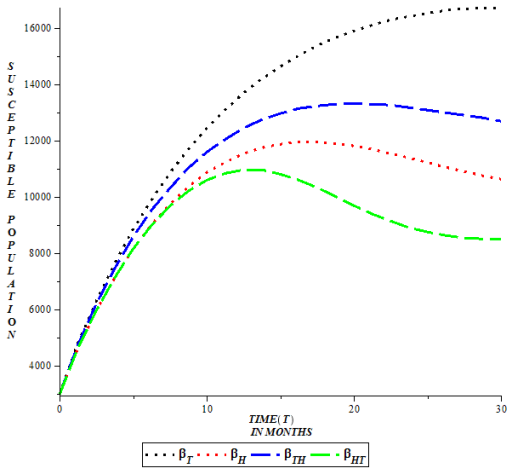

Fig. 2. Plots of susceptible individuals against time t at $\beta_H = \beta_{TH} = \beta_{HT} = \beta_T = 0.2$

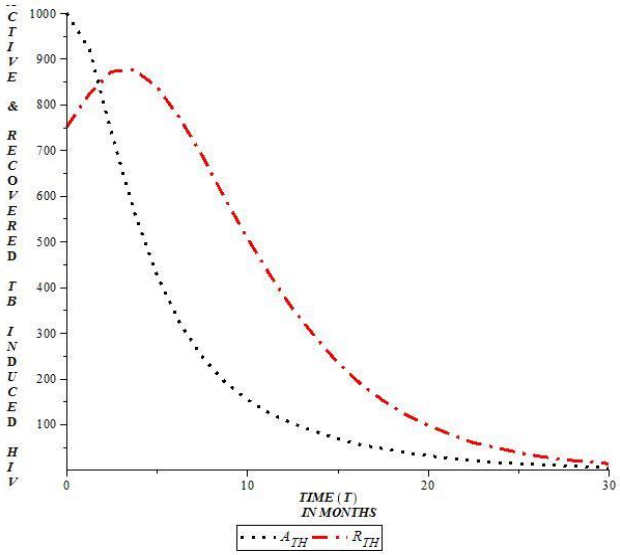

Fig. 3. Plots of A_{TH}& R_{TH} against time t, in the presence of treatment

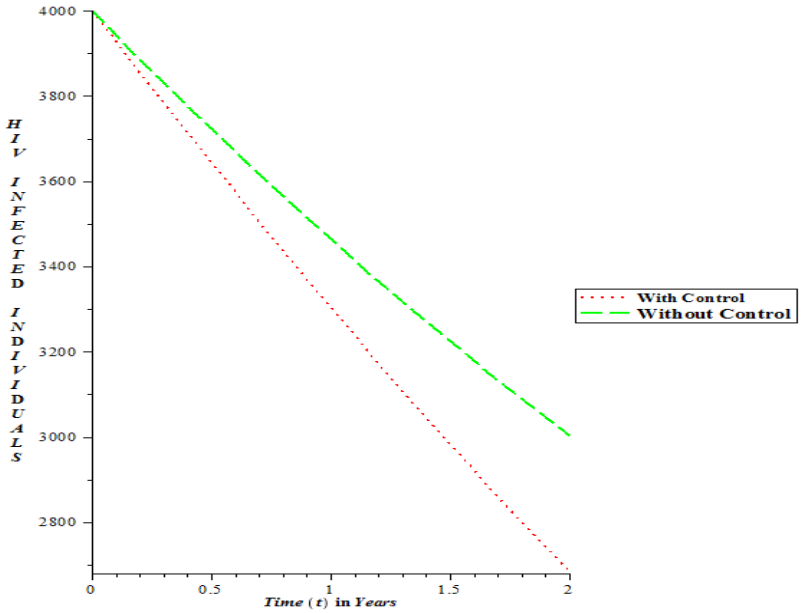

Fig. 4. Plots of HIV infected individuals against time t

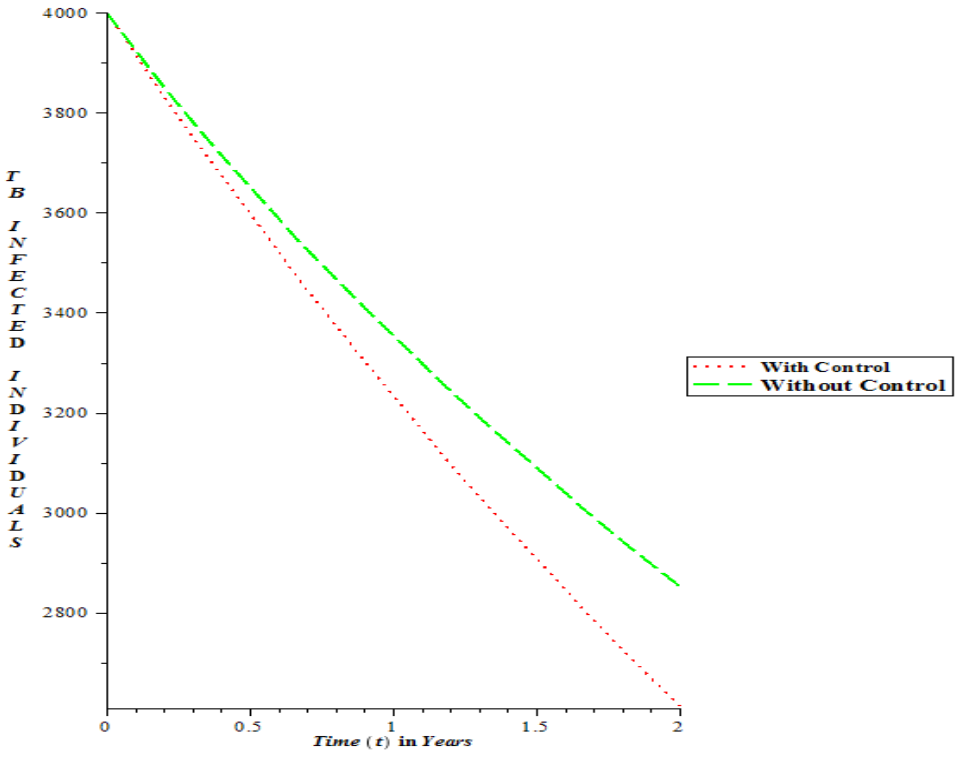

Fig. 5. Plots of TB infected individuals against time t

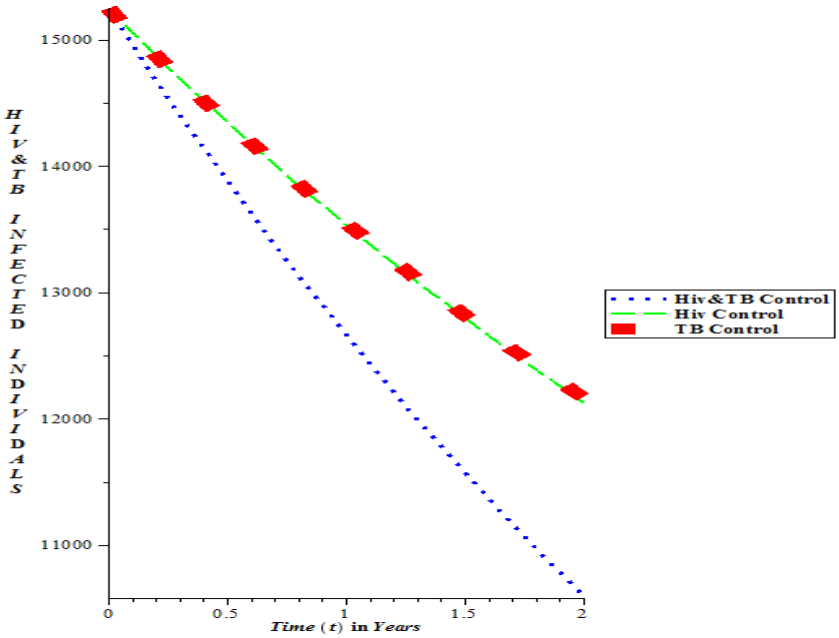

Fig. 6. Plots of HIV & TB, HIV and TB infected individuals against time t

6.1 Discussion

This research deals with the formulation and analysis of new robust mathematical model to have better understanding of optimal control on the dynamical spread of HIV-TB co-infection and to have better control strategies of the two diseases.

Fig. 2 Shows the effect of effective contact rates on susceptible individuals. It is shown from the graph that, effective contact rate (β_H) has pronounced effect on the susceptible individuals than effective contact rate (β_T), which means that, the rate at which HIV infection reduces the susceptible population is higher than the TB disease. Fig. 3 Shows the importance of timely treatment on HIV and TB individuals, pronounce effect of treatment was shown on active TB and HIV individuals when it is almost one and half year of treatment, the treatment reduces the population of active TB and HIV from 1000 to 840 and increases recovered TB and HIV individuals from 750 to 870.Fig. 4 Shows that HIV infected individuals reduced when there is control measure compared to when there is no control. It reduced HIV infected population from 4000 to 2580 within two (2) years of control intervention. Fig. 5 Shows the effect of control U_4 on TB infected individuals, the control reduces the infected individuals from 4000 to 2600 when $U_4 = 0.99$ within two (2) years of control intervention. Fig. 6. Compared when HIV is first treated, when TB is first treated and when the two diseases are treated simultaneously. The simultaneous treatment of the disease yields better results. It shows less HIV-TB infected individuals when both are treated jointly, compared to when they are treated separately.

Optimal control analysis was carried out for different control strategies and the result shows that simultaneous treatment of HIV-TB disease together with campaign, given and boosting of the immune by using necessary drugs yield a better result compared to when the two diseases are treated separately.

Effective contact rate of infected individuals among susceptible individuals needs to be reduced to guarantee disease free environment, the disease becomes more endemic due to the increment in effective contact rate, most especially β_H and β_{HT} . The system becomes unstable whenever β_H and $\beta_T > 0.3$. It was also shown that TB fuels the progression of HIV into full blown AIDS. Likewise HIV increases latent TB to active TB in the absence of treatment, it was shown that in the presence of treatment, the rate of active TB and HIV

decreases as the treatment increases and consequently, TB and HIV recovery cases increase rapidly.

7. CONCLUSION

In conclusion, epidemiological features such as detection of infected undetected individuals, treatment of infected individuals, minimizing the effective contact rate and boosting of natural immunity play vital roles in the control of the spread of HIV- TB co-infection.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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