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TUBERCULOSIS AND HIV/AIDS CO-DYNAMICS: A MATHEMATICAL MODEL AND SENSITIVITY ANALYSIS

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Abstract. The study's aim is to investigate the role of treatment at any stage of infection in reducing the expansion of both Tuberculosis and HIV infection in the community. For this, we formulate and analyze a new non-linear compartmental system to study the dynamic of the diseases. The results indicate that the endemic equilibrium point for sub-models is locally and globally asymptotically stable whenever the basic reproduction number is over than 1 and unstable otherwise. A sensitivity analysis is performed in order to discover the parameters having an important impact on the reproduction number. Finally, the effect of variable transmission probabilities, treatment rates, and the stability of the co-infection endemic equilibrium point are indicated through a numerical simulation of the full model via MATLAB.

Keywords: co-infection; mathematical model; tuberculosis; HIV; sensitivity analysis.

2020 AMS Subject Classification: 70K20, 37B25, 93B35, 37M05.

1. INTRODUCTION

Tuberculosis (TB) disease is caused by small bacillus known as Mycobacterium Tuberculosis Bacteria, which spread into the air when a person with untreated TB disease sneezes, coughs or laughs; anyone close can breathe in these TB bacillus and get infected with tuberculosis, TB

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often affects the lungs, but it may additionally have an impact on other parts of the body. In accordance with the World Health Organisation (WHO) [17], Tuberculosis is the third leading cause of death, behind COVID-19 and before Acquired Immunodeficiency Syndrome (AIDS). In the year 2021, 1.6 million individuals passed on of TB. An estimated of 10.6 million people developed Tuberculosis worldwide in 2021, this concerns 6 million men, 3.4 million women and 1.2 million children. TB disease is present in all regions of the world; in 2021, the WHO having recorded the highest number of novel TB cases in Asia (46% of all novel cases), then comes the African region (23%) and the Western Pacific Region (18%) placed in third. However, it is a preventable and curable disease. In some countries, like Morocco, the Tuberculosis vaccine (BCG) is given to babies and young children as a preventive measure.

The Human Immunodeficiency Virus (HIV) is a retrovirus that assaults a person's immune system, specially CD4⁺ cells which are implied to protect the body. It uses the cell's machinery to produce other viruses. HIV can be transmitted through the trade of a variety of body liquids from contaminated individuals, such as breast milk, blood, vaginal secretions and semen. Worldwide, most HIV infections are transmitted sexually [9]. HIV remains a major global public health issue, having declared 38.4 million individuals carrying HIV at the end of 2021, two thirds of whom live in the WHO Africa region. In the same year, an estimated of 650000 individuals passed on from HIV related causes and 1.5 million of new contaminated cases [1].

HIV infection is not curable; however, providing access to accurate diagnosis and treatment, an antiretroviral drugs, notably the highly active antiretroviral therapy (HAART), HIV infection has turned into a controllable chronic illness. Untreated HIV can progress to AIDS phase where opportunistic diseases appear often after many years. Individuals having HIV are 14 to 18 times more susceptible to contract Tuberculosis compared to people who do not have HIV; they are more likely to develop tuberculosis if they possess both TB and HIV infections, since HIV manipulates the immune system by making it weak in response to TB. Worldwide, Tuberculosis is the driving cause of passing in HIV-infected patients because number one, it's the most common HIV associated opportunistic disease; secondly, if untreated, it damages the lungs rendering people susceptible to other more disseminated forms of disease.

A Co-infection is the simultaneous contamination of a single person with two or more distinctive pathogens or diverse strains of the selfsame pathogen[2]. Co-infection with different pathogen strains is especially common in HIV, but it happens in numerous other infections. Co-infection with diverse pathogen species is additionally thought to be an awfully common occurrence; the most distributed combinations are HIV and Tuberculosis; this is our current topic; HIV and Hepatitis, HIV and Malaria, and others.

Mathematical models have confirmed their utility to describe the dynamics of infectious disease, and to gain a deeper understanding of various factors that affect the disease transmission. Many papers have formulated and analyzed mathematical models using the ordinary differential equations approach to model the transmission, spread, treatment of infectious disease such as [20][14][4][8]; many others have treated co-infection like [21][12][10][16][22], in particular, D. Kirschner (1999)[9] described the dynamic interaction of HIV virus and TB bacteria with the immune system and explored the effects of treatment on TB infection in the co-infected patient; R. Naresh and A.Tripathi(2005)[15] proved that these infectious diseases(HIV and TB) become more endemic due to immigration; C.P.Bhunu(2009)[6] showed that antiretroviral therapy for AIDS cases has a strong impact on TB epidemics; Tanvi(2020) [19] incorporated the effect of ART in HIV-TB co-infectives on occurrence of IRIS complication. To the best of our knowledge, the sensitivity analysis in an HIV/AIDS-Tuberculosis model has never been performed, despite its utility in determining the value of each parameter included in the model.

The current study aims to perform sensitivity analysis on an HIV/AIDS Tuberculosis model by integrating possible transmission ways. In fact, sensitivity analysis analyze how sensitive a model is to variations in its parameters and changes in its structure. Furthermore, it is utilized to identify parameters with a high impact on the basic reproduction number, so that intervention efforts can directly target it. Interestingly, our analytical and numerical results indicate that the transmission rate of each disease might have a significant effect on disease spread, focusing on the necessity of pharmaceutical preventive measures. In addition, the impacts of treatment for single contaminated people with HIV/AIDS or TB, as well as the co-infected patients with HIV/AIDS and tuberculosis, are numerically illustrated.

The following is how this paper is structured: The model is presented in section 2, two sub-models are analyzed in Section 3, the stability of the associated disease-free equilibrium of the full model is treated in Section 4, the sensitivity analysis and the stability of the endemic equilibrium of the full model are carried out with numerical simulations in Section 5, and in Section 6, results and discussions are presented as a conclusion.

2. THE MATHEMATICAL MODEL

Motivated by the discussions above and the analysis of epidemiological models [2], we formulated a model in order to simulate the impact of treatment at any stage of the mono-disease and the co-infection disease by incorporating compartments of infected people taking specific treatments for HIV infection only, TB disease only, or HIV-TB co-infection. For this, we partitioned the overall human populace, denoted by $N(t)$ at any given time t , into nine classes depending on their infection: susceptible class $S(t)$ of both HIV and TB, Tuberculosis infected class $B(t)$, Tuberculosis treated class $T_B(t)$; HIV infected class $V(t)$ which contains, clinically speaking, the infected of the first phase (primo-infection) and the second phase (asymptomatic); AIDS class $A(t)$ of infected people who have developed opportunistic diseases; HIV treated class $T_V(t)$; HIV-TB class $I_{BV}(t)$ which brings together individuals who are contaminated with HIV and who have developed tuberculosis; AIDS-TB $I_{BA}(t)$ class which contains individuals who have AIDS disease and developed tuberculosis as an opportunistic disease or as a result of contact by an infectious individual; and treated co-infection class $T_{BV}(t)$, so that :

$$N(t) = S(t) + B(t) + T_B(t) + V(t) + A(t) + T_V(t) + I_{BV}(t) + I_{BA}(t) + T_{BV}(t).$$

Assuming that the population is homogeneous in each class and that the overall human population is variable. We consider that AIDS-contaminated individuals are isolated due to their state of illness and hence do not transmit HIV; HIV is not vertically transmitted; and treated infected individuals can't transmit HIV; therefore, susceptible people become infected with HIV following successful contact by an HIV-infected or HIV-TB co-infected individual. Thus, the force of infection for HIV is given as:

$$\lambda_V = \beta_V (V + c_1 I_{BV}),$$

where c_1 is an adjustment parameter that takes into account the increase in infectivity due to HIV-TB co-infected persons compared to HIV infected persons only, and β_V is the HIV

transmission rate.

Also, there is temporary immunity for tuberculosis contaminated individuals, and they become susceptible a new time after treatment with proportion p where $0 \leq p < 1$; susceptible people acquire TB infection by successful contact with individuals from B , I_{BV} , or I_{BA} classes at the force:

$$\lambda_B = \beta_B (B + c_2 I_{BV} + c_3 I_{BA}),$$

where $c_3 > c_2$ are an adjustment parameters that take into account the increase in infectivity due to HIV-TB and AIDS-TB co-infected persons compared to TB-infected persons only; and β_B is the TB transmission rate.

The above description is shown in the following diagram:

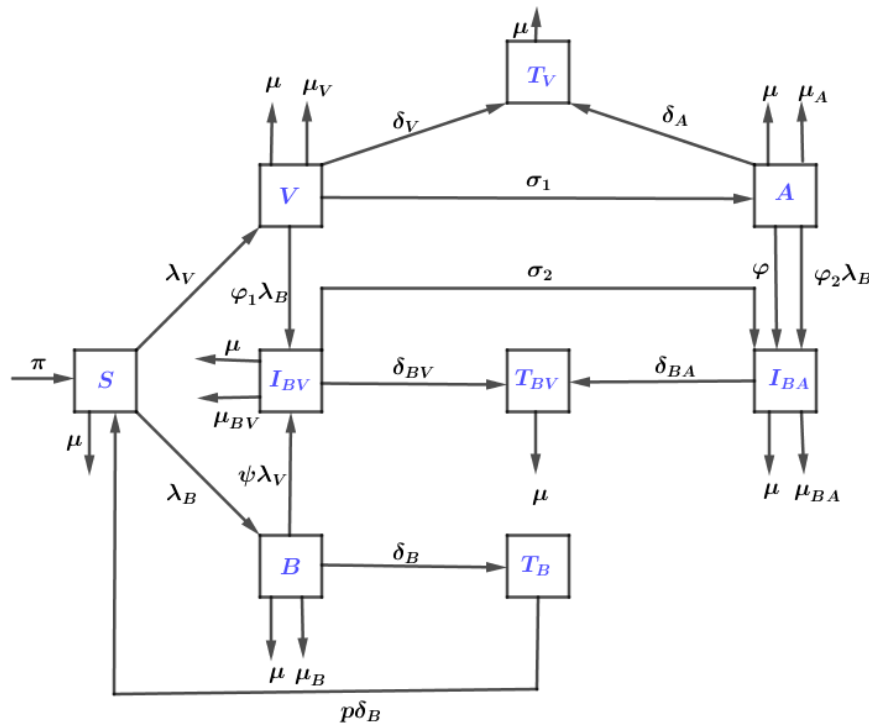


FIGURE 1. Flow diagram of the model

Using the flow diagram 1, the system of differential equations of the HIV/AIDS-TB co-infection model is given by:

$$(1) \quad \left\{ \begin{array}{l} \frac{dS}{dt} = \pi + p\delta_B T_B - (\lambda_V + \lambda_B + \mu)S \\ \frac{dB}{dt} = \lambda_B S - (\mu + \mu_B + \delta_B + \psi\lambda_V)B \\ \frac{dV}{dt} = \lambda_V S - (\mu + \mu_V + \delta_V + \sigma_1 + \varphi_1\lambda_B)V \\ \frac{dA}{dt} = \sigma_1 V - (\mu + \mu_A + \varphi_2\lambda_B + \varphi + \delta_A)A \\ \frac{dI_{BV}}{dt} = \varphi_1\lambda_B V + \psi\lambda_V B - (\mu + \mu_{BV} + \delta_{BV} + \sigma_2)I_{BV} \\ \frac{dI_{BA}}{dt} = \varphi A + \varphi_2\lambda_B A + \sigma_2 I_{BV} - (\mu + \mu_{BA} + \delta_{BA})I_{BA} \\ \frac{dT_B}{dt} = \delta_B B - (\mu + p\delta_B)T_B \\ \frac{dT_V}{dt} = \delta_V V + \delta_A A - \mu T_V \\ \frac{dT_{BV}}{dt} = \delta_{BV} I_{BV} + \delta_{BA} I_{BA} - \mu T_{BV}. \end{array} \right.$$

The parameters and state variables are described in the following tables:

Parameter	Biological Meaning
π	Recruitment rate
β_V	HIV transmission rate
β_B	TB transmission rate
μ	Natural death rate
μ_B	TB death rate
μ_V	HIV death rate
μ_A	AIDS death rate
μ_{BV}	HIV-TB death rate
μ_{BA}	AIDS-TB death rate
δ_B	TB-treatment rate
δ_V	HIV-treatment rate
δ_{BV}	HIV-TB treatment rate
δ_{BA}	AIDS-TB treatment rate
σ_1	Progression rate from HIV class to AIDS class
σ_2	Progression rate from HIV-TB class to AIDS-TB class
p	Portion of TB infected who become susceptible again
ψ	The adjustment parameter of the susceptibility of TB-infected to HIV
ϕ	Progression rate to tuberculosis as an opportunistic disease
ϕ_1	The adjustment parameter of the susceptibility of HIV-infected to tuberculosis
ϕ_2	The adjustment parameter of the susceptibility of AIDS-infected to tuberculosis
c_1	The adjustment parameter to ensure increase in infectivity due to HIV-TB infected persons compared to HIV infected persons only
c_2, c_3	The adjustment parameters to ensure increase in infectivity due to HIV-TB and AIDS-TB infected persons compared to TB infected persons only, respectively

TABLE 1. Biological Significance of Model Parameters.

Variables	Biological Significance
$N(t)$	All population
$S(t)$	Susceptible individuals
$B(t)$	TB contaminated individuals
$T_B(t)$	TB treated individuals
$V(t)$	HIV-contaminated individuals
$A(t)$	AIDS-contaminated individuals
$T_V(t)$	HIV treated individuals
$I_{BV}(t)$	HIV-TB co-infected individuals
$I_{BA}(t)$	AIDS-TB co-infected individuals
$T_{BV}(t)$	HIV-TB treated individuals

TABLE 2. Biological Significance of State Variables.

The right-hand side functions of system (1) satisfy the Picard-Lindelöf theorem [13] which gives a set of conditions under which an initial value problem has a unique solution; on the other hand, we study the positivity and boundedness of the solutions, which are essential in the proof of stability.

2.1. Positivity and boundedness of the system solution. The HIV-Tuberculosis co-infection model will be epidemiologically acceptable if all its state variables are positive and bounded at any time t ; hence, the dynamic of model (1) will be studied in the following invariant region:

$$\Omega = \left\{ (S(t), B(t), T_B(t), V(t), A(t), T_V(t), I_{BV}(t), I_{BA}(t), T_{BV}(t)) \in \mathbb{R}_+^9; 0 < N(t) \leq \frac{\pi}{\mu} \right\}.$$

2.1.1. Positivity of solutions.

Theorem 2.1. *Given that the initial conditions of the system (1), $S(0), B(0), T_B(0), V(0), A(0), T_V(0), I_{BV}(0), I_{BA}(0), T_{BV}(0)$ are all positives, the solutions $S(t), B(t), T_B(t), V(t), A(t), T_V(t), I_{BV}(t), I_{BA}(t), T_{BV}(t)$ are all positives for all $t > 0$.*

Proof. Let us define:

$$(2) \quad t^* = \sup \{t \geq 0; S(t) > 0, B(t) > 0, V(t) > 0, A(t) > 0, I_{BV}(t) > 0, I_{BA}(t) > 0, T_B(t) > 0, \\ T_V(t) > 0, T_{BV}(t) > 0\},$$

the positivity of the initial conditions and the continuity of the state variables guarantee that $t^* > 0$; if $t^* = +\infty$ then the positivity holds; but if $0 < t^* < +\infty$, then $S(t^*) = 0$ or $B(t^*) = 0$ or $V(t^*) = 0$ or $A(t^*) = 0$ or $I_{BV}(t^*) = 0$ or $I_{BA}(t^*) = 0$ or $T_B(t^*) = 0$ or $T_V(t^*) = 0$ or $T_{BV}(t^*) = 0$; in this case, from the first equation of (1), we have got:

$$\frac{dS}{dt} + (\lambda_V + \lambda_B + \mu)S \geq p\delta_B T_B;$$

using Method of Integrating Factors, we obtain:

$$e^{\int_0^{t^*} ((\lambda_V(u) + \lambda_B(u) + \mu)) du} S(t^*) \geq S(0) + \int_0^{t^*} p\delta_B T_B e^{\int_0^t (\lambda_V(u) + \lambda_B(u) + \mu) du} dt,$$

then,

$$S(t^*) \geq FS(0) + F \int_0^{t^*} p\delta_B T_B e^{\int_0^t (\lambda_V(u) + \lambda_B(u) + \mu) du} dt,$$

where $F = e^{-\int_0^{t^*} (\lambda_V(u) + \lambda_B(u) + \mu) du}$; for the meaning of t^* , $T_B(t) > 0$ for all $t \in [0, t^*]$; then $S(t^*) > 0$ hence $S(t^*) \neq 0$. We proceed in the same way, we obtain that all state variables are non-zero at t^* , which means that t^* is not finite; therefore, all solutions of the system (1) are positive. \square

2.1.2. Boundedness of solutions.

Theorem 2.2. *All the positive solutions of the co-infection model (1) are bounded in the region Ω .*

Proof. We have assumed that $N(t) = S(t) + B(t) + T_B(t) + V(t) + A(t) + I_{BV}(t) + I_{BA}(t) + T_{BV}(t)$; adding all the differential equations given in (1), the derivative of the total population $N(t)$ is given by:

$$(3) \quad \frac{dN}{dt} = \pi - \mu N - \mu_B B - \mu_V V - \mu_A A - \mu_{BV} I_{BV} - \mu_{BA} I_{BA}.$$

If there is no death from both HIV and TB, then equation (3) becomes:

$$\frac{dN}{dt} \leq \pi - \mu N,$$

using Method of Separation of Variables, we obtain:

$$N(t) \leq \frac{\pi}{\mu} - \left(\frac{\pi}{\mu} - N(0) \right) e^{-\mu t},$$

then

$$\lim_{t \rightarrow +\infty} N(t) \leq \frac{\pi}{\mu} < +\infty;$$

since N is the sum of all variables, and all variables are positive, then each of the state variables is less than $\frac{\pi}{\mu}$, which completes the demonstration. □

3. ANALYSIS OF SUB-MODELS

3.1. Tuberculosis sub-model analysis. In this section, we assume there is no HIV-contamination in the community, i.e, $V = A = I_{BA} = I_{BV} = T_V = T_{BV} = 0$, $\lambda_V = 0$, and $\lambda_B = \beta_B B$ in global model. Then, the Tuberculosis sub-model is given by:

$$(4) \quad \begin{cases} \frac{dS}{dt} = \pi + p\delta_B B - (\mu + \lambda_B) S \\ \frac{dB}{dt} = \lambda_B S - (\mu + \mu_B + \delta_B) B \\ \frac{dT_B}{dt} = \delta_B B - (\mu + p\delta_B) T_B, \end{cases}$$

where the total population is given by $N(t) = S(t) + I_B(t) + T_B(t)$, and initial conditions $S(0) > 0$, $B(0) \geq 0$, $T_B(0) \geq 0$. The following region $\Omega_B = \left\{ (S(t), B(t), T_B(t)) \in \mathbb{R}_+^3; 0 < N(t) \leq \frac{\pi}{\mu} \right\}$ will considered as a feasible region for the Tuberculosis sub-model.

Stability analysis of disease-free equilibrium

By simple calculation, we get that $E_B^0 = \left(\frac{\pi}{\mu}; 0; 0 \right)$ is the unique disease-free equilibrium point.

3.1.1. The Basic Reproduction Number of the TB sub-model. The basic reproduction number has a very important role in epidemiological models. It is characterized by the number of new infections that an infected person can create in a susceptible population. It can be used to direct and assess the disease control methods, and it is useful in predicting how severe a disease outbreak would be. According to the van den Driessche and Warmouth approach [25], the basic reproduction number denoted by \mathcal{R}_B^0 , is defined as a spectral radius of the next generation matrix FV^{-1} , where F is a matrix which contains the rates of new infections, and V is a matrix which contains the transfer of individuals inside and outside of infectious compartments. Mathematically, $\mathcal{R}_B^0 = \rho(FV^{-1})$ is the spectral radius of the next generation matrix.

Considering the system (4), we obtain the values of the transmission matrix \mathcal{F} and transition matrix \mathcal{V} as follows:

$$\mathcal{F} = \begin{pmatrix} \beta_B B S \end{pmatrix} \quad \text{and} \quad \mathcal{V} = \begin{pmatrix} (\mu + \mu_B + \delta_B) B \end{pmatrix},$$

finally, we have got:

$$\mathcal{R}_B^0 = \rho(\mathcal{F}\mathcal{V}^{-1}) = \frac{\beta_B \pi}{\mu(\mu + \mu_B + \delta_B)}.$$

3.1.2. Local stability of the disease-free equilibrium E_B^0 .

Theorem 3.1. *The disease-free equilibrium point E_B^0 is locally asymptotically stable if $\mathcal{R}_B^0 < 1$.*

Proof. The local stability of E_B^0 of system (4) can be studied from Jacobian matrix at E_B^0 , without loss a generality we pose $x_1 = \mu + \mu_B + \delta_B$ and $x_2 = \mu + \rho\delta_B$, then the matrix $J(E_B^0)$ is given by:

$$J(E_B^0) = \begin{bmatrix} -\mu & -\frac{\beta_B \pi}{\mu} & p\delta_B \\ 0 & \frac{\beta_B \pi}{\mu} - x_1 & 0 \\ 0 & \delta_B & -x_2 \end{bmatrix}.$$

Then, the characteristic equation of the above Jacobian matrix is given by:

$$P(\lambda) = \det(J(E_B^0) - \lambda I) = \begin{vmatrix} -\mu - \lambda & -\frac{\beta_B \pi}{\mu} & p\delta_B \\ 0 & \frac{\beta_B \pi}{\mu} - x_1 - \lambda & 0 \\ 0 & \delta_B & -x_2 - \lambda \end{vmatrix} = 0$$

$$\Leftrightarrow \lambda_1 = -\mu \quad \text{or} \quad \lambda_2 = x_1 (\mathcal{R}_B^0 - 1) \quad \text{or} \quad \lambda_3 = -x_2.$$

Systematically λ_1 , λ_3 are negatives, and λ_2 is also negative if and only if $\mathcal{R}_B^0 < 1$.

Hence, E_B^0 is locally asymptotically stable if $\mathcal{R}_B^0 < 1$.

□

3.1.3. Global stability of the disease free-equilibrium E_B^0 .

Theorem 3.2. *The disease-free equilibrium point E_B^0 is globally asymptotically stable if $\mathcal{R}_B^0 \leq 1$.*

Proof. To justify global stability of E_B^0 , we utilize the direct method of lyapunov; let define a lyapunov function L such that:

$$\begin{aligned} L : \quad \mathbb{R}_+^3 &\rightarrow \mathbb{R}_+ \\ (S, B, T_B) &\mapsto L(S, B, T_B) = aB \end{aligned}$$

By calculation of the derivative function of L , we have got:

$$\begin{aligned} \frac{dL}{dt} &= a \frac{dB}{dt} \\ &= a(\beta_B S B - x_1 B) \\ &= a(\beta_B S - x_1) B. \end{aligned}$$

We can choose $a = 1 > 0$, and taking account that $S \leq S^0 = \frac{\pi}{\mu}$, then

$$\begin{aligned} \frac{dL}{dt} &\leq (\beta_B S^0 - x_1) B \\ &\leq x_1 \left(\frac{\beta_B \pi}{\mu x_1} - 1 \right) B \\ &\leq x_1 (\mathcal{R}_B^0 - 1) B. \end{aligned}$$

$$\frac{dL}{dt} \leq 0 \quad \text{if} \quad \mathcal{R}_B^0 \leq 1;$$

$$\text{and} \quad \frac{dL}{dt} (E_B^0) = 0 \quad \text{if} \quad B = 0 \quad \text{or} \quad \mathcal{R}_B^0 = 1.$$

From this we see that E_B^0 is the only singleton in the set $\left\{ (S, B, T_B) \in \Omega_B; \frac{dL}{dt} = 0 \right\}$

Therefore, by the principle of [18], E_B^0 is globally asymptotically stable if $\mathcal{R}_B^0 \leq 1$.

□

Stability analysis of the endemic equilibrium point

3.1.4. Existence of tuberculosis endemic equilibrium point. The endemic equilibrium point of the Tuberculosis sub-model denoted arbitrary by $E_B^* = (S^*, B^*, T_B^*)$, it's occurs where the infection continues within the community i.e, $(S^* \neq 0, B^* \neq 0, T_B^* \neq 0)$, and it can be determined by making the right-hand side of equations (of system (2)) as zero. After some calculations, we obtain:

$$\begin{cases} \pi = p\delta_B T_B^* - (\mu + \beta_B B^*) S^* \\ \beta_B S^* = x_1 \\ \delta_B B^* = x_2 T_B^*, \end{cases}$$

then we have,

$$\begin{cases} S^* = \frac{x_1}{\mu \mathcal{R}_B^0} \\ I_B^* = \frac{\mu x_1 x_2 (\mathcal{R}_B^0 - 1)}{\beta_B (x_1 x_2 - \delta_B^2)} \\ T_B^* = \frac{\delta_B \mu x_1 (\mathcal{R}_B^0 - 1)}{\beta_B (x_1 x_2 - p\delta_B^2)}, \end{cases}$$

We can observe directly that E_B^* exist if $\mathcal{R}_B^0 > 1$.

3.1.5. Global stability of the endemic equilibrium point.

Theorem 3.3. *The endemic equilibrium point E_B^* is globally asymptotically stable if $\mathcal{R}_B^0 > 1$.*

Proof. Let define a lyapunov function L on \mathbb{R}_+^3 and with value in \mathbb{R}_+ such that :

$$L = A_1 [(S - S^*) + (B - B^*) + (T - T_B^*)]^2 + A_2 \left[B - B^* \ln \left(\frac{B}{B^*} \right) \right] + A_3 [T_B - T_B^*]^2.$$

Let pose:

$$A_1 = \frac{1}{2}, A_2 = \frac{\mu_B + 2\mu}{\beta_B}, A_3 = \frac{\mu_B + 2\mu}{2\delta_B},$$

Computing the time derivative of L , we obtain:

$$(5) \quad \frac{dL}{dt} = 2A_1 [(S - S^*) + (B - B^*) + (T - T_B^*)] \frac{d(S + B + T_B)}{dt} + A_2 \left[1 - \frac{B^*}{B} \right] \frac{dB}{dt} + 2A_3 [T_B - T_B^*] \frac{dT_B}{dt};$$

by adding the equations of the system (4), we have got:

$$\frac{dS}{dt} + \frac{dB}{dt} + \frac{T_B}{dt} = \pi - \mu N - \mu_B B,$$

assess at endemic point, we obtain:

$$\pi = \mu (S^* + B^* + T_B^*) + \mu_B B^*;$$

then,

$$\begin{aligned} (6) \quad \frac{dL}{dt} = & -\mu [(S - S^*) + (T_B - T_B^*)]^2 - 2\mu [(S - S^*) + (T_B - T_B^*)] (B - B^*) - \mu (B - B^*)^2 \\ & - \mu_B (S - S^*) (B - B^*) - \mu_B (B - B^*)^2 - \mu_B (T_B - T_B^*) (B - B^*) + \mu_B (S - S^*) (B - B^*) \\ & + 2\mu (B - B^*) (S - S^*) + \mu_B (T_B - T_B^*) (B - B^*) + 2\mu (T_B - T_B^*) (B - B^*) \\ & - \frac{\mu_B + 2\mu}{\delta_B} (\mu + p\delta_B) (T_B - T_B^*)^2, \end{aligned}$$

thus, we have got:

$$\frac{dL}{dt} = -\mu [(S - S^*) + (T_B - T_B^*)]^2 - (\mu + \mu_B) (B - B^*) - \frac{\mu_B + 2\mu}{\delta_B} (\mu + p\delta_B) (T_B - T_B^*)^2.$$

Clearly, the derivative of lyapunov function is negative on Ω_B and is zero only at the endemic equilibrium E_B^* ; we deduce that E_B^* is globally asymptotically stable if $\mathcal{R}_B^0 > 1$.

□

3.2. HIV/AIDS sub-model analysis. Proceeding in the same way, we analyze and study the HIV/AIDS sub-model. By setting $B = I_{BV} = I_{BA} = T_B = T_{BV} = 0$, we obtain the following HIV/AIDS only model:

$$(7) \quad \begin{cases} \frac{dS}{dt} = \pi - (\lambda_V + \mu)S \\ \frac{dV}{dt} = \lambda_V S - (\mu + \mu_V + \delta_V + \sigma_1)V \\ \frac{dA}{dt} = \sigma_1 V - (\mu + \mu_A + \delta_A)A \\ \frac{dT_V}{dt} = \delta_V V + \delta_A A - \mu T_V, \end{cases}$$

where:

$$\lambda_V = \beta_V V \quad \text{and} \quad \lambda_B = 0.$$

The initial conditions are $S(0) > 0, V(0) \geq 0, A(0) \geq 0, T_V(0) \geq 0$, and the total population is given by: $N(t) = S(t) + V(t) + A(t) + T_V(t)$.

To make future expressions easier to manipulate, we propose the following notations: $y_1 = \mu + \mu_V + \delta_V + \sigma_1$ and $y_2 = \mu + \mu_A + \delta_A$. The system (7) becomes:

$$(8) \quad \begin{cases} \frac{dS}{dt} = \pi - (\beta_V V + \mu)S \\ \frac{dV}{dt} = \beta_V VS - y_1 V \\ \frac{dA}{dt} = \sigma_1 V - y_2 A \\ \frac{dT_V}{dt} = \delta_V V + \delta_A A - \mu T_V. \end{cases}$$

Based on biological considerations, all feasible solutions of HIV/AIDS system (8) enter the region:

$$\Omega_V = \left\{ (S(t), V(t), A(t), T_V(t)) \in \mathbb{R}_+^4; 0 < N(t) \leq \frac{\pi}{\mu} \right\},$$

which is positively invariant.

Stability analysis of disease-free equilibrium

The HIV/AIDS sub-model has a disease-free equilibrium $E_V^0 = (S^0, V^0, A^0, T_V^0)$, it is obtained by solving the differential system (8). Taking account that $V = A = T_V = 0$, we have got:

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

3.2.1. *The Basic Reproduction Number of the HIV/AIDS sub-model.* Applying the precedent approach to determine the basic reproduction number of the HIV/AIDS sub-model, we obtain the values of \mathcal{F} and \mathcal{V} as follows:

$$\mathcal{F} = \begin{pmatrix} \beta_V VS \\ 0 \end{pmatrix} \quad \text{and} \quad \mathcal{V} = \begin{pmatrix} y_1 V \\ -\sigma_1 V + y_2 A \end{pmatrix}.$$

By evaluating the Jacobian matrix of \mathcal{F} and \mathcal{V} at $E_V^0 = (S^0, 0, 0, 0)$, the matrix F and V are obtained as follow:

$$F = \begin{pmatrix} \frac{\beta_V \pi}{\mu} & 0 \\ 0 & 0 \end{pmatrix} \quad \text{and} \quad V = \begin{pmatrix} y_1 & 0 \\ -\sigma_1 & y_2 \end{pmatrix}.$$

Therefore,

$$FV^{-1} = \begin{pmatrix} \frac{\beta_V \pi}{\mu y_1} & 0 \\ 0 & 0 \end{pmatrix}.$$

By selecting the largest eigenvalue of FV^{-1} , the basic reproduction number is

$$\mathcal{R}_V^0 = \frac{\beta_V \pi}{\mu(\mu + \mu_V + \delta_V + \sigma_1)}.$$

3.2.2. Local stability of the disease-free equilibrium E_V^0 .

Theorem 3.4. *The disease-free equilibrium point E_V^0 is locally asymptotically stable if $\mathcal{R}_V^0 < 1$.*

Proof. We evaluate the Jacobian of the system (8) at $E_V^0 = (\frac{\pi}{\mu}, 0, 0, 0)$, then we have:

$$J(E_V^0) = \begin{pmatrix} -\mu & -\frac{\beta_V \pi}{\mu} & 0 & 0 \\ 0 & \frac{\beta_V \pi}{\mu} - y_1 & 0 & 0 \\ 0 & \sigma_1 & -y_2 & 0 \\ 0 & \delta_V & \delta_A & -\mu \end{pmatrix}.$$

By putting $K_1 = -\frac{\beta_V \pi}{\mu}$, and $K_2 = \frac{\beta_V \pi}{\mu} - y_1$, we get the characteristic equation of the Jacobian matrix as follow:

$$\det(J(E_V^0) - \lambda I) = \begin{vmatrix} -\mu - \lambda & K_1 & 0 & 0 \\ 0 & K_2 - \lambda & 0 & 0 \\ 0 & \sigma_1 & -y_2 - \lambda & 0 \\ 0 & \delta_V & \delta_A & -\mu - \lambda \end{vmatrix} = 0.$$

As a result of some computations, we have:

$$(-\mu - \lambda)^2 (K_2 - \lambda) (-y_2 - \lambda) = 0,$$

then, the eigenvalues of the Jacobian matrix are:

$$\begin{cases} \lambda_1 = -\mu \\ \lambda_2 = y_1 (\mathcal{R}_V^0 - 1) \\ \lambda_3 = -y_2. \end{cases}$$

λ_1 and λ_3 are strictly negatives because the system's parameters are all strictly positives, and $\lambda_2 < 0$ if $\mathcal{R}_V^0 < 1$.

Hence, E_V^0 is locally asymptotically stable if $\mathcal{R}_V^0 < 1$. \square

3.2.3. Global stability of the disease free equilibrium E_V^0 .

Theorem 3.5. *The disease-free equilibrium point E_V^0 is globally asymptotically stable if $\mathcal{R}_V^0 \leq 1$.*

Proof. To show global stability of the disease-free equilibrium E_V^0 , we applied Lyapunov function method [7].

Assume $a \in \mathbb{R}_+^*$, we consider the following Lyapunov function:

$$\begin{aligned} L : \quad \mathbb{R}_+^4 &\rightarrow \mathbb{R}_+ \\ (S, V, A, T_V) &\mapsto L(S, V, A, T_V) = aV \end{aligned}$$

L is positive definite.

Computing the time derivative of the preceding function, we obtain:

$$\begin{aligned} \frac{dL}{dt} &= a \frac{dV}{dt} \\ &= a(\beta_V V S - y_1 V) \\ &= a(\beta_V S - y_1) V. \end{aligned}$$

Taking account that $S \leq S^0 = \frac{\pi}{\mu}$, we have got:

$$\begin{aligned} \frac{dL}{dt} &\leq a(\beta_V S^0 - y_1) V \\ &\leq ay_1 \left(\frac{\beta_V \pi}{\mu y_1} - 1 \right) V \\ &\leq ay_1 (\mathcal{R}_V^0 - 1) V. \end{aligned}$$

As all the parameters of the model are positive, it is obvious that: $\frac{dL}{dt} \leq 0$ if $\mathcal{R}_V^0 \leq 1$, and the equality holds only when $E = E_V^0$.

As a result, if $\mathcal{R}_V^0 \leq 1$, it follows from LaSalle's invariance principle that E_V^0 is globally asymptotically stable in Ω_V . \square

Stability analysis of the endemic equilibrium point

3.2.4. Existence of the HIV/AIDS endemic equilibrium point. The endemic equilibrium point of the HIV/AIDS sub-model is obtained by resolving the following system:

$$(9) \quad \begin{cases} \pi - (\beta_V V^* + \mu) S^* = 0 \\ \beta_V V^* S^* - y_1 V^* = 0 \\ \sigma_1 V^* - y_2 A^* = 0 \\ \delta_V V^* + \delta_A A^* - \mu T_V^* = 0. \end{cases}$$

The first equation of the system (9) gives

$$S^* = \frac{\pi}{\beta_V V^* + \mu}.$$

By inserting S^* in the second equation of (9), we get:

$$(10) \quad V^* = \frac{\pi}{y_1} - \frac{\mu}{\beta_V} = \frac{\mu}{\beta_V} \left(\frac{\beta_V \pi}{\mu y_1} - 1 \right) = \frac{\mu}{\beta_V} (\mathcal{R}_V^0 - 1),$$

substituting V^* in the expression of S^* , it yields:

$$(11) \quad S^* = \frac{y_1}{\beta_V} = \frac{\pi}{\mu \mathcal{R}_V^0}.$$

From the third equation of the system (9), we find:

$$A^* = \frac{\sigma_1}{x_2} V^*,$$

with the expression of V^* , it becomes:

$$(12) \quad A^* = \frac{\pi \sigma_1}{y_1 y_2} - \frac{\mu \sigma_1}{\beta_V y_2} = \frac{\mu \sigma_1}{\beta_V y_2} \left(\frac{\beta_V \pi}{\mu y_1} - 1 \right) = \frac{\mu \sigma_1}{\beta_V y_2} (\mathcal{R}_V^0 - 1).$$

The fourth equation of the system (9) gives:

$$T_V^* = \frac{\delta_V V^* + \delta_A A^*}{\mu}.$$

By inserting (10) and (12) in the expression of T_V^* , we have:

$$(13) \quad T_V^* = \left(\frac{\delta_V}{\beta_V} + \frac{\delta_A \sigma_1}{y_2 \beta_V} \right) (\mathcal{R}_V^0 - 1).$$

It is clear that S^*, V^*, A^*, T_V^* are all positives if $\mathcal{R}_V^0 > 1$. Hence, E_V^* exists whenever $\mathcal{R}_V^0 > 1$.

3.2.5. Global Stability of the HIV/AIDS endemic equilibrium point.

Theorem 3.6. *The endemic equilibrium point E_V^* is globally asymptotically stable if $\mathcal{R}_V^0 > 1$.*

Proof. Let the Lyapunov function

$$\begin{aligned} L : \quad \mathbb{R}_+^4 &\rightarrow \mathbb{R}_+ \\ (S, V, A, T_V) &\mapsto L(S, V, A, T_V) = a_1 \left(S - S^* - S^* \ln \left(\frac{S}{S^*} \right) \right) \\ &\quad + a_2 \left(V - V^* - V^* \ln \left(\frac{V}{V^*} \right) \right). \end{aligned}$$

Then,

$$\begin{aligned} \frac{dL}{dt} &= a_1 \left(\frac{dS}{dt} - \frac{S^*}{S} \frac{dS}{dt} \right) + a_2 \left(\frac{dV}{dt} - \frac{V^*}{V} \frac{dV}{dt} \right) \\ &= a_1 \left(1 - \frac{S^*}{S} \right) \frac{dS}{dt} + a_2 \left(1 - \frac{V^*}{V} \right) \frac{dV}{dt} \\ &= a_1 \left(1 - \frac{S^*}{S} \right) (\pi - (\lambda_V + \mu)S) + a_2 \left(1 - \frac{V^*}{V} \right) (\lambda_V S - (\mu + \mu_V + \delta_V + \sigma_1)V). \end{aligned}$$

At the endemic equilibrium point E_V^* , we obtain from the system (4) that $\pi = (\lambda_V^* + \mu)S^*$, and $\mu + \mu_V + \delta_V + \sigma_1 = \frac{\lambda_V^* S^*}{V^*}$.

Then, we have:

$$\begin{aligned} \frac{dL}{dt} &= a_1 \left(1 - \frac{S^*}{S} \right) ((\lambda_V^* + \mu)S^* - (\lambda_V + \mu)S) + a_2 \left(1 - \frac{V^*}{V} \right) \left(\lambda_V S - \lambda_V^* S^* \frac{V}{V^*} \right) \\ &= -a_1 \mu \frac{(S - S^*)^2}{S} + (a_1 + a_2) \beta_V S^* V^* + (a_1 - a_2) \beta_V S^* V + (a_2 - a_1) \beta_V S V \\ &\quad - a_1 \beta_V \frac{S^{*2}}{S} V^* - a_2 \beta_V S V^*. \end{aligned}$$

Taking $a_1 = a_2$, we get:

$$\begin{aligned} \frac{dL}{dt} &= -a_1 \mu \frac{(S - S^*)^2}{S} + 2a_1 \beta_V S^* V^* - a_1 \beta_V \frac{S^{*2}}{S} V^* - a_1 \beta_V S V^* \\ &= -a_1 \mu \frac{(S - S^*)^2}{S} + a_1 \beta_V S^* V^* \left(2 - \frac{S^*}{S} - \frac{S}{S^*} \right). \end{aligned}$$

Using the property of arithmetic-geometric mean inequality, we can prove that $2 - \frac{S^*}{S} - \frac{S}{S^*} \leq 0$, and for $a_1 > 0$, we get that : $\frac{dL}{dt} \leq 0$.

Furthermore, $\frac{dL}{dt} = 0$ if and only if $E = E_V^*$. Therefore, we conclude by LaSalle's invariance principle that E_V^* is globally asymptotically stable if $\mathcal{R}_V^0 > 1$. \square

4. THE HIV/AIDS-TUBERCULOSIS CO-INFECTION MODEL ANALYSIS

This section will describe the full model equilibrium point, the basic reproduction number of the system, and the local stability analysis of the disease-free equilibrium point.

The disease-free equilibrium of the HIV/AIDS-Tuberculosis system (1) is:

$$E_{BV}^0 = \left(\frac{\pi}{\mu}, 0, 0, 0, 0, 0, 0, 0 \right).$$

4.1. The Basic Reproduction Number of the HIV-Tuberculosis co-infection model. Applying the next generation operator method, the matrix of new infections F , and the matrix of transmission infections V are respectively given as follows:

$$F = \begin{pmatrix} \beta_B \frac{\pi}{\mu} & 0 & 0 & \beta_B c_2 \frac{\pi}{\mu} & \beta_B c_3 \frac{\pi}{\mu} \\ 0 & \beta_V \frac{\pi}{\mu} & 0 & \beta_V c_1 \frac{\pi}{\mu} & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \end{pmatrix}$$

and

$$V = \begin{pmatrix} \mu + \mu_B + \gamma_B & 0 & 0 & 0 & 0 \\ 0 & \mu + \mu_V + \delta_V + \sigma_1 & 0 & 0 & 0 \\ 0 & -\sigma_1 & \mu + \mu_A + \delta_A + \varphi & 0 & 0 \\ 0 & 0 & 0 & \mu + \mu_{BV} + \delta_{BV} + \sigma_2 & 0 \\ 0 & 0 & -\varphi & -\sigma_2 & \mu + \mu_{BA} + \delta_{BA} \end{pmatrix}.$$

The spectral radius of the matrix FV^{-1} was obtained, using MAPLE Calculator, as follow:

$$\mathcal{R}_{BV}^0 = \rho(FV^{-1}) = \max \left\{ \frac{\beta_B \pi}{\mu(\mu + \mu_B + \delta_B)}, \frac{\beta_V \pi}{\mu(\mu + \mu_V + \delta_V + \sigma_1)} \right\}.$$

Given that: $\mathcal{R}_B^0 = \frac{\beta_B \pi}{\mu(\mu + \mu_B + \delta_B)}$, and $\mathcal{R}_V^0 = \frac{\beta_V \pi}{\mu(\mu + \mu_V + \delta_V + \sigma_1)}$, we have got the expression of The basic reproduction number of the HIV/AIDS-Tuberculosis co-infection model as:

$$\mathcal{R}_{BV}^0 = \max \{ \mathcal{R}_B^0, \mathcal{R}_V^0 \}.$$

4.2. Local stability of the disease free equilibrium of the HIV-Tuberculosis co-infection model.

Theorem 4.1. *The disease-free equilibrium E_{BV}^0 is locally asymptotically stable if $\mathcal{R}_{BV}^0 < 1$.*

Proof. The Jacobian matrix of the system (1) at $E_{BV}^0 = (\frac{\pi}{\mu}, 0, 0, 0, 0, 0, 0, 0, 0)$ is given by:

$$J(E_{BV}^0) = \begin{pmatrix} -\mu & -\frac{\beta_B \pi}{\mu} & -\frac{\beta_V \pi}{\mu} & 0 & -\frac{\beta_V c_1 \pi}{\mu} - \frac{\beta_B c_2 \pi}{\mu} & -\frac{\beta_B c_3 \pi}{\mu} & p \delta_B & 0 & 0 \\ 0 & m_2 & 0 & 0 & \frac{\beta_B c_2 \pi}{\mu} & \frac{\beta_B c_3 \pi}{\mu} & 0 & 0 & 0 \\ 0 & 0 & m_3 & 0 & \frac{\beta_V c_1 \pi}{\mu} & 0 & 0 & 0 & 0 \\ 0 & 0 & \sigma_1 & m_4 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & m_5 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & \varphi & \sigma_2 & m_6 & 0 & 0 & 0 \\ 0 & \delta_B & 0 & 0 & 0 & 0 & m_7 & 0 & 0 \\ 0 & 0 & \delta_V & \delta_A & 0 & 0 & 0 & -\mu & 0 \\ 0 & 0 & 0 & 0 & \delta_{BV} & \delta_{BA} & 0 & 0 & -\mu \end{pmatrix},$$

where

$$\begin{cases} m_2 = \frac{\beta_B \pi}{\mu} - (\mu + \mu_B + \delta_B) \\ m_3 = \frac{\beta_V \pi}{\mu} - (\mu + \mu_V + \delta_V + \sigma_1) \\ m_4 = -(\mu + \mu_A + \delta_A + \varphi) \\ m_5 = -(\mu + \mu_{BV} + \delta_{BV} + \sigma_2) \\ m_6 = -(\mu + \mu_{BA} + \delta_{BA}) \\ m_7 = -p \delta_B. \end{cases}$$

The characteristic equation of the Jacobian matrix at E_{BV}^0 is given as:

$$(-\mu - \lambda)^3 (m_2 - \lambda) (m_3 - \lambda) (m_4 - \lambda) (m_5 - \lambda) (m_6 - \lambda) (m_7 - \lambda) = 0,$$

then, the eigenvalues of the Jacobian matrix $J(E_{BV}^0)$ are:

$$\left\{ \begin{array}{l} \lambda_1 = \lambda_2 = \lambda_3 = -\mu \\ \lambda_4 = m_2 = (\mu + \mu_B + \delta_B) (\mathcal{R}_B^0 - 1) \\ \lambda_5 = m_3 = (\mu + \mu_V + \delta_V + \sigma_1) (\mathcal{R}_V^0 - 1) \\ \lambda_6 = m_4 = -(\mu + \mu_A + \varphi + \delta_A) \\ \lambda_7 = m_5 = -(\mu + \mu_{BV} + \delta_{BV} + \sigma_2) \\ \lambda_8 = m_6 = -(\mu + \mu_{BA} + \delta_{BA}) \\ \lambda_9 = -p\delta_B. \end{array} \right.$$

Since the system's parameters are all strictly positive, $\lambda_1, \lambda_2, \lambda_3, \lambda_6, \lambda_7, \lambda_8, \lambda_9$ are strictly negatives.

On the other hand, $\lambda_4 < 0$ if $\mathcal{R}_B^0 < 1$, and $\lambda_5 < 0$ if $\mathcal{R}_V^0 < 1$.

Knowing that $\mathcal{R}_{BV}^0 = \max\{\mathcal{R}_B^0, \mathcal{R}_V^0\}$, we state that E_{BV}^0 is locally asymptotically stable if $\mathcal{R}_{BV}^0 < 1$. \square

4.3. Existence of the endemic equilibrium point of the HIV/AIDS-Tuberculosis co-infection Model. The endemic equilibrium point of the HIV/AIDS-Tuberculosis co-infection system (1), denoted by E_{BV}^* , is given by:

$$\left\{ \begin{array}{l} S^* = \frac{\pi + p\delta_B T_B^*}{\lambda_V^* + \lambda_B^* + \mu} \\ B^* = \frac{\lambda_B^* S^*}{\mu + \mu_B + \delta_B + \psi \lambda_V^*} \\ V^* = \frac{\lambda_V^* S^*}{\mu + \mu_V + \delta_V + \sigma_1 + \varphi_1 \lambda_B^*} \\ A^* = \frac{\sigma_1 V^*}{\mu + \mu_A + \varphi_2 + \lambda_B^* + \varphi + \delta_A} \\ I_{BV}^* = \frac{\varphi_1 \lambda_B^* V^* + \psi \lambda_V^* B^*}{\mu + \mu_{BV} + \delta_{BV} + \sigma_2} \\ I_{BA}^* = \frac{(\varphi + \varphi_2 \lambda_B^*) A^* + \sigma_2 I_{BV}^*}{\mu + \mu_{BA} + \delta_{BA}} \\ T_B^* = \frac{\delta_B B^*}{\mu + p\delta_B} \\ T_V^* = \frac{\delta_V V^* + \delta_A A^*}{\mu} \\ T_{BV}^* = \frac{\delta_{BV} I_{BV}^* + \delta_{BA} I_{BA}^*}{\mu}. \end{array} \right.$$

The analytical expression of E_{BV}^* is difficult to find. For this, we show its existence using numerical simulations. If HIV infection rules out, tuberculosis persists in the population. This means that HIV-free equilibrium point E_B^* occurs if $\mathcal{R}_B^0 > 1$ and $\mathcal{R}_V^0 < 1$ (i.e., $\mathcal{R}_{BV}^* > 1$). Conversely, TB-free equilibrium point E_V^* occurs if $\mathcal{R}_V^0 > 1$ and $\mathcal{R}_B^0 < 1$ (i.e., $\mathcal{R}_{BV}^* > 1$), which means that there is persistence of HIV infection while TB infection dies out.

When the two diseases coexist, attention turns to a HIV/AIDS-Tuberculosis endemic equilibrium point; Figure 3 indicates that if $\mathcal{R}_{BV}^* > 1$ (i.e. $\mathcal{R}_B^0 > 1$ and $\mathcal{R}_V^0 > 1$), then E_{BV}^* is globally asymptotically stable, which means that E_{BV}^* exists.

5. NUMERICAL SIMULATIONS AND SENSITIVITY ANALYSIS

Using Matlab, numerical simulations for the HIV/AIDS-Tuberculosis co-infection model given by the system (1) are done with the objective of describing the behavior of the system solutions over time and validating the previous results. Table 3 lists the parameters utilized in the simulations:

Parameter	Values
π	250
μ	0.2
μ_B	0.3
μ_V	0.2
μ_A	0.233
μ_{BV}	0.3
μ_{BA}	0.32
δ_B	0.7
δ_V	0.6
δ_A	0.3
δ_{BV}	0.498
δ_{BA}	0.23
σ_1	0.08
σ_2	0.3105
p	0.02
ψ	1
φ	0.02
φ_1	1.1
φ_2	1.4
c_1, c_2, c_3	1, 1, 1

TABLE 3. Fundamental model parameter..

5.1. HIV/AIDS-Tuberculosis co-infection model simulations. Here, Figure 2 shows that all the state variables are converging to the disease-free equilibrium point of the full model $E_{VB}^0 = \left(\frac{\pi}{\mu}, 0, 0, 0, 0, 0, 0, 0\right)$ for the set of parameters listed in Table 3 with $\beta_V = 0.0008$ and $\beta_B = 0.0009$. The basic reproduction numbers \mathcal{R}_B^0 and \mathcal{R}_V^0 for this set of parameters are 0.9375 and 0.9259 respectively, which means that the two diseases disappear from the population, and the disease-free equilibrium of the HIV/AIDS-Tuberculosis co-infection model is globally asymptotically stable.

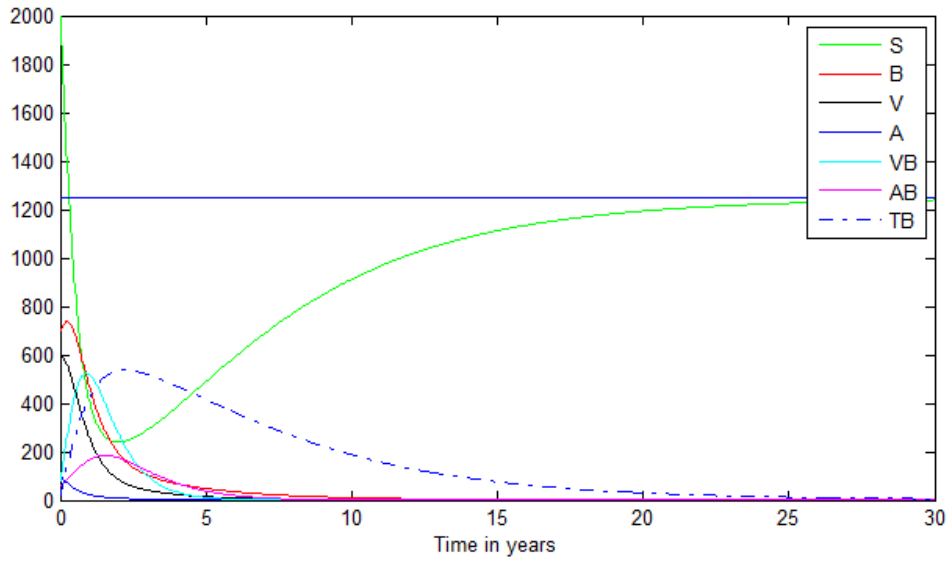


FIGURE 2. Dynamic comportement of infected classes of full HIV/AIDS-Tuberculosis co-infection model at $\mathcal{R}_V^0 < 1$ and $\mathcal{R}_B^0 < 1$.

Once more, system (1) is simulated through varying the parameters β_V as 0.008, β_B as 0.009, and conserving all other parameters as shown in Table 3. For this set of parameters, we get $\mathcal{R}_B^0 = 9.3750$ and $\mathcal{R}_V^0 = 9.2593$. Figure 3 indicates that whenever the co-infection equilibrium point E_{VB}^* exists, it is globally asymptotically stable. That means for $\mathcal{R}_V^0 > 1$ and $\mathcal{R}_B^0 > 1$, both the diseases will co-exist.

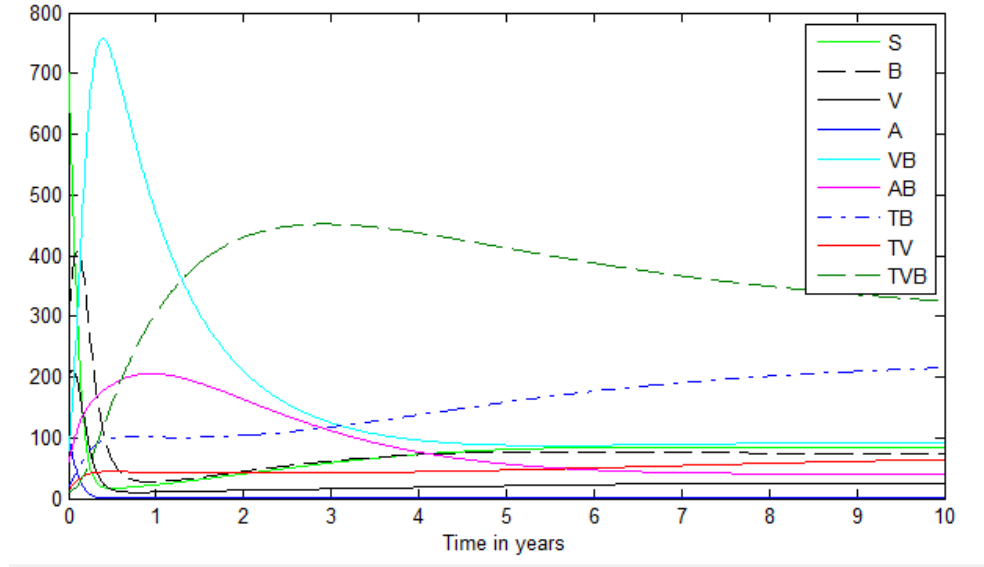


FIGURE 3. The stability of the endemic equilibrium point of the HIV/AIDS-Tuberculosis co-infection model at $\mathcal{R}_V^0 > 1$ and $\mathcal{R}_B^0 > 1$.

5.2. Sensitivity analysis of the model parameters. Sensitivity analysis is used to determine which are the most important factors influencing the disease transmission and infection control in the population. Epidemiologically, this study is utilized to identify parameters with a significant effect on the basic reproduction number and which should be the focus of intervention efforts [24]. To do this, We define the normalized forward sensitivity index of a variable with regard to a parameter as the ratio of the relative change in a variable to the relative change in a parameter. In cases when the variable is a differentiable function of the parameter, the sensitivity index can also be created alternatively using partial derivatives, as illustrated below:

Definition 5.1. *The normalized forward sensitivity index of \mathcal{R}_0 , that depends differentially on a parameter p , is defined by:*

$$\Upsilon_p^{\mathcal{R}_0} = \frac{\partial \mathcal{R}_0}{\partial p} \times \frac{p}{\mathcal{R}_0}.$$

A highly sensitive parameter needs to be attentively evaluated because a small change might result in significant quantitative change. On the other hand, a parameter that is insensitive requires less effort to estimate given that minor change will not significantly affect the quantity of interest. Moreover, the positive sign of the sensitivity index indicates that an increase (or

decrease) in the parameter's value will cause an increase (or decrease) in \mathcal{R}_0 , which asymptotically results in the persistence (or eradication) of the disease in the community.

Taking account the parameters values listed in Table 3 and the explicit formula for each basic reproduction number, the sensitivity indices of \mathcal{R}_B^0 and \mathcal{R}_V^0 are given in Tables 4 and 5, respectively.

Parameter	Sensitivity index
π	+1
β_B	+1
μ	-1.1667
μ_B	-0.2500
δ_B	-0.5833

TABLE 4. Sensitivity indices of \mathcal{R}_B^0 .

Parameter	Sensitivity index
π	+1
β_V	+1
μ	-1.1852
μ_V	-0.1852
δ_V	-0.5556
σ_1	-0.0741

TABLE 5. Sensitivity indices of \mathcal{R}_V^0 .

The results presented in tables 4 and 5 have significant implications for HIV and Tuberculosis transmission and control. From those tables, the most sensitive parameters to \mathcal{R}_B^0 and \mathcal{R}_V^0 are β_B , β_V , δ_B and δ_V . In fact, we have $\Upsilon_{\beta_B}^{\mathcal{R}_B^0} = +1$ and $\Upsilon_{\beta_V}^{\mathcal{R}_V^0} = +1$, which means that increasing (or decreasing) β_B and β_V by 10% increases (or decreases) \mathcal{R}_B^0 and \mathcal{R}_V^0 by 10% respectively. But also, $\Upsilon_{\delta_B}^{\mathcal{R}_B^0} = -0.5833$, which means that increasing δ_B by 10% decreases \mathcal{R}_B^0 by 5.8%, and $\Upsilon_{\delta_V}^{\mathcal{R}_V^0} = -0.5556$, which means that increasing δ_V by 10% decreases \mathcal{R}_V^0 by 5.5% and the number of the infectious individuals diminish accordingly.

Hence, we can state that each basic reproduction number is significantly decreased with a smaller transmission rate and a greater treatment rate. That is why investing more in single-illness infection therapies is significantly more efficient at reducing infection and deaths resulting from disease. This is corroborated by the recommendations of the WHO [3] which cites the protocol to be followed during the period of mono-infection on the one hand, and co-infection on the other hand; including anti-tuberculosis treatment to cure it since it is a curable disease; HAART treatment which must be taken at the time of diagnosis for those infected with HIV that is also considered as prevention of the onset of tuberculosis [23]; and the treatment of the co-infection which is a combination of the two treatments with a precise timing of taking which depends on the count of the CD4 cells of the co-infected patient [5]. Also, since the effect of all these parameters is coupled with two key parameters, the rate of transmission and the rate of cure for each disease, we address these two key parameters instead of addressing all the parameters. For this, we determine the thresholds at which each basic reproduction rate becomes less than one. This is presented in what follow.

5.3. Simulations of the reproduction numbers with various parameter values. Utilizing data from Table 3 and the ode45 technique, numerical simulations were carried out for the reproduction numbers with varied treatment and transmission rates values. Here, we obtained the results shown in Figures 4, 5.

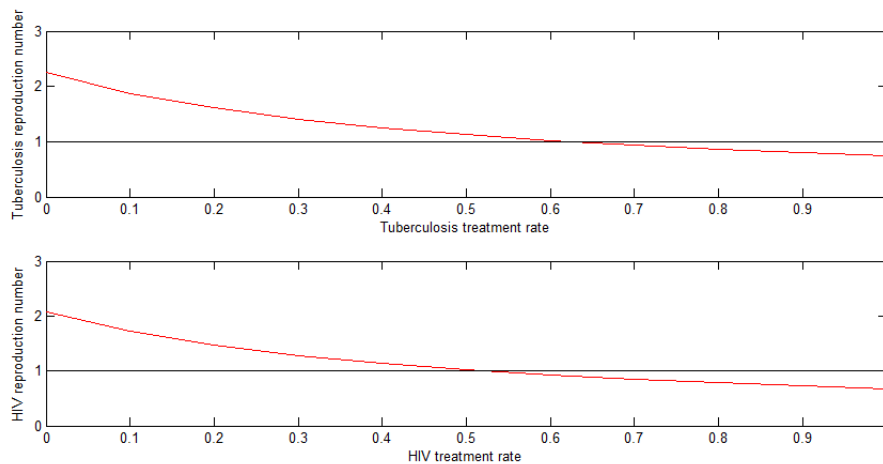


FIGURE 4. Simulation of \mathcal{R}_B^0 and \mathcal{R}_V^0 respectively for different values of treatment rates γ_B and γ_V

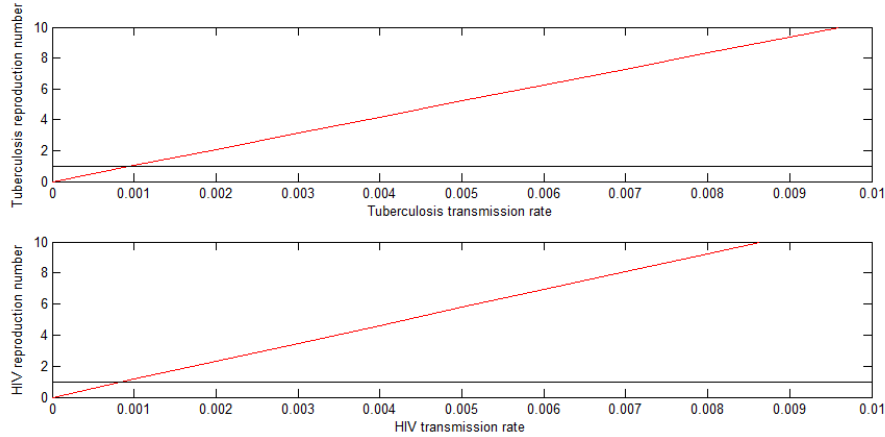


FIGURE 5. Simulation of \mathcal{R}_B^0 and \mathcal{R}_V^0 respectively for different values of transmission rates β_B and β_V

It is obvious from Figure 4 that tuberculosis infection dies out whenever $\delta_B > 0.625$ at $\beta_B = 0.0009$, and HIV/AIDS infection disappears if $\delta_V > 0.52$ at $\beta_V = 0.0008$. Similarly, Figure 5 shows that tuberculosis infection dies out if $\beta_B < 0.00096$, while the HIV-AIDS infection dies out if $\beta_V < 0.000864$.

5.4. Simulations of infected classes with various treatment rates. Using the numerical simulations, Figures from 6 to 10 have illustrated the impacts of treatment at each infected class of the HIV/AIDS-Tuberculosis co-infection model (1).

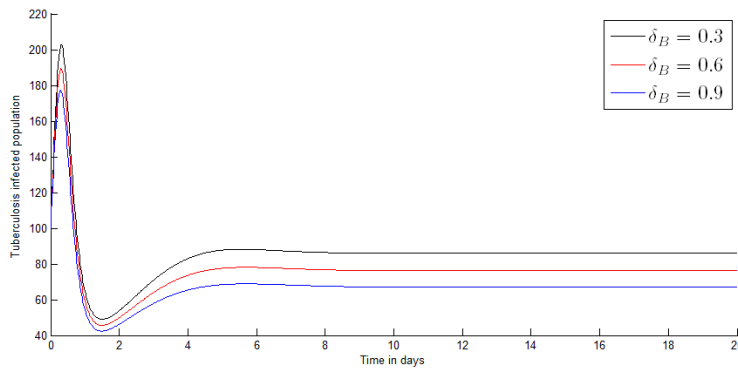


FIGURE 6. Treatment's impact on tuberculosis infection

Figure 6 indicates that when the tuberculosis treatment rate δ_B increases from 0.3 to 0.9, the tuberculosis infection decreases.

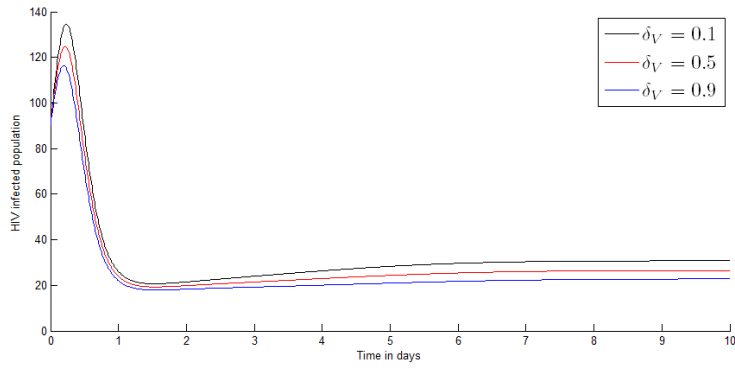


FIGURE 7. Treatment’s impact on HIV infection

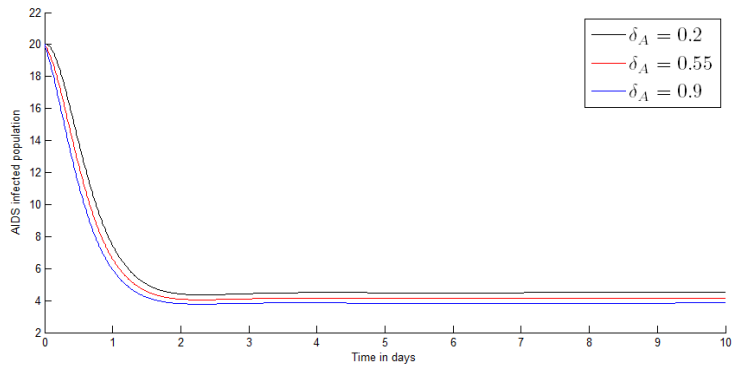


FIGURE 8. Treatment’s impact on AIDS infection

Similarly, Figures 7 and 8 show that increasing δ_V from 0.1 to 0.9 and δ_A from 0.2 to 0.9 will decrease HIV and AIDS infections respectively.

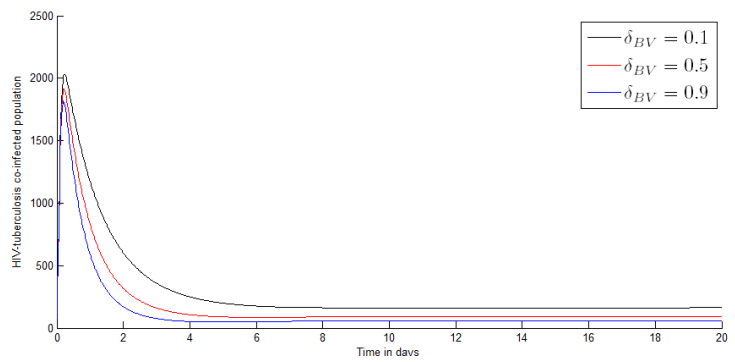


FIGURE 9. Treatment’s impact on HIV-tuberculosis co-infection

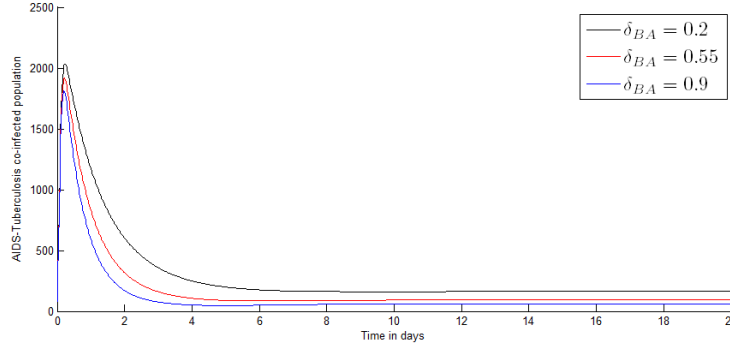


FIGURE 10. Treatment's impact on AIDS-tuberculosis co-infection

Figure 9 indicates that the number of HIV-Tuberculosis co-infected persons has significantly dropped with an increment in treatment rate δ_{BV} . Furthermore, the impact of treatment in AIDS-Tuberculosis co-infected individuals is also considered as the number of those patients decreases when δ_{BA} rises from 0.2 to 0.9. This fact is shown in Figure 10.

6. CONCLUSION

In this paper, the proposed model is a mathematical model whose objective is the examination of the feasible expansion of the co-infection of HIV and TB diseases. The positivity and boundedness properties of the model solutions are proved in a biologically feasible region. In addition, we computed and analyzed the local and global stabilities of the equilibrium points of the sub-models in terms of the basic reproduction numbers. Mathematical analysis proves that the disease free equilibrium points are locally and globally stable whenever $\mathcal{R}_B^0 < 1$ and $\mathcal{R}_V^0 < 1$; Otherwise, there exists the endemic equilibrium point of each disease which is locally and globally asymptotically stable. Accordingly, when $\mathcal{R}_{BV}^0 > 1$, the stability of the co-infection equilibrium point E_{BV}^0 is established. Moreover, sensitivity analysis results shows that the principal factors involved in the illness spreading are the transmission rates and the treatment rates too. Finally, numerical simulations show that minimizing the spread of the co-infection HIV/AIDS-Tuberculosis requires an important reduction and a simultaneous increase in the transmission rate and the treatment rate respectively.

CONFLICT OF INTERESTS

The authors declare that there is no conflict of interests.

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