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Optimal Control Strategy for TB-HIV/AIDS Co-Infection Model in the Presence of Behaviour Modification

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Abstract: A mathematical model for a transmission of TB-HIV/AIDS co-infection that incorporates prevalence dependent behaviour change in the population and treatment for the infected (and infectious) class is formulated and analyzed. The two sub-models, when each of the two diseases are considered separately are mathematically analyzed. The theory of optimal control analysis is applied to the full model with the objective of minimizing the aggregate cost of the infections and the control efforts. In the numerical simulation section, various combinations of the controls are also presented and it has been shown in this part that the optimal combination of both prevention and treatment controls will suppress the prevalence of both HIV and TB to below 3% within 10 years. Moreover, it is found that the treatment control is more effective than the preventive controls.

Keywords: TB-HIV co-infection; behaviour change; dynamical systems; optimal control; equilibrium; treatment; stability; Human Immunodeficiency Virus (HIV); tuberculosis (TB)

1. Introduction

Tuberculosis (TB) is the second leading cause of death in the world next to the Human Immunodeficiency Virus (HIV) [1], which is mainly caused by the bacteria called *Mycobacterium tuberculosis* and usually acquired via air born infection from someone who has active TB. It particularly affects the lungs (pulmonary TB) but can also affect other organs of the body such as kidney, brain, blood, bones, glands (extra-pulmonary TB) [1–4]. Not all individuals infected by TB develop active TB. Only around 10% of those infected with *Mycobacterium tuberculosis* develop active TB disease and become infectious. Whereas, around 90% of the people infected with the bacteria remain latently infected and individuals in the latent stage do not transmit TB. However, there is a high risk of developing an active TB for individuals whose immune system is weakened due to the presence of HIV, malnutrition or diabetes. Infected individuals can be treated through anti-TB drugs such as Isoniazid, Rifampicin, Pyrazinamide, Ethambutol and Streptomycin [1,3].

The global report of TB by World Health Organization (WHO) indicated that in 2015, 10.4 million people were infected with TB and 1.8 million died due to the disease (including 0.4 million among people with HIV) [5]. Over 95% of TB deaths occur in low and middle income countries. In the same year, an estimated 1 million children became infected with TB and 170,000 children died of TB (excluding children with HIV) and an estimated 49 million lives were saved through TB diagnosis and

treatment between 2000 and 2015. More than 20% of TB cases worldwide are attributed to smoking and people who are infected with HIV are 26 to 31 times more likely to become infected with TB [4].

The Human Immunodeficiency Virus (HIV) infects cells of immune system such as helper T cells (specifically CD4+ T cells), macrophages, and dendritic cells. HIV compromises the human immune system and reduces the ability of the body to fight back infections and diseases. The most advanced stages of HIV infection is usually called Acquired Immunodeficiency Syndrome (AIDS). AIDS is one of the leading causes of death worldwide that is affecting virtually every nation. Even if HIV/AIDS is not permanently curable, main methods used to fight against it are preventive mechanisms (which include: abstinence, faithfulness and protection) which mainly rely on the level of behavioral change of the population, and providing Antiretroviral Therapy (ART) for those infected.

In 2016, an estimated 36.7 million people were living with HIV (including 1.8 million newly infected people in the same year) and 1 million people died of AIDS related illness. Since the start of the epidemic, an estimated 76.1 million people have been infected with HIV and 35 million people died of AIDS related illness [6]. Individuals infected with HIV are more likely to develop TB disease because of the deficiency in their immunity, and HIV infection is the most powerful risk factor for progression from TB infection directly to the infectious stage [7]. In the WHO report of 2017, it is indicated that TB remains the leading cause of death among people living with HIV, accounting for around one in three AIDS related deaths [8]. Collaborative TB/HIV activities (including HIV testing, ART and TB preventive measures) are crucial for the reduction of TB-HIV co-infection. Even though, those collaborative activities can save people from dying, significant challenges are there to fully implement them. As has been indicated in literature, ART is not being delivered to TB-HIV co-infected patients in the majority of the countries with the largest number of TB/HIV patients; the pace of treatment scale-up for TB/HIV patients has slowed, and only a small fraction of TB/HIV infected individuals received TB preventive therapy [9]. As a result, the reduction of TB related deaths among people living with HIV has slowed in recent years.

Since epidemiological and mathematical models play fundamental role in the study of the dynamics of such diseases, various models have been used to investigate the transmission dynamics and treatment strategy of different infectious diseases such as TB and HIV/AIDS. One of the classical models to describe the transmission dynamics of TB was formulated in 1962 by Waaler et al. [10]. They used a particular linear function to model infection rates. In this model, the equation for the latent and infectious classes were assumed to be uncoupled with the equation for the susceptible class. Following this and by modifying some part of the model structure, a lot of mathematical models have been developed and analyzed for TB (drug sensitive and drug resistant) disease transmission [10–15]. Multi-drug resistance (MDR) TB strain has also been developed in the course of time partly due to the mismanagement in the treatment of TB patients. This includes wrong diagnosis and delayed diagnosis, wrong or interrupted treatment, and the misuse of TB drugs [4,16]. Hence, mathematical models (such as [11,12,15]) that include multiple strain of TB have been used to study the effect of these new strains. A two strain model is formulated and mathematically analyzed by Castillo-Chavez and Feng [15]. In this model, the drug resistant strain is assumed to be not treatable; latently infected, infectious and treated individuals are assumed to be re-infected with the drug resistant strain. However, the model did not take into account long and variable periods of latency as well as the role of preventive education for the society. Another mathematical model to study a two strain TB infection that include diagnosis, treatment and health education as an intervention mechanism is proposed by Maliyani et al. [17]. In the study of this model, it is indicated that diagnosis of the MDR-TB strain has a major impact in the eradication of drug sensitive TB and in the reduction of MDR-TB.

The role of vaccination at birth and behavior change through education in a two age group TB model in the presence of medical treatment was investigated by Awoke T.D. and Kassa S.M. [3]. The authors used optimal control theory to propose a cost effective strategy for intervention in reducing the burden of the drug sensitive TB in the population. Moreover, it is shown that in addition

to vaccination and medical treatment, behavior change through education about the preventive mechanisms of the disease have significant impact to reduce the burden of the disease.

Different researchers have also studied the dynamics of HIV/AIDS disease transmission (see for example, [18–21]). Since proper HIV/AIDS medical treatment could decrease not only HIV prevalence but also TB notification rate, different researchers have developed a two strain TB-HIV/AIDS co-infection model and studied the dynamics of such a model (see for instance, [9,22–28]). However, the mathematical analysis of these models remain challenging as the transmission modes are very different.

Due to the role of optimal control theory to determine the best intervention control strategy with minimum aggregate cost of intervention, Silva et al. [9] and Agusto et al. [27] studied TB-HIV/AIDS co-infection model. From their optimal control simulations they came up independently with a result that treating co-infected individuals at optimal level can decrease the prevalence of the disease in addition to case finding and case holding strategies. However, the model in [9,27] assume that human behaviour remains constant, and hence the contact rates of the population remain unchanged while the disease progressed even if the size of the epidemics grows. However, it is well known that human behaviour changes as the burden of the disease increases [29]. Moreover, preventive education and the participation of the population in reducing their risky behaviour are well accepted public health strategy in combating communicable diseases. Therefore, it is necessary to include in the model both preventive mechanisms as well as treatment interventions and study the effect.

In this paper, we introduce the behaviour change function in to the TB-HIV/AIDS co-infection model and analyze the model. We will also study the mathematical control analysis of the model to propose an optimal control strategy for the public health planning in combating the two diseases. The current model aims to answer specific questions about the likely impact of change of behaviour by individuals on the burden of TB-HIV/AIDS co-infection in a hypothetical population.

The paper is organized as follows: in Section 2 we give the description of the model and analyze the model mathematically. In Section 3, we formulate the control problem for the model and apply the mathematical control analysis to find the necessary conditions for the optimal controls. Some numerical simulations are shown in Section 4 to illustrate the trajectory of the subpopulation in the dynamics when various combination of controls are applied. The paper is then concluded with some conclusive remarks in Section 5.

2. Mathematical Model with Behavior Change and Treatment

We modified the usual TB-HIV co-infection model (for example the one in [9]) by introducing two additional cohorts, E_T which represents the section of the population that decided to use any of the available preventive mechanisms against TB infection, and E_H which represents the section of the population that uses any of the mechanisms that prevent or reduce the risk of infection by HIV. The population in each of these two cohorts are assumed to enjoy a reduced susceptibility against the infection of the corresponding disease. Therefore, the total population at time t, is divided into the following epidemiological subgroups: $S(t)$, Susceptible individuals; $E_T(t)$, Educated individuals about TB; $L_T(t)$, individuals infected with TB in latent stage; $I_T(t)$, TB-infected individuals who have active TB disease and are infectious; $R_T(t)$, Successfully treated with TB; E_H, Educated individuals about HIV/AIDS ; $I_H(t)$, HIV-infected individuals with no clinical symptoms of AIDS; $L_{TH}(t)$, TB-latent individuals co-infected with HIV; $I_{TH}(t)$, HIV-infected individuals (pre-AIDS) co-infected with active TB disease; $T_H(t)$, HIV-infected individuals under treatment for HIV infection; $A_H(t)$, HIV-infected individuals with AIDS clinical symptoms; $A_T(t)$, HIV-infected individuals with AIDS symptoms and co-infected with active TB; $R_H(t)$, TB-recovered individuals with HIV-infection without AIDS symptoms.

The total population at time t, denoted by $N(t)$, is given by $N(t) = S(t) + E_T(t) + E_H(t) + L_T(t) + I_T(t) + R_T(t) + I_H(t) + L_{TH}(t) + R_H(t) + I_{TH}(t) + T_H(t) + A_H(t) + A_T(t)$. The Susceptible population is increased by the recruitment of individuals (assumed susceptible) into the population at

a rate Π. Susceptible individuals acquire TB infection from individuals with active TB at a variable rate λ_T, which is given by,

$$\lambda_T(t) = \frac{\beta_1(I_T(t) + I_{TH}(t) + A_T(t))}{N(t)}, \tag{1}$$

where, β_1 is the effective transmission rate for TB infection. Similarly, susceptible individuals acquire HIV infection at a variable rate λ_H, given by

$$\lambda_H(t) = \frac{\beta_2(I_H(t) + I_{TH}(t) + L_{TH}(t) + R_H(t) + \eta_c T_H(t) + \eta_a(A_H(t) + A_T(t)))}{N(t)}, \tag{2}$$

where β_2 is the effective transmission rate for HIV. The modification parameter $\eta_a \geq 1$ accounts for the relative infectiousness of individuals with AIDS symptoms, in comparison to those infected with HIV with no AIDS symptoms. Individuals with AIDS symptoms are more infectious than HIV-infected individuals (pre-AIDS) because they have a higher viral load and there is a positive correlation between viral load and infectiousness [30]. On the other hand, $\eta_c \leq 1$ accounts to the partial restoration of the immune function of individuals with HIV infection that use correctly ART [31].

Only approximately 10% of infected people with *Mycobacterium tuberculosis* are considered to develop active TB disease. While the rest (approximately 90%) of infected people will develop latent TB disease [4]. Hence, if a fraction g of infected people develop latent TB, then the remaining $(1-g)$ proportion of infected population will develop or progress to the stage of active TB disease and suffer from the additional disease induced death at a rate of d_T. Latently infected individuals progress to the I_T class due to the presence of reactivation at a rate b or due to reinfection at a rate of k.

When the risk of the disease in the population increases, people may get more awareness about the disease and they may apply different self-protective measures. This will affect the contact rate per unit of time, by decreasing the incidence rate of the disease. Therefore, behavior change through awareness creation is important in fighting against the disease. If we add an 'educated' compartment (E_T or E_H) into the usual SIR model, it is possible to observe that individuals in educated class are exposed to the infection with a rate smaller than other susceptible individuals. However, the recruitment rate into educated classes vary through time corresponding to the total proportion of people affected by the disease. This recruitment function describes the learning effect of population which can be measured indirectly by observing behavior modification of individuals towards their exposedness to the disease [29]. The behavior change function ($e(t)$) is assumed to be described as a function of the prevalence $p(t)$ of the disease at any time t. At the beginning of the outbreak, normally people understand very little about the disease and the reaction could be almost none whereas at high prevalence some susceptible individuals will change their behavior and start applying any of the possible self protective measures to reduce the risk of any possible infection. This implies that $e(p = 0\%) = 0$ and $e(p = 100\%) = 1$. Here, self-protective measures for TB and HIV may be any of the following. Applying any of the existing protective measures against HIV infection (from abstinence to using self-protective devices, such as condoms) similarly for TB infection, one may apply any of the protective measures, like opening windows of public transport vehicles while in use, keeping the rooms used by infected individuals ventilated, advising and helping a friend or a family member who shows some symptoms of TB to be diagnosed at a health center, separating the nutritional equipments of infectious individuals and using gloves in the case of helping them in cleaning their sputum, and wearing appropriate masks while meeting people who are possibly infectious.

Therefore, we can describe the two behaviour change functions as

$$e_T(p_T) = \frac{\alpha \times p_T^n}{p_{T*}^n + p_T^n} \quad \text{or equivalently} \quad e_T(t) = \frac{\alpha \times (I_T + I_{TH} + A_T)^n}{N^n p_{T*}^n + (I_T + I_{TH} + A_T)^n}$$

and

$$e_H(p_H) = \frac{\alpha \times p_H^n}{p_{H*}^n + p_H^n} \qquad \text{or equivalently}$$

$$e_H(t) = \frac{\alpha \times [I_H + I_{TH} + L_{TH} + R_H + \eta_c T_H + \eta_a (A_H + A_T)]^n}{N^n p_{H*}^n + [I_H + I_{TH} + L_{TH} + R_H + \eta_c T_H + \eta_a (A_H + A_T)]^n},$$

where p_{T*} and p_{H*} are the prevalence producing half of the maximum behavioral change value of TB and HIV respectively; $\lambda_T = \beta_1 p_T$ and $\lambda_H = \beta_2 p_H$ represent the force of infection for TB and HIV respectively with $p_T = \frac{I_T + I_{TH} + A_T}{N}$ and $p_H = \frac{I_H + I_{TH} + L_{TH} + R_H + \eta_c T_H + \eta_a (A_H + A_T)}{N}$; n is a hill coefficient that portrays the rate of reaction by the population and α is the saturation level of e (which we took it to be one in this context). If we denote by α_T the mean education rate at which susceptible individuals receive a convincing message about TB to move into the educated class per unit of time, $\alpha_T e_T$ will give us the actual recruitment rate to the cohort of TB educated class from the susceptible class. Similarly if α_H is the counterpart of α_T for the HIV educated cohort, $\alpha_H e_H$ will give us the actual recruitment rate to the cohort of HIV/AIDS educated class from the susceptible class.

However, every protective measure may not be absolutely effective due to the choice of different measures taken by the population with varying coefficients of effectiveness. If we denote the average effectiveness of all existing self protective measures for TB disease by γ, then $1 - \gamma$ will be the average failure of self-protective measures for TB. Hence, we assumed that individuals in the TB educated class may be infected with TB only due to the failure of existing self-protective measures. Similarly, if we denote the average effectiveness of all existing self protective measures about HIV/AIDS by γ_1, then $1 - \gamma_1$ will represent the average failure of self-protective measures for HIV, and we assumed that individuals in E_H class get infected by HIV only due to the failure of the self-protective measures.

Educated individuals about HIV/AIDS in the E_H class may be well informed about HIV/AIDS disease transmission, symptoms and their mode of transmission but they may not have the required information about preventive, control and treatment mechanisms of the TB disease in its full form. Then ν proportion ($\nu < 1$) of individuals from E_H class may contract TB infection and join the latent stage (L_T). Therefore, it is assumed that individuals in the HIV/AIDS class may be infected with TB like any of the individuals in other epidemiological classes but with a reduced rate. Similarly, those in the E_T class may also get infected with HIV, but with a reduced rate of ν_1 ($\nu_1 < 1$). For simplicity of the analysis, it is assumed that there is no intersection between the class of E_T and the class of E_H.

We assume that TB treated or recovered individuals R_T acquire partial immunity and hence their rate of infection is reduced by θ with $\theta \leq 1$. Individuals with active TB disease suffer from additional TB-induced death rate of d_T. On the other hand, since individuals who are infected by active TB, I_T, are more susceptible to HIV infection, it is assumed that they get infected at a rate of $\delta \lambda_H$, where the modification parameter $\delta \geq 1$ accounts for higher probability of individuals in class I_T to become HIV positive. HIV infected individuals with (no AIDS symptoms) progress to the AIDS class A_H at a rate of ε. HIV infected individuals with AIDS symptoms are treated for HIV at a rate of ψ and suffer from additional AIDS-induced death rate of d_A. Individuals in the class I_H are also susceptible to TB infection at a rate $\rho \lambda_T$, where $\rho \geq 1$ is a modification parameter depicting the fact that HIV infection is a driver of TB epidemic [32]. HIV infected individuals (pre-AIDS) could be co-infected by TB disease and are assumed to join the active stage I_{TH}. A fraction r of I_{TH} individuals are assumed to receive simultaneously TB and HIV treatments at a rate of p and hence they will get cured from TB but remain in T_H. Moreover, assume that there are a fraction $1 - r$ of I_{TH} individuals who show symptoms of TB but are not diagnosed for HIV. These individuals will be recruited at a rate of τ to receive only TB treatment. Individuals in the class I_{TH} that do not take any of the TB or HIV treatments are assumed to progress to the class A_T at a rate of ε_1, and suffer from the additional TB-HIV/AIDS induced death rate of d_{TA}. Moreover, a fraction τ_1 from the class of L_{TH} are also assumed to recover from TB. Individuals in the class L_{TH} are assumed to be more likely to progress to active TB disease

either due to reactivation at a rate of b_1 or through reinfection at a rate of k_1. Similarly, HIV infection make individuals more susceptible to TB reinfection when compared to non HIV positive individuals. The modification parameter associated to the TB reinfection rate, for individuals in the class of R_H, is taken to be θ_1 with $\theta_1 \geq 1$. Individuals in this class are assumed to progress to class A_H at a constant rate of ω. In addition, people in the classes of L_{TH} and R_H are recruited to receive ART in the same rate as those in I_H. However, individuals in AIDS group (A_H) are assumed to receive ART at a rate of ψ and those who are co-infected with TB (A_T) are also recruited at a rate of ψ_1 to receive treatments for both HIV/AIDS and TB and then progress to the T_H class. The description of the parameter used in the model is given in Table 1.

Table 1. Symbols and Description of Parameters.

Parameters	Description
Π	Recruitment rate
β_1	tuberculosis (TB) Transmission rate
β_2	Human Immunodeficiency Virus (HIV) Transmission rate
b	Endogenous reactivation rate for TB
k	Reinfection rate for TB infection
b_1	Endogenous reactivation rate of TB for individuals pre-infected with HIV
k_1	Reinfection rate of TB infection for individuals pre-infected with HIV
μ	Per capita natural mortality rate
d_T, d_H, d_{TA}	Per capita TB, HIV, TB-HIV co-infection- induced death rates
τ	TB treatment rate for I_T individuals
τ_1	The rate at which individuals from L_{TH} class recover from TB
σ	Rate of recruitment for I_H individuals to receive HIV treatment
m	Rate at which individual who are Latently infected with TB progress to I_T
g	The proportions of susceptible individuals who get infected with TB and move to L_T
$\delta, \rho, \theta, \theta_1$	Modification parameters
ε	The rate of progression of individuals from I_H class to A_H
ε_1	The rate of progression of individuals from I_{TH} class to A_T
ψ	Rate of recruitment of individuals in A_H class for HIV Treatment
ψ_1	Rate of recruitment of individuals in A_T class for HIV Treatment
ξ	Rate of failure to properly adhere to HIV treatment rules
ω	The rate at which individuals from R_H class progress to A_H
γ	The average effectiveness of all existing self protective measures for TB
γ_1	The average effectiveness of all existing self protective measures for HIV
p	Rate at which individuals in I_{TH} class to receive treatment for both HIV and TB
α_T	Rate of dissemination of information about TB disease in the population
α_H	Rate of dissemination of information about HIV/AIDS (Acquired Immunodeficiency Syndrome) disease in the population
r	Fraction of individuals from I_{TH} class that receive treatments for TB

With the above assumptions and description of the model variables, the TB-HIV co-infection dynamics, whose schematic diagram is given in Figure 1, can be described by the following deterministic system of non-linear ODE:

$$\begin{cases} \dot{S} = & \Pi - [\lambda_T + \lambda_H + \mu + \alpha_T e_T + \alpha_H e_H]S \\ \dot{E_T} = & \alpha_T e_T S - [(1-\gamma)\lambda_T + \nu_1 \lambda_H + \mu]E_T \\ \dot{L_T} = & g\lambda_T S + (1-\gamma)\lambda_T E_T + \theta\lambda_T R_T + \nu\lambda_T E_H - (A_1 + \lambda_H + k\lambda_T)L_T \\ \dot{I_T} = & (1-g)\lambda_T S + (b + k\lambda_T)L_T - (A_2 + \tau + \delta\lambda_H)I_T \\ \dot{R_T} = & \tau I_T + mL_T - (\mu + \lambda_H + \theta\lambda_T)R_T \\ \dot{E_H} = & \alpha_H e_H S - [\nu\lambda_T + (1-\gamma_1)\lambda_H + \mu]E_H \\ \dot{I_H} = & \lambda_H S + \nu_1 \lambda_H E_T + (1-\gamma_1)\lambda_H E_H + \lambda_H R_T - (A_3 + \sigma + \rho\lambda_T)I_H \\ \dot{L_{TH}} = & \lambda_H L_T + \theta_1 \lambda_T R_H - (A_4 + \sigma + k_1\lambda_T)L_{TH} \\ \dot{I_{TH}} = & (b_1 + k_1\lambda_T)L_{TH} + \rho\lambda_T I_H + \delta\lambda_H I_T - (A_5 + q)I_{TH} \\ \dot{R_H} = & \tau_1 L_{TH} + qI_{TH} - (A_6 + \sigma + \theta_1\lambda_T)R_H \\ \dot{A_H} = & \varepsilon I_H + \xi T_H + \omega R_H - (A_7 + \psi + \rho_1\lambda_T)A_H \\ \dot{T_H} = & \sigma(L_{TH} + I_H + R_H) + \psi A_H + pI_{TH} + \psi_1 A_T - A_8 T_H \\ \dot{A_T} = & \rho_1\lambda_T A_H + \varepsilon_1 I_{TH} - A_9 A_T \end{cases} \tag{3}$$

where,

$A_1 = b + m + \mu$ $A_2 = \mu + d_T$ $A_3 = \varepsilon + \mu$
$A_4 = \tau_1 + b_1 + \mu$ $A_5 = (1-r)p + \varepsilon_1 + \mu + d_T$ $A_6 = \omega + \mu$
$A_7 = \mu + d_A$ $A_8 = \xi + \mu$ $A_9 = \psi_1 + \mu + d_{TA}$

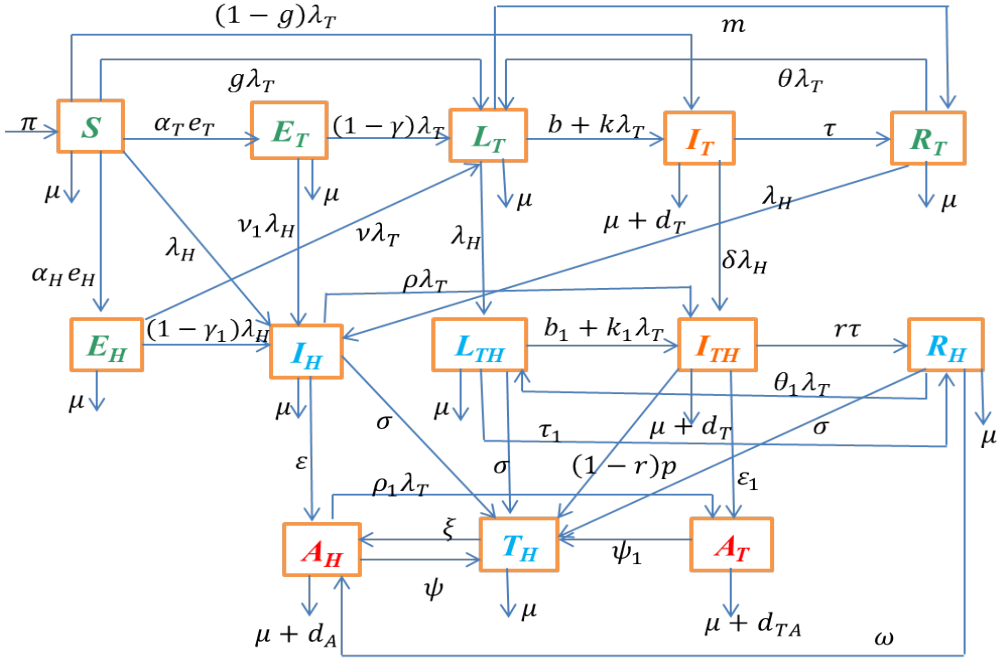

Figure 1. Schematic diagram for TB-HIV/AIDS compartmental model that includes behavior change and treatment.

2.1. Positivity and Boundedness of Solutions

For the TB-HIV/AIDS co-infection model system (3) to be epidemiologically meaningful, it is important to analyze that all its state variables are non-negative at all times. In other words, solutions of the model system (3) with non-negative initial data will remain non-negative for all time $t > 0$.

Indeed, since the model (3) considers human populations, all the variables and parameters of the model are non-negative. Then consider the following biological feasible region.

$$\Omega = \{(S, E_T, L_T, I_T, R_T, E_H, I_H, L_{TH}, I_{TH}, R_H, A_H, A_T, T_H) \in \mathbb{R}^{13}_+ : N \leq \frac{\Pi}{\mu}\}.$$

We establish in the following the positive invariance of Ω (i.e., all solutions in Ω remain in Ω at all times). The rate of change of total population, which is obtained by adding all the equations in the model system (3), is given by

$$\frac{dN(t)}{dt} = \Pi - \mu N(t) - d_T I_T(t) - d_T I_{TH}(t) - d_A A_H(t) - d_{TA} A_T(t) \tag{4}$$

It is simple to observe that for $N > \frac{\Pi}{\mu}$, $\frac{dN}{dt} < 0$. Using the Standard Comparison Theorem [33], it is possible to show the boundedness of $N(t)$ as follows.

$$\begin{aligned}
\dot{N}(t) &= \dot{S}(t) + \dot{E_T}(t) + \dot{L}_T(t) + \dot{I}_T(t) + \dot{L}_{TH}(t) + \dot{I}_{TH}(t) + \dot{R_T}(t) + \dot{I}_H(t) + \dot{R}_H(t) \\
&\quad + \dot{A_H}(t) + \dot{T}_H(t) + \dot{A}_T(t) \\
\dot{N}(t) &= \Pi - \mu N(t) - (d_T I_T(t) + d_T I_{TH}(t) + d_A A_H(t) + d_{TA} A_T(t)) \\
\dot{N}(t) &\leq \Pi - \mu N(t).
\end{aligned}$$

Therefore, from this last inequality it follows that

$$N(t) \leq \tfrac{\Pi}{\mu} + e^{-\mu t}(N(0) - \tfrac{\Pi}{\mu}), \quad \text{since} \quad e^{-\mu t} \leq 1, \quad \text{for all} \quad t \geq 0.$$

Then, if $N(0) \leq \frac{\Pi}{\mu}$, we get $N \leq \frac{\Pi}{\mu}$ for all $t \geq 0$. That means, the model system (3) can be considered as bieng epidemiologically and mathematically well posed [34]. Therefore, every solution of the model system (3) with initial conditions in Ω remains there for $t > 0$. This result can be summarized in the following Lemma.

Lemma 1. *The region Ω is positively invariant for the model system (3) with non-negative conditions in $\mathbb{R}^{13}_+$, where $\mathbb{R}^{13}_+$ represents the non-negative orthant of the 13-dimensional real space $\mathbb{R}^{13}$.*

2.2. Analysis of the Sub-Models

In this section, we analyze the models for HIV only (in the absence of TB) and for TB only (in the absence of HIV) separately to draw some conclusions.

2.2.1. TB-Only Model

The sub-model of system (3) with no HIV/AIDS disease, that is when $(E_H = I_H = L_{TH} = I_{TH} = R_H = A_H = A_T = A_{TH} = 0)$, is analyzed as follows.

$$\begin{aligned}
\dot{S} &= \Pi - [\lambda_T + \mu + \alpha_T e_T] S(t) \\
\dot{E_T} &= \alpha_T e_T S - ((1-\gamma)\lambda_T + \mu) E_T \\
\dot{L}_T &= g\lambda_T S + (1-\gamma)\lambda_T E_T + \theta\lambda_T R_T - (A_1 + k\lambda_T) L_T \\
\dot{I}_T &= (1-g)\lambda_T S + (b + k\lambda_T) L_T - (A_2 + \tau) I_T \\
\dot{R_T} &= \tau I_T + m L_T - (\mu + \theta\lambda_T) R_T
\end{aligned} \tag{5}$$

where, $\lambda_T = \dfrac{\beta_1 I_T}{N}$, $e_T = \dfrac{I_T^n}{N^n P_{T*}^n + I_T^n}$ and $N = S + E_T + L_T + I_T + R_T$.

Analogous to Lemma 1 we can prove that $\Omega_1 = \{(S, E_T, L_T, I_T, R_T) \in \mathbb{R}^5_+ : N \leq \frac{\Pi}{\mu}\}$ is positively invariant and attracting. Thus, the dynamics of TB only model will be considered in Ω_1.

2.2.2. Local Stability of Disease Free Equilibrium

The model subsystem (5) has a disease free equilibrium (DFE), obtained by setting the right hand side of the equations in the model to zero in the absence of TB infection, is given by $\mathcal{E}_0^T = (S^*, E_T^*, L_T^*, I_T^*, R_T^*) = (\frac{\Pi}{\mu}, 0, 0, 0, 0)$. The local stability of $\mathcal{E}_0^T$ can be established using the next-generation operator method on the system (5).

Definition 1. *The basic reproduction number, basic reproduction ratio or basic reproductive rate is defined as the average number of secondary infections that occur when one infective is introduced into a completely susceptible host populatio [35].*

We can calculate the basic reproduction ratio(number), $\mathcal{R}_0^T$, using the next generation approach proposed by van den Driesseche and Watmough [36]. According to this approach, in order to compute the basic reproduction number, it is important to distinguish new infections from all other class transitions in the population. The infected classes are L_T and I_T. We can write system (5) as: $\dot{x} = \mathcal{F}(x) - \mathcal{V}(x)$, $\mathcal{V} = \mathcal{V}^- - \mathcal{V}^+$, where $x = (S, E_T, L_T, I_T, R_T)$. $\mathcal{F}$ is the rate of appearance of new infection in each class, $\mathcal{V}^+$ is the rate of transfer into each class by all other means, and $\mathcal{V}^-$ is the rate of transfer of the infectious individuals out of each class.

Using system of differential equations below (where the underlined terms represent the new infections in each class),

$$\begin{array}{l} \dot{L}_T = \underline{g\lambda_T S} + \underline{(1-\gamma)\lambda_T E_T} + \underline{\theta\lambda_T R_T} - (b+\mu+m+k\lambda_T)L_T \\ \dot{I}_T = \underline{(1-g)\lambda_T S} + (b+k\lambda_T)L_T - (\tau+\mu+d_T)I_T \\ \dot{S} = \Pi - \lambda_T S - \mu S - \alpha_T e_T S \\ \dot{E}_T = \alpha_T e_T S - (1-\gamma)\lambda_T E_T - \mu E_T \\ \dot{R}_T = \tau I_T + mL_T - (\mu+\theta\lambda_T)R_T \end{array} ,$$

the associated matrices, $\mathcal{F}(x)$ for the new infection terms, and $\mathcal{V}(x)$ for the remaining transition terms are respectively given by,

$$\mathcal{F}(x) = \begin{pmatrix} g\lambda_T S + (1-\gamma)\lambda_T E_T + \theta\lambda_T R_T \\ (1-g)\lambda_T S \\ 0 \\ 0 \\ 0 \end{pmatrix} \tag{6}$$

$$\text{and} \quad \mathcal{V}(x) = \begin{pmatrix} (b+m+\mu+k\lambda_T)L_T \\ (\tau+\mu+d_T)I_T - (b+k\lambda_T)L_T \\ (\lambda_T+\mu+\alpha_T e_T)S - \Pi \\ ((1-\gamma)\lambda_T+\mu)E_T - \alpha_T e_T S \\ (\mu+\theta\lambda_T)R_T - \tau I_T - mL_T \end{pmatrix} \tag{7}$$

Evaluating the partial derivatives of (6) at $\mathcal{E}_0^T$ and bearing in mind that system (3) has two TB only infected classes, namely L_T and I_T, we obtain

$$F = \begin{pmatrix} 0 & g\beta_1 \\ 0 & \beta_1(1-g) \end{pmatrix}$$

Similarly, partial differentiation of (7) with respect to L_T and I_T at $\mathcal{E}_0^T$ gives

$$V = \begin{pmatrix} b+m+\mu & 0 \\ -b & \tau+\mu+d_T \end{pmatrix}$$

The basic reproduction number of TB only sub-model is defined, following van den Driessche and Watmough [36], as the spectral radius of the next generation matrix, FV^{-1} and it is given by:

$$\mathcal{R}_0^T = \left(\frac{\beta_1}{b+m+\mu}\right)\left(\frac{b+(1-g)(m+\mu)}{\tau+\mu+d_T}\right). \tag{8}$$

Therefore, we have the following conclusion from [36].

Lemma 2. *The disease free equilibrium (DFE) of the TB-only model system (5) is locally asymptotically stable (LAS) if* $\mathcal{R}_0^T < 1$ *and unstable if* $\mathcal{R}_0^T > 1$.

The threshold quantity $\mathcal{R}_0^T$ is the reproduction number for TB and it measures the average number of new TB infections generated by a single TB-infected individual in a population where a certain fraction of infected individuals are treated.

2.2.3. HIV-Only Model

The sub-model of (3) with no TB disease, that is when ($E_T = L_T = I_T = R_T = L_{TH} = I_{TH} = R_H = A_T = 0$), is analyzed as follows.

$$\begin{aligned} \dot{S} &= \Pi - (\lambda_H + \mu + \alpha_H e_H)S \\ \dot{E}_H &= \alpha_H e_H S - ((1-\gamma)\lambda_H + \mu)E_H \\ \dot{I}_H &= \lambda_H S + (1-\gamma_1)\lambda_H E_H - (A_3+\sigma)I_H \\ \dot{A}_H &= \varepsilon I_H + \omega R_H - (A_7+\psi)A_H + \xi T_H \\ \dot{T}_H &= \sigma I_H + \psi A_H - A_8 T_H \end{aligned} \quad , \tag{9}$$

where, $\lambda_H = \dfrac{\beta_2(I_H + \eta_c T_H + \eta_a A_H)}{N}$ and $e_H = \dfrac{(I_H + \eta_c T_H + \eta_a A_H)^n}{N^n P_H^n + [I_H + \eta_c T_H + \eta_a A_H]^n}$
$N = S + E_H + I_H + A_H + T_H$.

Analogous to Lemma 2, we can prove that $\Omega_2 = \{(S, E_H, I_H, A_H, T_H) \in \mathbb{R}_+^5 : N \leq \dfrac{\Pi}{\mu}\}$ is positively invariant and attracting. Thus, the dynamics of HIV only model will be considered in Ω_2.

2.2.4. Local Stability of Disease Free Equilibrium

The model subsystem (9) has a DFE, obtained by setting the right hand side of the equations in the model zero and in the absence of HIV infection is given by $\mathcal{E}_0^H = (S^*, E_H^*, I_H^*, T_H^*, A_H^*) = (\frac{\Pi}{\mu}, 0, 0, 0, 0)$. The local stability of $\mathcal{E}_0^H$ can be established using the next-generation operator method on the system (9). Using a similar procedure as in the previous subsection on the subsystem:

$$\begin{aligned} \dot{I}_H &= \underline{\lambda_H S} + \underline{(1-\gamma_1)\lambda_H E_H} - (A_3+\sigma)I_H \\ \dot{A}_H &= \varepsilon I_H - (A_7+\psi)A_H + \xi T_H \\ \dot{T}_H &= \sigma I_H + \psi A_H - A_8 T_H \\ \dot{S} &= \Pi - (\lambda_H + \mu + \alpha_H e_H)S \\ \dot{E}_H &= \alpha_H e_H S - ((1-\gamma)\lambda_H + \mu)E_H, \end{aligned} \tag{10}$$

the associated matrices, $\mathcal{F}(x)$ for the new infection terms, and $\mathcal{V}(x)$ for the remaining transition terms are respectively given by,

$$\mathcal{F}(x) = \begin{pmatrix} \lambda_H S + (1-\gamma_1)\lambda_H E_H \\ 0 \\ 0 \\ 0 \\ 0 \end{pmatrix} \tag{11}$$

$$\text{and} \quad \mathcal{V}(x) = \begin{pmatrix} (A_3+\sigma)I_H \\ (A_7+\psi)A_H - \varepsilon I_H - \xi T_H \\ A_8 T_H - \sigma I_H - \psi A_H \\ (\lambda_H + \mu + \alpha_H e_H)S - \pi \\ ((1-\gamma)\lambda_H + \mu)E_H - \alpha_H e_H S \end{pmatrix} \tag{12}$$

Evaluating the partial derivatives of (11) at $\mathcal{E}_0^H$ and bearing in mind that system (3) has three HIV/AIDS only infected classes, namely I_H, A_H and T_H, we obtain

$$F = \begin{pmatrix} \beta_2 & \eta_a\beta_2 & \eta_c\beta_2 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{pmatrix}$$

Similarly, partial differentiation of (12) with respect to I_H, A_H and T_H at $\mathcal{E}_0^H$ gives

$$V = \begin{pmatrix} \varepsilon+\mu+\sigma & 0 & 0 \\ -\varepsilon & \mu+\psi+d_A & -\xi \\ -\sigma & -\psi & \xi+\mu \end{pmatrix}$$

The basic reproduction number of HIV/AIDS only sub-model is defined, following van den Driessche and Watmough [36], as the spectral radius of the next generation matrix, FV^{-1} and it is given by:

$$\mathcal{R}_0^H = \frac{\beta_2\left[(\mu+\eta_c\sigma)C_4 + \xi C_1 + \varepsilon C_2\right]}{C_1\left[\mu C_4 + \xi C_5\right]} \tag{13}$$

where, $C_1 = \eta_a\varepsilon + \sigma + \mu + d_A, C_2 = \eta_a\mu + \eta_c\psi, C_3 = \varepsilon + \sigma + \mu, C_4 = \psi + \mu + d_A$, and $C_5 = \mu + d_A$

The basic reproduction number $\mathcal{R}_0^H$ represents the expected average number of new HIV infections produced by a single HIV-infected individual when in contact with a completely susceptible population.

2.3. Analysis of the Full Model

Consider now the full model (3), with DFE given by

$$\mathcal{E}_0 = (S^*, E_T^*, L_T^*, I_T^*, R_T^*, E_H^*, I_H^*, L_{TH}^*, I_{TH}^*, R_H^*, A_H^*, A_T^*, T_H^*) = \left(\frac{\Pi}{\mu}, 0,0,0,0,0,0,0,0,0,0,0,0\right).$$

Using the same procedure like in Section 2.2.1 to calculate basic reproduction number, the associated matrices $\mathcal{F}$ and $\mathcal{V}$ can be determined as below. Here the underlined terms are new infections in each class.

$$
\begin{aligned}
\dot{L}_T &= \underline{g\lambda_T S} + \underline{(1-\gamma)\lambda_T E_T} + \underline{\theta\lambda_T R_T} + \underline{\nu\lambda_T E_H} - (A_1 + \lambda_H + k\lambda_T)L_T \\
\dot{I}_T &= \underline{(1-g)\lambda_T S} + (b + k\lambda_T)L_T - (A_2 + \tau + \delta\lambda_H)I_T \\
\dot{I}_H &= \underline{\lambda_H S} + \underline{\nu_1\lambda_H E_T} + \underline{(1-\gamma_1)\lambda_H E_H} + \underline{\lambda_H R_T} - (A_3 + \sigma + \rho\lambda_T)I_H \\
\dot{L}_{TH} &= \lambda_H L_T + \theta_1\lambda_T R_H - (A_4 + \sigma + k_1\lambda_T)L_{TH} \\
\dot{I}_{TH} &= (b_1 + k_1\lambda_T)L_{TH} + \rho\lambda_T I_H + \delta\lambda_H I_T - (A_5 + r\tau)I_{TH} \\
\dot{R}_H &= \tau_1 L_{TH} + r\tau I_{TH} - (A_6 + \sigma + \theta_1\lambda_T)R_H \\
\dot{A}_H &= \varepsilon I_H + \omega R_H - (A_7 + \psi + \rho_1\lambda_T)A_H + \xi T_H \\
\dot{A}_T &= \rho_1\lambda_T A_H + \varepsilon_1 I_{TH} - A_9 A_T \\
\dot{T}_H &= \sigma(L_{TH} + I_H + R_H) + (1-r)pI_{TH} + \psi A_H + \psi_1 A_T - A_8 T_H \\
\dot{S} &= \Pi - [\lambda_T + \lambda_H + \mu + \alpha_T e_T + \alpha_H e_H]S \\
\dot{E}_T &= \alpha_T e_T S - ((1-\gamma)\lambda_T + \nu_1\lambda_H + \mu)E_T \\
\dot{R}_H &= \tau_1 L_{TH} + r\tau I_{TH} - (A_6 + \sigma + \theta_1\lambda_T)R_H \\
\dot{E}_H &= \alpha_H e_H S - [\nu\lambda_T + (1-\gamma_1)\lambda_H + \mu]E_H
\end{aligned}
\tag{14}
$$

The associated matrices $\mathcal{F}(x)$ for new infections terms, and $\mathcal{V}(x)$ for the remaining transition terms are respectively given by

$$
\mathcal{F}(x) = \begin{pmatrix}
g\lambda_T S + (1-\gamma)\lambda_T E_T + \theta\lambda_T R_T + \nu\lambda_T E_H \\
(1-g)\lambda_T S \\
\lambda_H S + \lambda_H R + (1-\gamma_1)\lambda_H E_H + \nu_1\lambda_H E_T \\
0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0
\end{pmatrix}
\tag{15}
$$

$$
\mathcal{V}(x) = \begin{pmatrix}
(A_1 + \lambda_H + k\lambda_T)L_T \\
(A_2 + \sigma + \delta\lambda_H)I_T - (b + k\lambda_T)L_T \\
(A_3 + \sigma + \rho\lambda_T)I_H \\
(A_4 + \sigma + k_1\lambda_T)L_{TH} - \lambda_H L_T - \theta_1\lambda_T R_H \\
(A_5 + r\tau)I_{TH} - (b_1 + k_1\lambda_T)L_{TH} - \rho\lambda_T I_H - \delta\lambda_H I_T \\
(A_6 + \sigma + \theta_1\lambda_T)R_H - \tau_1 L_{TH} - r\tau I_{TH} \\
(A_7 + \psi + \rho_1\lambda_T)A_H - \varepsilon I_H - \omega R_H - \xi T_H \\
A_8 T_H - \sigma(L_{TH} + I_H + R_H) - \psi A_H - (1-r)pI_{TH} - \psi_1 A_T \\
A_9 A_T \rho_1\lambda_T A_H - \varepsilon_1 I_{TH} \\
(\lambda_T + \lambda_H + \mu + \alpha_T e_T + \alpha_H e_H)S - \Pi \\
(\nu_1\lambda_H + \mu + (1-\gamma)\lambda_T)E_T - \alpha_T e_T S \\
(\mu + \lambda_H + \theta\lambda_T)R_T - \tau I_T \\
(\nu\lambda_T + (1-\gamma_1)\lambda_H + \mu)E_H - \alpha_H e_H S
\end{pmatrix}
\tag{16}
$$

Evaluating the partial derivatives of (15) at $\mathcal{E}_0$ and bearing in mind that system (14) has nine infected classes, namely $L_T, I_T, I_H, L_{TH}, I_{TH}, R_H, A_H, A_T$ and T_H , we obtain

$$F = \begin{pmatrix} 0 & g\beta_1 & 0 & 0 & g\beta_1 & 0 & 0 & g\beta_1 & 0 \\ 0 & (1-g)\beta_1 & 0 & 0 & (1-g)\beta_1 & 0 & 0 & (1-g)\beta_1 & 0 \\ 0 & 0 & \beta_2 & \beta_2 & \beta_2 & \beta_2 & \beta_2\eta_a & \beta_2\eta_a & \beta_2\eta_c \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \end{pmatrix}$$

Similarly, partial differentiation of (16) with respect to $L_T, I_T, I_H, L_{TH}, I_{TH}, R_H, A_H, A_T$ and T_H at $\mathcal{E}_0$ gives

$$V = \begin{pmatrix} A_1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ -b & A_2+\sigma & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & A_3+\sigma & 0 & 0 & 0 & -\psi & 0 & -\xi \\ 0 & 0 & 0 & A_4+\sigma & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & -b-k_1 & A_5+r\tau & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & \tau_1 & -r\tau & A_6+\sigma & 0 & 0 & 0 \\ 0 & 0 & -\varepsilon & 0 & 0 & -\omega & A_7+\psi & 0 & -\xi \\ 0 & 0 & -\sigma & -\sigma & -(1-r)p & -\sigma & -\psi & -\psi_1 & A-8 \\ 0 & 0 & 0 & 0 & -\varepsilon & 0 & 0 & A_9 & 0 \end{pmatrix}$$

Then, following van den Driessche and Watmough [36], the basic reproduction number is given by the spectral radius of the next generation matrix. Then, the dominant eigenvalues of the matrix FV^{-1} are,

$$\mathcal{R}_0^T = \frac{\beta_1\left[b+(1-g)(m+\mu)\right]}{A_1(\tau+\mu+d_T)}, \qquad \text{and} \qquad \mathcal{R}_0^H = \frac{\beta_2\left[(\mu+\eta_c\sigma)C_4+\xi C_1+\varepsilon C_2\right]}{C_1\left[\mu C_4+\xi C_5\right]}$$

where, $A_1 = b+m+\mu, C_1 = \eta_a\varepsilon+\sigma+\mu+d_A, C_2 = \eta_a\mu+\eta_c\psi, C_3 = \varepsilon+\sigma+\mu, C_4 = \psi+\mu+d_A$, and $C_5 = \mu+d_A$

Thus, the basic reproduction number $\mathcal{R}_0$ of the model (3) is given by

$$\mathcal{R}_0 = \max\left\{\mathcal{R}_0^T, \mathcal{R}_0^H\right\} \tag{17}$$

Lemma 3. *Suppose the disease transmission of the full model is given by (3). If $\mathcal{E}_0$ is a DFE of the model, then $\mathcal{E}_0$ is locally asymptotically stable if $\mathcal{R}_0 < 1$ and unstable otherwise, where $\mathcal{R}_0$ is the reproduction number defined in (17).*

3. Formulation of the Control

The possible interventions for TB and HIV/AIDS co-infection can be categorized as (1) applying preventive education and (2) treatment of infected individuals. In the following we will describe what specific control measures can be taken corresponding to each of the two intervention categories.

1. Preventive Education

   (a) Different programs have been designed so far to enlighten the population about the risk factors of TB disease and about possible preventive mechanisms. Such preventive mechanisms are self-protective actions, like using masks and gloves while contacting TB infected individuals and consistently ventilating rooms and vehicles that are used commonly by other individuals who are especially more likely to be infectious of a TB disease.

By applying such self-initiated protective measures an individual can reduce the risk of contracting the disease. Let the current level of preventive education campaigns about TB disease by various agents have convinced up to $100 \times (\alpha_{T0} \times e)\%$ (for some $1 > \alpha_{T0} > 0$) of the population to effectively participate in the self protective schemes available to them. If more choices of self-protective measure are offered to the population and if the awareness campaigns are intensified, more individuals may decide to choose and use at least one of these preventive measures. This helps individuals to reduce their risk of being infected by TB. This could be considered as an effort made by individuals and health care campaigners to help susceptible individuals from getting infected easily by TB.

On the other hand, the same educational information can help individuals who are infected by TB but are not taking part in any of the self-protective actions about the disease so that they can change their risky behavior. These individuals may need to visit appropriate health centers regularly and take the prescribed medicine properly until the end of the specified time given from doctors. Moreover, they need to take any preventive actions against HIV so that they will not be co-infected by HIV.

Assume that the control function $u_1(t)$ measures the rate at which additional susceptible individuals are convinced to take part in behaviour modification about TB disease. Then, its application in the dynamics is modelled by simply replacing the term α_T in the model system (3) by $(\alpha_{T0} + u_1(t))$. We assume that the larger the proportion of the educated class, the lower will be the proportion of individuals in the susceptible population. Because of practicality and economic limitations on the maximum rate of convincing individuals for behaviour modification, we assume that $\alpha_{Tmax} > 0$ to be the maximum rate such that $0 \leq \alpha_{T0} + u_1(t) \leq \alpha_{Tmax} \leq 1$.

(b) The expansion and improvement of HIV and AIDS education around the world is critical to preventing the spread of HIV [37]. Those convinced to apply any of the preventive mechanisms against HIV infection, will enjoy a reduced risk of infection by HIV. Therefore, they will be better off as compared to individuals with risky behaviour.

Moreover, it is also important to educate (or enlighten) people who are already infected by HIV so that they take maximum possible protective action against TB as their immune system is most likely be compromised due to the HIV infection.

Assume that the control function $u_2(t)$ measures the rate at which additional susceptible individuals are convinced to take part in behaviour modification about HIV/AIDS disease. Then its application in the dynamics is modelled by simply replacing the term α_H in (3) by $(\alpha_{H0} + u_2(t))$. Because of practicality and economic limitations on the maximum rate of convincing individuals for behaviour modification, we also assume that $\alpha_{Hmax} > 0$ to be the maximum rate as indicated in [37] and $0 \leq \alpha_{H0} + u_2(t) \leq \alpha_{Hmax} \leq 1$.

2. Treatment of infected individuals

(a) TB treatment for individuals who are infected by TB bacteria.

TB infected individuals can be treated with appropriate medicine and become non-infectious within an average treatment period of 6 months [11]. Such treatments not only help the infected individuals to recover from the disease, but also make them non infectious and thereby reducing the force of infection in the dynamics of the disease. Therefore, investing on treatments also have a positive impact on the reduction of the burden of the disease in the society in general.

Assume that the control function $u_3(t)$ measures the rate at which additional infectious individuals are recruited to receive TB treatment at any time t. If the current rate of TB treatment is τ_0 proportion from the total infected people, this control measure will be introduced in the dynamics as $(\tau_0 + u_3(t))$ by replacing the parameter τ. In addition, we assumed that only an r fraction of people from the I_{TH} classes are recruited to receive

TB treatment while others receive both types simultaneously. Due to economic and logistic reasons, there could be limitations on the maximum rate to be achieved. Thus, we assume that the constant $\tau_{\max} \leq 1$ represents the maximum rate of recruitment for treatment of infected individuals with $0 \leq \tau_0 + u_3(t) \leq \tau_{\max} \leq 1$.

(b) Treating HIV infected individual using ARV.

Similar to the case of TB, treating HIV infected individuals with ARV will reduce their level of infectiousness by suppressing their viral load while helping them to regain their immunity thereby get a better quality of life. This treatment may also reduce the rate of co-infection by TB.We assume that the rate of recruiting individuals to receive ART is the same for both I_H and A_H classes, and we take $\psi = \sigma$. Moreover, it is assumed in this work that the rate of receiving treatment for both HIV and TB simultaneously is taken to be the maximum possible (which is p) and we require no additional effort in this regard.

Let the control function $u_4(t)$ measures the rate at which additional infected individuals with HIV virus are recruited to receive ARV at any time t. If the current rate of recruitment is σ_0 proportion from among all HIV infected individuals, then this control measure can be introduced in the dynamics as $\sigma_0 + u_4(t)$ in place of the parameter σ and ψ (which are assumed to be equal). Similar to the TB case we assume that there is a limitation on the maximum rate of treating people with ARV. Thus, we may represent the maximum recruitment rate to be $\sigma_{\max} \leq 1$ and therefore, we have $0 \leq \sigma_0 + u_4(t) \leq \sigma_{\max} \leq 1$.

After applying all these four control functions described above in to the model system, the corresponding system of differential equation can be written as follows.

$$\begin{cases} \frac{dS}{dt} = & \Pi - [\lambda_T + \lambda_H + \mu + (\alpha_{T0} + u_1)e_T + (\alpha_{H0} + u_2)e_H]S \\ \frac{dE_T}{dt} = & (\alpha_{T0} + u_1)e_T S - [(1-\gamma)\lambda_T + \nu_1\lambda_H + \mu]E_T \\ \frac{dL_T}{dt} = & g\lambda_T S + (1-\gamma)\lambda_T E_T + \theta\lambda_T R_T + \nu\lambda_T E_H - (A_1 + \lambda_H + k\lambda_T)L_T \\ \frac{dI_T}{dt} = & (1-g)\lambda_T S + (b + k\lambda_T)L_T - (\tau_0 + u_3)I_T - (A_2 + \delta\lambda_H)I_T \\ \frac{dR_T}{dt} = & (\tau_0 + u_3)I_T + mL_T - (\mu + \lambda_H + \theta\lambda_T)R_T \\ \frac{dE_H}{dt} = & (\alpha_{H0} + u_2)e_H S - [\nu\lambda_T + (1-\gamma_1)\lambda_H + \mu]E_H \\ \frac{dI_H}{dt} = & \lambda_H S + \nu_1\lambda_H E_T + (1-\gamma_1)\lambda_H E_H + \lambda_H R_T - (\sigma_0 + u_4)I_H - (A_3 + \rho\lambda_T)I_H \\ \frac{dL_{TH}}{dt} = & \lambda_H L_T + \theta_1\lambda_T R_H - (\sigma_0 + u_4)L_{TH} - (A_4 + k_1\lambda_T)L_{TH} \\ \frac{dI_{TH}}{dt} = & (b_1 + k_1\lambda_T)L_{TH} + \rho\lambda_T I_H + \delta\lambda_H I_T - r(\tau_0 + u_3)I_{TH} - A_5 I_{TH} \\ \frac{dR_H}{dt} = & \tau_1 L_{TH} + r(\tau_0 + u_3)I_{TH} - (\sigma_0 + u_4)R_H - (A_6 + \theta_1\lambda_T)R_H \\ \frac{dA_H}{dt} = & \varepsilon I_H + \xi T_H + \omega R_H - (\sigma_0 + u_4)A_H - (A_7 + \rho_1\lambda_T)A_H \\ \frac{dT_H}{dt} = & (\sigma_0 + u_4)(L_{TH} + I_H + R_H + A_H) + (1-r)pI_{TH} + \psi_1 A_T - A_8 T_H \\ \frac{dA_T}{dt} = & \rho_1\lambda_T A_H + \varepsilon_1 I_{TH} - A_9 A_T \end{cases}, \tag{18}$$

where,
$$\begin{array}{lll} A_1 = b + m + \mu & A_2 = \mu + d_T & A_3 = \varepsilon + \mu \\ A_4 = \tau_1 + b_1 + \mu & A_5 = (1-r)p + \varepsilon_1 + \mu + d_T & A_6 = \omega + \mu \\ A_7 = \mu + d_A & A_8 = \xi + \mu & A_9 = \psi_1 + \mu + d_{TA} \end{array}$$

For all $t \in [0, t_f]$, $0 \leq u_1(t) \leq \alpha_{Tmax} - \alpha_{T0}, 0 \leq u_2(t) \leq \alpha_{Hmax} - \alpha_{H0}$, $0 \leq u_3(t) \leq \tau\max - \tau_0$, $0 \leq u_4(t) \leq \sigma_{\max} - \sigma_0$. The total size of population is bounded above by $\frac{\pi}{\mu}$ and bounded below by some $N^0 > 0$. Since the state variables are partitions of the total population, the suprimum of the total population is also the suprimum of each of the state variables. This implies that each of the state variables are bounded below by 0 and bounded above by the same bound with the total population.

Thus, with controlled model system (18) and given initial population size of each compartment to be $S^0, E_T^0, L_T^0, I_T^0, L_{TH}^0, R_T^0, E_H^0, I_H^0, I_{TH}^0, A_H^0, R_H^0, A_T^0$ and T_H^0, *our main goal in this work is to find or propose the best strategy in terms of either in combination or independent efforts of preventive education and treatment that will minimize the total number of new infections and the total number of people that die due to the two infectious diseases (TB and HIV) in the planning period while at the same time also minimizing the total cost of*

interventions. We considered the optimal control problem with a fixed terminal time problem because most governments cannot continue the implementation of the interventions indefinitely; rather they may choose a program that the disease is eradicated or is driven below specified level within a set time frame.

If we are given the initial value for the populations size of each cohort to be $S^0, E_T^0, L_T^0, I_T^0, L_{TH}^0, R_T^0, E_H^0, I_H^0, I_{TH}^0, A_H^0, R_H^0, A_T^0, T_H^0$ and the control trajectory, i.e., the values of $u(t)$ over the whole time interval $0 < t < T$, then we can integrate (18) to get the state trajectory, i.e., the values of $S, E_T, L_T, I_T, L_{TH}, R_T, E_H, I_H, I_{TH}, A_H, R_H, A_T$ and T_H, over the same time interval. We want to choose the control trajectory so that the control and the corresponding state trajectories minimize the objective cost function, or simply the objective function which is given by.

$$\begin{aligned}\mathbf{J}(u_1,u_2,u_3,u_4) = \int_0^{t_f} \Big[& C_1 I_T(t) + C_2 I_H(t) + C_3 I_{TH}(t) + C_4 A_H(t) + C_5 A_T(t) \\ & + D_1 u_3(t)\left(I_T(t) + I_{TH}(t)\right) + D_2 u_4(t)\left(L_{TH}(t) + I_H(t) + R_H(t) + A_H(t)\right) \\ & + \frac{B_1}{2}u_1^2(t) + \frac{B_2}{2}u_2^2(t) + \frac{B_3}{2}u_3^2(t) + \frac{B_4}{2}u_4^2(t)\Big]\, dt,\end{aligned} \tag{19}$$

where the constants C_1, C_2, C_3, C_4, C_5, D_1, D_2 and $B_i, i = 1,2,3,4$ can be considered as values that will balance the units of measurement and also may indicate the importance of one type of intervention over the other. $C_1 I_T$, $C_2 I_H$, $C_3 I_{TH}$, $C_4 A_H$ and $C_5 A_T$ represent the cost on the population of actively infected individuals with TB, that of HIV infected individuals with no clinical symptoms of AIDS, that of TB infected individuals who are also co-infected with HIV, and that of individuals who progressed to AIDS stage respectively. Moreover, the terms $D_1 u_3(t)(I_T(t) + I_{TH}(t))$ and $D_2 u_4(t)(I_H(t) + L_{TH}(t) + R_H(t) + A_H(t))$ represent the cost of individual treatment for TB and HIV respectively, where as $\frac{B_1}{2}u_1^2$, $\frac{B_2}{2}u_2^2$, $D_1 u_3(t) I_T(t) + \frac{B_3}{2}u_3^2$, $D_2 u_4(t) I_H(t) + \frac{B_4}{2}u_4^2$ represent the cost of producing and administering educational materials about TB, about HIV, and the cost of production and administration of treatment for TB patients, and for HIV/AIDS patients respectively. The treatment cost may include the cost of the medical tests and diagnosis, drug cost, hospitalization cost and the like. However, the cost of initial investment for the educational materials and pharmaceutical drugs as well as their administrative costs are not linearly related with the number of individuals persuaded or treated. The variables in this part are squared to amplify the effects of large variations and to de-emphasize contributions of small variations. Since implementation of any public health intervention has increasing costs with reaching higher fraction of the population, we took a quadratic cost function to represent this situation. On the the other hand the unit cost of drugs used for treatment depends linearly with the number of units applied (or number of people treated), hence we used the linear cost to capture this fact.

So we seek to find optimal controls $u_1^*, u_2^*, u_3^*, u_4^*$ such that

$$\mathbf{J}(u_1^*, u_2^*, u_3^*, u_4^*) = \min_{\mathbf{u}\in\mathcal{U}} J(u_1,u_2,u_3,u_4), \tag{20}$$

where

$$\begin{aligned}\mathcal{U} = \; & \{(u_1(t),u_2(t),u_3(t),u_4(t)) \in \mathbb{R}^4 \mid u_1(t),u_2(t),u_3(t),u_4(t) \text{ are Lebesgue integrable,} \\ & u_1(t) \in [0, \alpha_{Tmax} - \alpha_{T0}], u_2(t) \in [0, \alpha_{Hmax} - \alpha_{H0}], u_3(t) \in [0, \tau_{\max} - \tau_0], u_4(t) \in [0, \sigma_{\max} - \sigma_0]\}\end{aligned}$$

Existence and Characterization of Optimal Control Solution

Theorem 1 (Existence of optimal control solution)**.** *There exists an optimal control $u_1^*(t), u_2^*(t), u_3^*(t), u_4^*(t)$ and corresponding solutions $S^*, E_T^*, L_T^*, I_T^*, I_H^*, L_{TH}^*, R_T^*, E_H^* I_{TH}^*, A_H^*, R_H^*, A_T^*$ and T_H^* to the state initial value problem (18)–(20) that minimizes $J(u_1,u_2,u_3,u_4)$ over $\mathcal{U}$.*

Proof. The non trivial requirements on the set of admissible controls $\mathcal{U}$ and on the set of end conditions are verified by Fleming and Rishel's theorem.

A. The set of all solutions to system (18)–(20) with corresponding control functions in $\mathcal{U}$ is non-empty.
B. The state system can be written as a linear function of the control variables with coefficients dependent on time and the state variables.
C. The integrand L in (19) from objective functional with $L(\mathbf{x},\mathbf{u},t) = C_1 I_T(t) + C_2 I_H(t) + C_3 I_{TH}(t) + C_4 A_H(t) + C_5 A_T(t) + D_1 u_3(t)\,(I_T(t) + I_{TH}(t)) + D_2 u_4(t)\,(L_{TH}(t) + I_H(t) + R_H(t) + A_H(t)) + \frac{B_1}{2}u_1^2(t) + \frac{B_2}{2}u_2^2(t) + \frac{B_3}{2}u_3^2(t) + \frac{B_4}{2}u_4^2(t)$ is convex on $\mathcal{U}$, and additionally it satisfies $L(\mathbf{x},\mathbf{u},t) \geq \delta_1 \mid (u_1,u_2,u_3,u_4) \mid^{\beta} - \delta_2$ where $\delta_1 > 0$ and $\beta > 1$.

In order to establish condition A, we refer to Picard-Lindelöf's theorem from [38,39]. If the solutions to the state equations are bounded and if the state equations are continuous and Lipschitz in the state variables, then there is a unique solution corresponding to every admissible control $\mathcal{U}$.

It is indicated that the total population is bounded below by a positive nonzero number N_0 and bounded above by $\frac{\Pi}{\mu}$ as well as each of the state variables are bounded. With the bounds established above, it follows that the state system is continuous and bounded. It is equally direct to show the boundedness of the partial derivatives with respect to the state variables in the state system, which establishes that the system is Lipschitz with respect to the state variables (see [40]). This completes the proof that condition A holds.

Condition B is verified by observing the linear dependence of the state equations on controls u_1, u_2, u_3 and u_4. Finally, to verify condition C by definition from [41,42] any constant, linear and quadratic functions are convex. Therefore, $L(\mathbf{x},\mathbf{u},t)$ is convex on $\mathcal{U}$. To prove the bound on the L we note that by the definition of $\mathcal{U}$, we have

$$
\begin{aligned}
&B_4 u_4^2 \leq B_4 \; since \; u_4 \in [0,1] \\
&\frac{B_4}{2}u_4^2 \leq \frac{B_4}{2}, \qquad \frac{B_4}{2}u_4^2 - \frac{B_4}{2} \leq 0 \\
&L(\mathbf{x},\mathbf{u},t) = C_1 I_T(t) + C_2 I_H(t) + C_3 I_{TH}(t) + C_4 A_H(t) + C_5 A_T(t) \\
&+ D_1 u_3(t)\,(I_T(t) + I_{TH}(t)) + D_2 u_4(t)\,(L_{TH}(t) + I_H(t) + R_H(t) + A_H(t)) \\
&+ \frac{B_1}{2}u_1^2(t) + \frac{B_2}{2}u_2^2(t) + \frac{B_3}{2}u_3^2(t) + \frac{B_4}{2}u_4^2(t) \\
&\geq \frac{B_1}{2}u_1^2(t) + \frac{B_2}{2}u_2^2(t) + \frac{B_3}{2}u_3^2(t) + \frac{B_4}{2}u_4^2(t) - \frac{B_4}{2} \\
&\Rightarrow L(\mathbf{x},\mathbf{u},t) \geq \min(\frac{B_1}{2},\frac{B_2}{2},\frac{B_3}{2},\frac{B_4}{2})(u_1^2 + u_2^2 + u_3^2 + u_4^2) - \frac{B_4}{2} \\
&\Rightarrow L(\mathbf{x},\mathbf{u},t) \geq \min(\frac{B_1}{2},\frac{B_2}{2},\frac{B_3}{2},\frac{B_4}{2})|(u_1,u_2,u_3,u_4)|^2 - \frac{B_4}{2}
\end{aligned}
$$

Therefore, $L(\mathbf{x},\mathbf{u},t) \geq \delta_1 |(u_1,u_2,u_3,u_4)|^{\beta} - \delta_2$; where $\delta_1 = \min((\frac{B_1}{2},\frac{B_2}{2},\frac{B_3}{2},\frac{B_4}{2}), \delta_2 = \frac{B_4}{2}$ & $\beta = 2$.

□

The necessary conditions that an optimal solution must satisfy come from Pontryagin's maximum principle (PMP). This principle converts (18)–(20) in to a problem of minimizing a Hamiltonian, H, with respect to u_1, u_2, u_3, u_4 together with the state equation and the adjoint condition. Here, the Hamiltonian is given by

$$
\begin{aligned}
H(\mathbf{x},\mathbf{u},\mathbf{h},t) \quad = \quad & C_1 I_T(t) + C_2 I_H(t) + C_3 I_{TH}(t) + C_4 A_H(t) + C_5 A_T(t) \\
& + D_1 u_3(t)\,(I_T(t) + I_{TH}(t)) + D_2 u_4(t)\,(L_{TH}(t) + I_H(t) + R_H(t) + A_H(t)) \\
& + \frac{B_1}{2}u_1^2(t) + \frac{B_2}{2}u_2^2(t) + \frac{B_3}{2}u_3^2(t) + \frac{B_4}{2}u_4^2(t),
\end{aligned} \tag{21}
$$

where, the f_i's represent the right hand side of the differential equation of the ith state variable in system (18), $\mathbf{x} = (S, E_T, L_T, I_T, R_T, E_H, I_H, L_{TH}, I_{TH}, R_H, A_H, A_T, T_H)$, $\mathbf{u} = (u_1, u_2, u_3, u_4)$ and $\mathbf{h} = (h_1, h_2, h_3, h_4, h_5, h_6, h_7, h_8, h_9, h_{10}, h_{11}, h_{12}, h_{13})$.

If $(u_1^*, u_2^*, u_3^*, u_4^*)$ is an optimal control vector for the problem (which is yet to be determined), then from Pontryagin's Maximum Principle we have the following conditions:

Optimality Conditions:

The first conditions that we will consider from the Pontryagin's Maximum principle is the minimization of the Hamiltonian H with respect to the control variables, u_1, u_2, u_3, u_4. Since the cost function is convex, if the optimal control occurs in the interior region we must have $\frac{\partial H}{\partial u_i} = 0$. Therefore,

(i) for the control u_1 we must have,

$$\frac{\partial H}{\partial u_1} = B_1 u_1 - h_1 e_T S + h_2 e_T S = 0 \Rightarrow \bar{u}_1 = \frac{1}{B_1}(h_1 - h_2)\, e_T S.$$

(ii) for the control u_2 we must have

$$\frac{\partial H}{\partial u_2} = B_2 u_2 - h_1 e_H S + h_6 e_H S = 0 \Rightarrow \bar{u}_2 = \frac{1}{B_2}(h_1 - h_6)\, e_H S.$$

(iii) for the control u_3 we must have

$$\begin{aligned} \frac{\partial H}{\partial u_3} &= D_1 I_T + B_3 u_3 - h_4 I_T + h_5 R_T + h_{10}\varepsilon_1 I_{TH} - h_{13}\varepsilon_1 I_{TH} = 0 \\ &\Rightarrow \quad \bar{u}_3 = \frac{1}{B_3}\left[(h_4 - D_1) I_T - h_5 R_T + (h_{13} - h_{10})\varepsilon_1 I_{TH}\right]. \end{aligned}$$

(iv) Similarly, for the control u_4 we must have

$$\begin{aligned} \frac{\partial H}{\partial u_4} &= D_2 I_H + B_4 u_4 - h_7 I_H - h_8 L_{TH} - h_{10} R_H - h_{11} A_H + h_{12}(L_{TH} + I_H + R_H + A_H) = 0 \\ &\Rightarrow \quad \bar{u}_4 = \frac{1}{B_4}\left[(h_7 - h_{12} - D_2) I_H + (h_8 - h_{12}) L_{TH} + (h_{10} - h_{12}) R_H + (h_{11} - h_{12}) A_H\right]. \end{aligned}$$

And therefore, the optimal controls on the given bounded intervals are given by

$$\begin{aligned} u_1^* &= \min\{\alpha_{Tmax}, \max\{\alpha_{T0}, \bar{u}_1\}\}, & u_2^* &= \min\{\alpha_{Hmax}, \max\{\alpha_{H0}, \bar{u}_2\}\}, \\ u_3^* &= \min\{\tau_{\max}, \max\{\tau_0, \bar{u}_3\}\}, & u_4^* &= \min\{\sigma_{\max}, \max\{\sigma_0, \bar{u}_4\}\}. \end{aligned} \tag{22}$$

The adjoint (co-state) equations:

From the second condition of the Pontryagin's Maximum Principle, we must have $\frac{\partial H}{\partial x_i} = -\frac{\mathrm{d}h_i}{\mathrm{d}t}$ at the optimal controls for each $i = 1, 2, \ldots, 13$.

Therefore, we need to calculate and solve the system,

$$\begin{aligned} &\dot{h}_1 = -\frac{\partial H}{\partial S} \quad \dot{h}_2 = -\frac{\partial H}{\partial E_T} \quad \dot{h}_3 = -\frac{\partial H}{\partial L_T} \quad \dot{h}_4 = -\frac{\partial H}{\partial I_T} \quad \dot{h}_5 = -\frac{\partial H}{\partial R_T} \\ &\dot{h}_6 = -\frac{\partial H}{\partial E_H} \quad \dot{h}_7 = -\frac{\partial H}{\partial I_H} \quad \dot{h}_8 = -\frac{\partial H}{\partial L_{TH}} \quad \dot{h}_9 = -\frac{\partial H}{\partial I_{TH}} \quad \dot{h}_{10} = -\frac{\partial H}{\partial R_H} \\ &\dot{h}_{11} = -\frac{\partial H}{\partial A_H} \quad \dot{h}_{12} = -\frac{\partial H}{\partial T_H} \quad \dot{h}_{13} = -\frac{\partial H}{\partial A_T} \end{aligned} \tag{23}$$

together with the transversality conditions,

$$h_i(t_f) = 0, \quad \text{for all } i = 1, 2, \ldots, 13. \tag{24}$$

Solving the above two conditions together with the state equation (equation system (18)) gives us the required optimal solution and the corresponding state variables.

4. Numerical Simulation and Results

In this section we shall carry out simulations to demonstrate the output of optimal control values and the corresponding impacts on the dynamics of the disease by varying some of the parameter values. In addition, we will also consider the what if analysis on the system when some of the controls are missing and when all of the controls are being used.

We estimate the results by using fourth order Runge-Kutta method in solving the state equation system (18), and the adjoint (or co-state) equation system (23), together with the optimality Equation (22).

The process begins with an initial guess on the control variables. Then, the state equations are simultaneously solved forward in time starting from the initial conditions and the adjoint equations are solved backward in time starting from the transversality conditions (24). The control is updated by inserting the new values of the state and adjoint vectors into its characterization (Equation (22)), and the process is repeated until convergence occurs.

We used fixed final time $t_f = 10$ years and the initial conditions are estimated as follows. We assumed that more than half of the population (55%) belongs to the subgroup of susceptible class ($S(0) = 16{,}500$) and that a big percentage about 31% is infected with TB in latent stage (i.e., $L_T(0) = 9249$). This is justified from the fact that "about one third of the world's population has latent TB", as it is indicated from the webpage of the World Health Organization (WHO [5]). The value for the fraction of people infected with HIV is assumed to be about 4.17% ($I_H(0) = 1250$) based on HIV and AIDS information from AVERT.org [8]. We also assumed that there is very little information about the disease in the population; and hence only 0.2% is educated about TB preventions (i.e., $E_T(0) = 60$) and only about 0.27% is educated about HIV preventions (i.e., $E_H(0) = 80$). Other initial values of the sub-populations are assumed for numerical purpose to be as below. $R_T(0) = 50, I_H(0) = 1250, L_{TH}(0) = 500$, $I_{TH}(0) = 500, T_H(0) = 300$, $A_H(0) = 250, A_T(0) = 200, R_H(0) = 250$.

The constants in the cost functional are taken as follows: coefficients for cost of infection are $C_1 = 10, C_2 = 16, C_3 = 20, C_4 = 280, C_5 = 300$, coefficients for cost of individual treatment are $D_1 = 2, D_2 = 6$, and coefficients for cost of production and administering the control efforts are $B_1 = 200, B_2 = 200, B_3 = 400, B_4 = 800$. These constants can also serve as values that balance the different measure of quantities in the sum and may also indicate the level of importance of one of the control type over the other.

Therefore, using the parameter values from Table 2 and the above initial population data the state system evolves according to the trajectories indicated in Figure 2.

The result of using various control mechanisms can be summarized from the graph of prevalence (in Figure 3a,b) and the graph of the corresponding marginal cost functions (in Figure 3c). In the simulation, we first integrated the system without any control values. The second phase is to optimize the objective function **J** by using only the prevention controls (u_1 and u_2) and then using only the treatment controls (u_3 and u_4), finally using all the controls together. As can be seen from the graph, when all the interventions are applied simultaneously the gain in prevalence is significant in both diseases with very less total cost as compared to other combinations. Treatment is more effective as compared to the prevention controls. However, the combination of both preventive and treatment controls yields in less aggregate cost, with a slight gain also in the prevalence of both diseases.

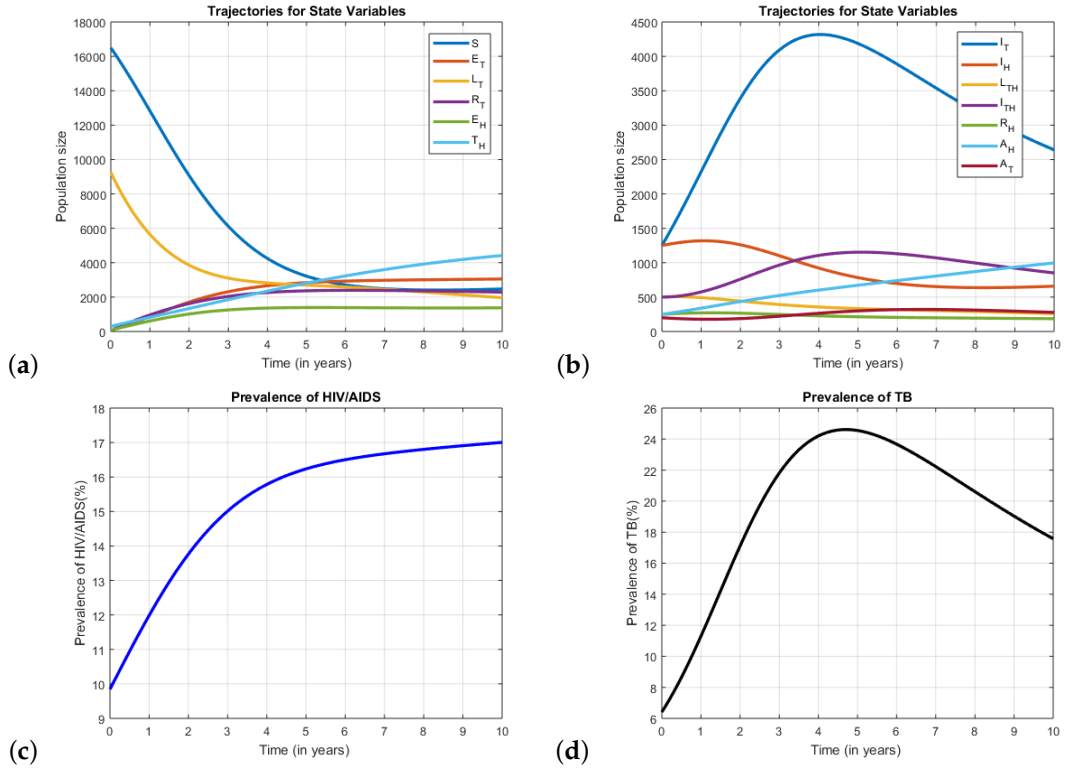

Figure 2. Graphs for the trajectories for the sub-populations in (**a**,**b**) and the corresponding values for the prevalence in (**c**,**d**), when no control efforts are applied. In this case, parameter values $\beta_1 = 1.5$ and $\beta_2 = 0.36$ are used and the rest of the parameters are as in Table 2.

Table 2. Symbols and Description of Parameters.

Parameters	Description	Value	References
Π	Recruitment rate	1500	[27]
β_1	TB Transmission rate	Variable	
β_2	HIV Transmission rate	Variable	
b	Endogenous reactivation rates for TB	0.003	[3,43]
k	Reinfection rates for TB infection	0.02	[3,43]
b_1	Endogenous reactivation rates of TB for individuals pre-infected with HIV	0.2	Assumed
k_1	Reinfection rates of TB infection for individuals pre-infected with HIV	0.5	Assumed
μ	Per capita natural rate of mortality	1/48	Assumed
d_T, d_H, d_{TA}	TB, HIV, both TB & HIV death rates	0.1, 0.2, 0.33	[9,15]
σ_0	Baseline HIV treatment rate	0.16	Assumed
τ_0	Baseline TB treatment rate	0.16	Assumed
τ_1	Rate at which individuals from L_{TH} class recover from TB infection	0.2	[9,13,15]
m	Rate at which TB-Latent individuals progress to I_T	0.5	[9,13,15]
g	Proportion of susceptibles individuals who get infected by TB and move to L_T	0.85	[3]
$\delta, \rho_1, \rho, \theta, \theta_1$	Modification parameters	1.03, 1.17, 1.07, 0.9, 1	[9]
η_a, η_c	Modification parameters	1.05, 0.08	[29]
ν, ν_1	Modification parameters	0.75, 0.5	Assumed
ε	The rate of progression of I_H to A_H	0.1	[27]
ε_1	The rate of progression of I_{TH} to A_T	0.2	Assumed
ψ	Treatment rate for individuals in A_H	0.33	[9]
ψ_1	HIV treatment rate for A_T individuals	0.33	[9]
ξ	Rate of failure to adhere to HIV treatments	0.08	Assumed
ω	Rate at which individuals in R_H progress to A_H	0.1	Assumed
r	fraction of individuals from I_{TH} that receive treatment only for TB	0.33	Assumed
p	Baseline rate at which individuals in I_{TH} receive treatments for both TB & HIV	0.40	Assumed
α_{T0}	Baseline rate of dissemination of information about TB disease	0.12	Assumed
α_{H0}	Baseline rate of dissemination of information about HIV	0.18	[29]
γ	Effectiveness of existing self-preventive measures for TB	0.93	Assumed
γ_1	Effectiveness of existing self-preventive measures for HIV	0.93	[37]
p_{T*}	Prevalence producing half of the maximum behavioural change value for TB	0.09	[3]
p_{H*}	Prevalence producing half of the maximum behavioural change value for HIV	0.09	[29]
n	Level of reaction of the population for diseases	2	[29]

In the strategy where all the controls are being applied concurrently, it it is optimal to apply all available resources to each of the control measures at the initial stage of the planning period. However, since our objective is to minimize the total aggregate cost of the population, it is optimal to decrease the intensity of the effort for educating people to apply all possible prevention methods against TB after nearly 4 years. Then, after nearly 9 years the effort on HIV education and on recruiting additional people for TB treatment can be reduced. However, giving treatment for HIV positive individuals should continue in its full intensity until the end of the planning period (see Figure 4a. On the other hand when either only prevention or only treatment controls are applied, one has to apply all the corresponding control measures at their full scale in the entire planning period (see graphs (b) and (c) in Figure 4). We observe that the result obtained when only treatment controls are applied is similar to the result reported in [9].

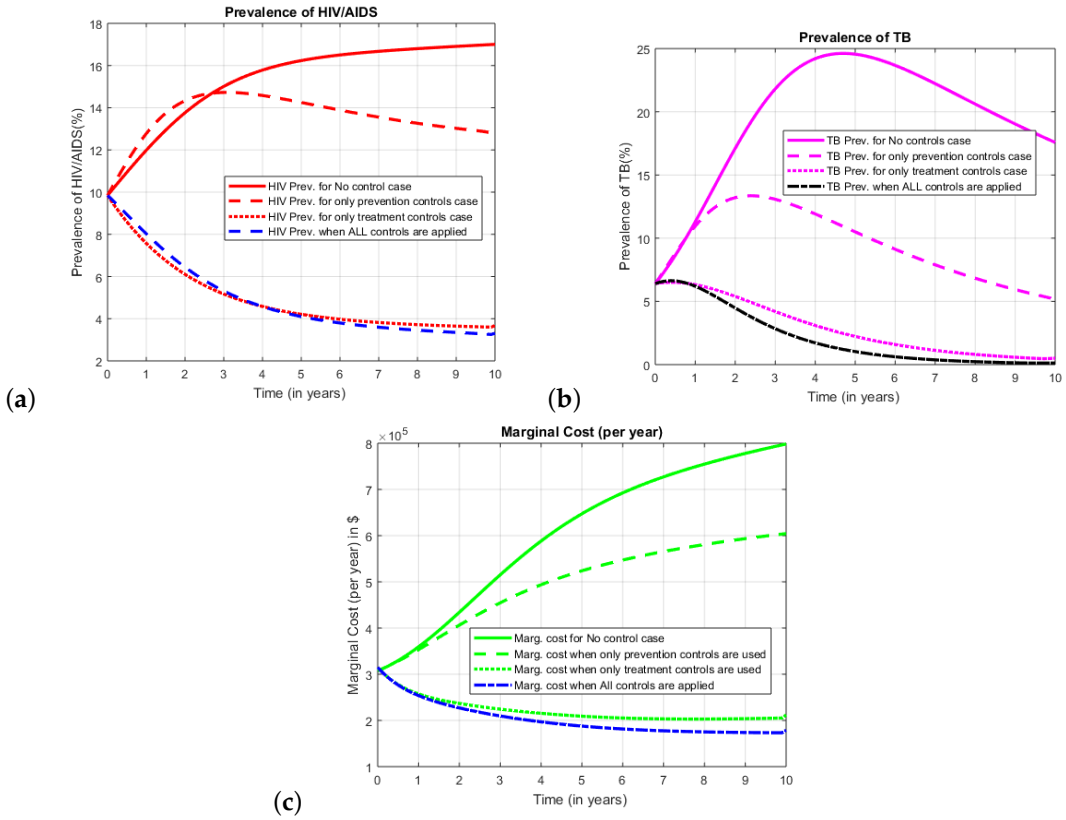

Figure 3. Graphs for the prevalence of (**a**) HIV and (**b**) TB and the corresponding values for the marginal cost in (**c**), when various combinations of control efforts are applied. All the parameter values are as described in the caption of Figure 2.

It can be seen from the results in the prevalence and marginal cost that it is optimal to include the preventive educational efforts in the control strategy. Otherwise, apply treatment control with all its full intensity could be costly for the authorities. In addition, applying the optimal control strategy reduces the burden of the two diseases to a level that they are unrecognizable in the society within 10 years. The trajectories for all the sub-populations in course of the optimal control strategy is shown in Figure 5.

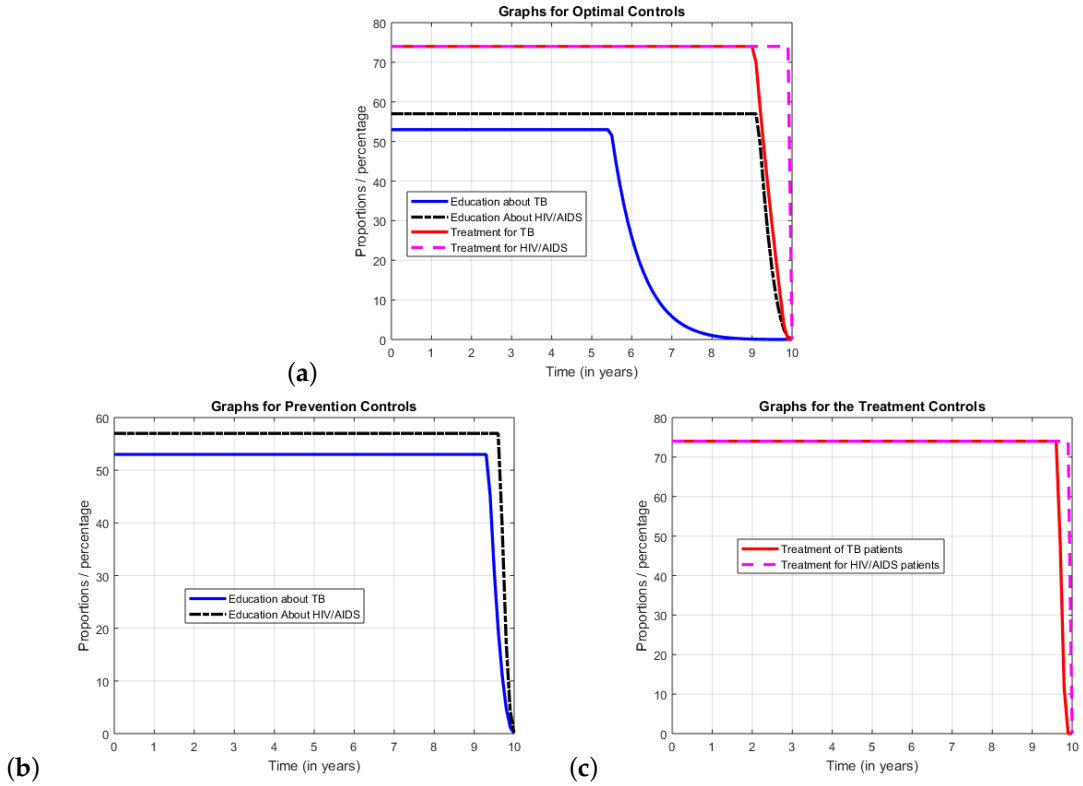

Figure 4. Graphs for the Optimal controls (**a**) when all the controls are applied and (**b**) when only preventive controls are applied, and (**c**) when only treatment controls are applied. All the parameter values are as described in the caption of Figure 2.

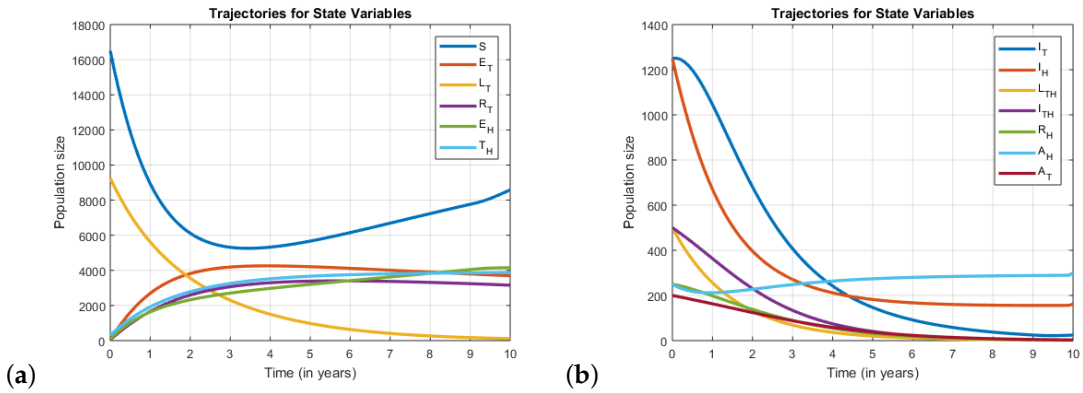

Figure 5. Graphs for the trajectories of the sub-populations when controls are applied. All the parameter values are as described in the caption of Figure 2.

When all controls are applied the size of the subpopulation under infection reduce significantly. Some of them, especially those related to TB decrease to values very close to zero. However, those values related to HIV/AIDS only cases may still remain high as compared to the TB case counterparts. This could be explained due to the fact that the treatment for TB makes the infected individuals recover from infection and their effect is seen within 6 months. However, the treatment for HIV does not make individuals fully non-infectious and the impact is seen in a longer time period. In addition, when only preventive controls are used the impact seems negligible or non at the beginning but one get a significant effect after a while. This could justified that preventive actions will make difference on the general population not immediately but at a latter stage. At the beginning even the prevalence increases slightly as there is no additional treatment regiment for those newly infected.

5. Conclusions

In this paper, we formulated and analyzed a continuous time dynamical model for the spread of TB-HIV/AIDS co-infection with prevalence dependent behaviour change. The behaviour change function is assumed to follow a logistic pattern depending on the prevalence of each of the two diseases. This made the model highly nonlinear and challenging for the mathematical analysis.

The model has been mathematically analysed both for the subsystem corresponding the cases that each disease type is isolated and in the case when there is co-infection. In addition an optimal control model that minimizes the aggregate cost of the infections (including production, administration and implementation of the control efforts). The model includes both intervention categories, preventive as well as treatment and numerical simulations are presented. In the analysis it has been indicated that the effect of prevention as well as treating the infected ones with the available pharmaceutical means affects significantly the optimal control strategy and its outcome.

From the simulation results it can be concluded that applying both preventive and treatment controls at the population level yields both economic as well as epidemiologic gains. However, one may achieve a similar epidemiologic result by applying only treatment controls if they are applied at their full scale. The impacts of the preventive controls are observed to be long term and the cost of implementing them is very low as compared to treatment. However, the cost of managing the infection is too high when the rate of transmission is relatively large. Therefore, more weight should be given to the case finding and treating strategy, but for the overall control effort to be optimal both economically and epidemiologically, implementing both prevention and treatment controls is recommended.

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