Mathematical modelling and sensitivity analysis of HIV-TB co-infection.

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Abstract

In this paper, we formulated a new nine (9) compartmental mathematical model to have better understanding of parameters that influence the dynamical spread of Human immunodeficiency virus (HIV) interacting with Tuberculosis (TB) in a population. The model is analyzed for all the parameters responsible for the disease spread in order to find the most sensitive parameters out of all.

Sub models of HIV and TB only were considered first, followed by the full HIV-TB co-infection model. Stability of HIV model only, TB model only and full model of HIV-TB co-infection were analyzed for the existence of the disease free and endemic equilibrium points. Basic Reproduction Number (R_0) was obtained using next generation matrix method (NGM), and it has been shown that the disease free equilibrium point is locally asymptotically stable whenever $R_0 < 1$ and unstable whenever this threshold exceeds unity. i.e. $R_0 > 1$.

The relative sensitivity solutions of the model with respect to each of the parameters is calculated, Parameters are grouped into two categories: sensitive parameters and insensitive parameters.

Numerical simulation was carried out by maple software using Runge-kunta method, to show the effect of each parameter on the dynamical spread of HIV-TB co-infection, i.e. detection of infected undetected individuals plays a vital role, it decreases infected undetected individuals. Also, increased in effective contact rate has a pronounced effect on the total population; it decreases susceptible individuals and increases the infected individuals. However, effective contact rate needs to be very low in order to guaranteed disease free environment.

Keywords

Human Immunodeficiency Virus; Tuberculosis; Reproduction number; Critical points; Sensitivity analysis; Stability.

Academic discipline

Mathematics

Subject classification

Mathematics subject classification

(Method/Approach)

Bio-Mathematics

1. INTRODUCTION.

Tuberculosis (TB) is an airborne infectious disease caused by Mycobacterium tuberculosis which affects the lung and other parts of the body [3]. TB infection occurs when droplet nuclei containing tubercle bacilli are inhaled into the lungs and deposited in the alveoli. It is spread when individuals with active TB disease cough, sneeze, sing, laugh or through interaction with infectious individual. After a person becomes infected, the tuberculosis bacteria are controlled by the person's immune system and the infection becomes latent. The infection becomes active, when the bacteria spread out of control most especially when the tubercle bacilli overwhelm the immune system and break out of the tubercles in the alveoli and spread to the lungs and other parts of the body via blood stream [24]. The risk of infection with the tubercle bacilli is directly related to the degree of exposure and less to genetic or other host factors. In those with HIV, the risk of developing active TB increases to nearly 18% per year [3,5]. TB is a major global cause of disability and death, especially in developing countries. Even in many countries where its overall incidence is low, TB remains a problem; In 2006, TB caused an estimated 1.7 million deaths and 8.9 million new cases of infection [23].

The early symptoms of active Tuberculosis include: Weight loss, Fever, loss of appetite, coughing out of blood, night sweats, and back pain among others.

TB is curable disease by the implementation of antibiotics, which decrease the mortality of TB to a minimal level, for instance, a 70% reduction in TB related mortality was recorded in the United State of America (USA) between 1945-1955 [2]. Many doctors prefer to hospitalize the patient in order to observe him or her during treatment, the method is called Direct Observed Therapy Short Course (DOTS), huge success has been achieved by this method. [1].

Human Immunodeficiency Virus (HIV) is caused by retrovirus infection; it progresses to Acquired Immunodeficiency Syndrome (AIDS) when proper treatment is not taken. HIV severely weakens immune system by attacks many blood cells, it causes havoc on the T-cell in the blood by destroying and decreasing their number, leading to decline in body's immunity to fight infection [20].. There are multiple modes of HIV transmission including Sexual intercourse, sharing needles with HIV infected persons, or via HIV-contaminated blood transfusions [21]. Infants may acquire HIV at delivery (Birth) or through breast feeding if the mother is HIV positive. This type of transmission is known as vertical transmission [6]. The term AIDS refers to only the last stage of the HIV infection after which death occurs. The HIV epidemic is sweeping the world both developed and developing nations as HIV has infected millions of people all over the world without any restriction of nationality, religion etc [18]. HIV infection in adults (75-80 percent) has been transmitted to one partner through unprotected sexual intercourse when the other partner is infected with HIV. Mother to child transmission (vertical infection accounts for more than 90 percent) of global infection to infants and children. As HIV infection progresses, immunity declines and patients tend to become more susceptible to common or even rare infections. The sexual transmission is believed globally responsible for the majority of new HIV infections [14,17]

The related spread of two or more infections has always been a cause of concern for human being. HIV-TB co-infection is the largest cause among them. Tuberculosis (TB) is the most common opportunistic disease affecting HIV positive people and the leading cause of death in patients with AIDS [8,12]. Also, the relative risk of death and development of other opportunistic infections is higher in HIV-TB co-infected patients as compared to those having only one disease out of the two. [15].

Persons co-infected with TB and HIV may spread the disease not only to other HIV-infected persons, but also members of the general population who do not participate in any of the high risk behaviours associated with HIV. [22]. In recent decades, the dramatic spread of the HIV epidemic in sub-Saharan Africa has resulted in notification rates of TB increasing up to 10 - times. The incidence of TB is also increasing in other high HIV prevalence countries where the population with HIV infection and TB overlap. [15].

Patients with latent *Mycobacterium tuberculosis* infection are at higher risk for progression into active TB if they are co-infected with HIV [15]. HIV significantly increases individual risk of progression to active TB in both primary TB and the reactivation of latent TB. Likewise TB fuels the progression of HIV to full blwn AIDS [10]. It is estimated that among 33.4 million people living with HIV worldwide, about one-third are also infected by MTB [11]. India has about 1.8 million new cases of tuberculosis annually. In 2012, of the estimated 1.2 million TB deaths, about one-quarter were HIV/TB co-infected patients [25]. The interaction of these deadly diseases is sweeping off the population and it is quite unfortunate that much work has not been done to model the co-infection of these deadly diseases at a population level.

Due to the threat poses by the interaction of HIV with TB, we formulated nine (9) new compartmental models to determine the parameters that influence the transmission of these deadly diseases using forward sensitivity method.

2. Mathematical model formulation.

A non linear mathematical model is formulated and analyzed to study the sensitivity of parameters involved in the basic reproduction number (R_0) on the dynamical spread of HIV- TB co-infection.

In modeling the dynamics, the total homogeneously mixing population at time t, denoted by N(t), is divided into (9) nine mutually–exclusive compartments of Susceptible (S(t)) individuals, Latently HIV $(L_H(t))$ individuals, HIV Undetected $(H_U(t))$ individuals, HIV Detected $(H_D(t))$ individuals, Treated HIV$(T_H(t))$ individuals, Latent TB $(L_T(t))$ individuals, TB Undetected $(T_U(t))$ individuals, TB Detected $(T_D(t))$ individuals and Recovered TB $(R_T(t))$ individuals So that,

$$N(t) = S + L_H + H_U + H_D + T_H + L_T + T_U + T_D + R_T \qquad (1)$$

The Susceptible population is increased by the recruitment of individuals into the population at rate π. the population decrease by natural death rate μ and by singly infected transmission individuals. Both singly infected individuals transmit either HIV or TB infection as follows (note that we split the disease transmission process into those generated by singly-infected infected individuals to make the formulation easier to follow).

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

$$\lambda_H = \beta_H \frac{(L_H + \eta_U H_U + \eta_{dH} H_D + \eta_{TH} T_H)}{N} \qquad (2)$$

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

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

$$\lambda_T = \beta_T \frac{(L_T + \eta_U T_U + \eta_{dT} T_D + \eta_{RT} R_T)}{N} \qquad (3)$$

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

Then,

$$\frac{dS}{dt} = \pi - \lambda_H S - \lambda_T S - \mu S \qquad (4)$$

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

$$\frac{dL_H}{dt} = \varepsilon_1 \lambda_H S - (\kappa_H + \mu) L_H \qquad (5)$$ The

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

$$\frac{dH_U}{dt} = (1-\varepsilon_1)\lambda_H S + (1-\omega_1)\kappa_H L_H - (\gamma_{UH} + \mu + \delta_{UH}) H_U \qquad (6)$$

The population of Detected infected HIV individual increases by the fraction of latently individuals who develop disease symptoms (at the rate $\omega_1 \kappa_H$), where ω_1 is the endogenous reactivation rate and the detection of undetected individual at the rate γ_{UH}. The population later decreased by treatment rate (τ_1) for HIV detected individual and finally reduced by the natural death rate, induced mortality death rate at μ and δ_{UH} respectively. Hence we have.

$$\frac{dH_D}{dt} = \omega_1 \kappa_H L_H + \gamma_{UH} H_U - (\tau_1 + \mu + \delta_{UH}) H_D \qquad (7)$$

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

Hence,

$$\frac{dT_H}{dt} = \tau_1 H_D - (\mu + \delta_{TH})T_H \tag{8}$$

A fraction ε_2 of the newly–infected individuals are assumed to show no disease symptoms initially. These individuals (Known as slow progression for TB) moved to the latently TB class (L_T). The remaining fraction $(1-\varepsilon_1)$ of the newly infected individuals are assumed to immediately display disease symptoms (Fast progressor for (TB)) and are moved to the undetected infected compartment (T_U). The population decreased by progression rate (κ_T) from latent TB class to infected undetected class andnatural death rate (μ).

$$\frac{dL_T}{dt} = \varepsilon_2 \lambda_T S - (\kappa_T + \mu)L_T \tag{9}$$

The population of undetected infectious individuals is increased by the infection of fast progressor at the rate $(1-\varepsilon_1)\lambda_T$ and the development of symptoms by latent individual at the rate $(1-\omega_2)\kappa_T$, where ω_2 is the fraction of exposed individuals who develop symptoms and are detected. detection of undetected individual at a rate (γ_{UH}), natural death at the rate (μ) and disease induced death at a rate (δ_{UT}). Hence, we have

$$\frac{dT_U}{dt} = (1-\varepsilon_2)\lambda_H S + (1-\omega_2)\kappa_T L_T - (\gamma_{UT} + \mu + \delta_{UT})T_U \tag{10}$$

The population of detected infectious individual increases by the fraction of latent individuals who develop diseases symptoms at a rate $\omega_2 \kappa_T$ and detection rate for undetected individual at the rate (γ_{UT}). The population is decreased by those that are treated who later moved to recovered compartment at the rate (τ_2), natural death rate (μ) and disease induced death at a rate (δ_{dT}) This gives

$$\frac{dT_D}{dt} = \omega_2 \kappa_T L_T + \gamma_{UT} T_U - (\tau_2 + \mu + \delta_{dT})T_D \tag{11}$$ Th

e population of TB recovered individual is increased by the treatment of detected individual (at the rate τ_2) this population later decreased by natural death and disease induced death (at a rate μ and δ_{RT}). Thus

$$\frac{dR_T}{dt} = \tau_2 T_D - (\mu + \delta_{RT})R_T \tag{12}$$

Hence, we have

$$\frac{dS}{dt} = \pi - \lambda_H S - \lambda_T S - \mu S$$

$$\frac{dL_H}{dt} = \varepsilon_1 \lambda_H S - K_1 L_H$$

$$\frac{dH_U}{dt} = (1 - \varepsilon_1) \lambda_H S + K_2 L_H - K_3 H_U$$

$$\frac{dH_D}{dt} = \omega_1 \kappa_H L_H + \gamma_{UH} H_U - K_4 H_D$$

$$\frac{dT_H}{dt} = \tau_1 H_D - K_5 T_H \qquad\qquad (13)$$

$$\frac{dL_T}{dt} = \varepsilon_2 \lambda_T S - K_6 L_T$$

$$\frac{dT_U}{dt} = (1 - \varepsilon_2) \lambda_T S + K_7 L_T - K_8 T_U$$

$$\frac{dT_D}{dt} = \omega_2 \kappa_T L_T + \gamma_{UT} T_U - K_9 T_D$$

$$\frac{dR_T}{dt} = \tau_2 T_D - K_{10} R_T$$

Where,

$$K_1 = (\kappa_H + \mu), \quad K_2 = (1 - \omega_1)\kappa_H, \quad K_3 = (\gamma_{UH} + \mu + \delta_{UH}), \quad K_4 = (\tau_1 + \mu + \delta_{dH}),$$
$$K_5 = (\mu + \delta_{RH}), \quad K_6 = (\kappa_T + \mu)L_T, \quad K_7 = (1 - \omega_2)\kappa_T L_T, \quad K_8 = (\gamma_{UT} + \mu + \delta_{UT}),$$
$$K_9 = (\tau_2 + \mu + \delta_{dT}), \quad K_{10} = (\mu + \delta_{RT})$$

Table 1. Description of parameters and variables

Parameters	Definitions
S	Susceptible individuals
L_H	Latent HIV individual
H_D	Detected HIV individual
H_U	Undetected HIV individual
L_T	Latent TB individual
T_U	Undetected TB individual
T_D	Detected TB individual
R_T	TB recover individual
T_H	Treated HIV individual
τ_1, τ_2	Treatment rate for Detected HIV and TB
λ_H, λ_T	Effective contact rates for HIV and TB
π	Recruitment rate into the population
μ	Natural death rate

$1 - \varepsilon_1$	Fast progressors for HIV
ε_2	Slow progressors for TB
$1 - \varepsilon_2$	Fast progressors for TB
κ_H	Progression rate of HIV.
κ_T	Progression rate of TB.
ω_1	Endogenous reactivation rate of HIV
ω_2	Endogenous reactivation rate of TB
γ_{UH}	Detection rate for undetected HIV
γ_{UT}	Detection rate for undetected TB
$\delta_{UT}, \delta_{dT}, \delta_{RT}$	Tuberculosis-induced mortality rate for classes T_U, T_D, R respectively
β_T, β_H	Effective contact rate for TB and HIV
δ_{UH}, δ_{dH}	HIV-induced mortality rate for classes H_U, H_D respectively
$\eta_U, \eta_{dH}, \eta_{TH}$	HIV Modification parameters for classes H_U, H_D, T_H respectively
$\eta_U, \eta_{dT}, \eta_{RT}$	TB Modification parameters for classes T_U, T_D, R_T respectively

3. Mathematical analysis

Lemma 1. The closed set

$D_1 = \{(S, L_H, \eta_U H_U, \eta_{dH} H_D, \eta_{TH} T_H, L_T, \eta_U T_U, \eta_{dH} T_D, \eta_{RT} R_T) \in R^9_+ : N \leq \pi / \mu$ is positively-invariant and attracting with respect to the model (1)

Proof: Consider the biologically-feasible region D, defined above. The rate of change of the total population, obtained by adding all equations of the model (13), is given by

$$\frac{dN}{dt} = \pi - \mu N - \delta_{UH} - \delta_{dH} - \delta_{TH} - \delta_{UT} - \delta_{dT} - \delta_{RT}. \tag{14}$$

It follows that $\frac{dN}{dt} < 0$ whenever $N > \frac{\pi}{\mu}$. Furthermore, since $\frac{dN}{dt} \leq \pi - \mu N$, it is clear that $N(t) \leq \frac{\pi}{\mu}$ if

$N(0) \leq \frac{\pi}{\mu}$. Therefore, all solutions of the model with initial conditions in D remain in D for all $t > 0$ (i.e., the ω-limits

sets of the system (13) are contained in D). Thus, D is positively-invariant and attracting. In this region, the model can be considered as been epidemiologically and mathematically well posed

3.1. Analysis of the sub-models. before analyzing the full model, it is pertinent to gain insights into the dynamics of the models for HIV only and TB only model.

3.1.1. *HIV-only model.* The HIV only model is given by

$$\frac{dS}{dt} = \pi - \lambda_H S - \lambda_T S - \mu S$$

$$\frac{dL_H}{dt} = \varepsilon_1 \lambda_H S - K_1 L_H$$

$$\frac{dH_U}{dt} = (1 - \varepsilon_1)\lambda_H S + K_2 L_H - K_3 H_U \qquad (15)$$

$$\frac{dH_D}{dt} = \omega_1 \kappa_H L_H + \gamma_{UH} H_U - K_4 H_D$$

$$\frac{dT_H}{dt} = \tau_1 H_D - K_5 T_H$$

Where,

$$\lambda_H = \beta_H \frac{(L_H + \eta_U H_U + \eta_{dH} H_D + \eta_T T_H)}{N} \qquad (16)$$

For this model, it can be shown that the region,

$$D_1 = \{(S + L_H + \eta_U H_U + \eta_{dH} H_D + \eta_T T_H) \in R^5_+ : N \le \pi/\mu$$

3.2. Stability of the disease free equilibrium (dfe)

Disease free equilibrium

For critical points, we set

$$\frac{dS}{dt} = \frac{dL_H}{dt} = \frac{dH_U}{dt} = \frac{dH_D}{dt} = \frac{dT_H}{dt} = 0$$

At disease free equilibrium, it is assumed that there is no infection, and then we set $\lambda_H = 0$

So, $L_H = 0, H_U = 0, H_D = 0, T_H = 0$

Disease free equilibrium of HIV model only is given by

$$\varepsilon_0 = \left\{ \frac{\pi}{\mu}, 0, 0, 0, 0 \right\} \qquad (17)$$

3.3. Derivation of basic reproduction number (r₀) for hiv only

The basic reproduction number R_H of the model () is calculated by using the next generation matrix (Driessche and Watmough, 2002). Using their approach (Driessche and Watmough, 2002), we have,

$$Fi = \begin{pmatrix} F1 \\ F2 \\ F3 \\ F4 \end{pmatrix} = \begin{pmatrix} \varepsilon_1 \lambda_H S \\ (1 - \varepsilon_1)\lambda_H S \\ 0 \\ 0 \end{pmatrix}$$

$$Vi = \begin{pmatrix} V1 \\ V2 \\ V3 \\ V4 \end{pmatrix} = \begin{pmatrix} -K_1 L_H \\ K_2 L_H - K_3 H_U \\ \omega_1 \kappa_H L_H + \gamma_{UH} H_U - K_4 H_D \\ \tau_1 H_D - K_5 T_H \end{pmatrix}$$

Where

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

and

$$V = \begin{pmatrix} K_1 & 0 & 0 & 0 \\ -K_2 & K_3 & 0 & 0 \\ -\omega_1 \kappa_H & -\gamma_{UH} & K_4 & 0 \\ 0 & 0 & -\tau_1 & K_5 \end{pmatrix}$$

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

$$R_H = \left\{ \begin{array}{l} \dfrac{1}{K_4 K_5 K_1 K_3} \big(\big(\big((K_4 \eta_U + \gamma_{UH} \eta_{dH})K_5 + \gamma_{UH} \eta_T \tau_1 \big)K_1(1-\varepsilon_1) + \\ \big((K_2 \gamma_{UH} \eta_{dH} + (\eta_{dH}\omega_1 \kappa_H + K_4)K_3 + K_4 K_2 \eta_U)K_5 + \eta_T \tau_1(\omega_1 \kappa_H K_3 + K_2 \gamma_{UH})\big)\varepsilon_1 \big)\beta_H \big) \end{array} \right\} \tag{18}$$

Lemma 2. The DFE of the HIV-only model (15), given by (18), is locally asymptotically stable (LAS) if $R_H < 1$, and unstable if $R_H > 1$.

The threshold quantity R_H is the basic reproduction number of the normalized model system

(15) for HIV infection in a population. It measures the average number of new secondary infections generated by a single infected individual in his or her infectious period in a susceptible population [1].

3.4. Local stability of disease free equilibrium (dfe) –hiv only

Theorem 1.: The disease free equilibrium of the system (3.115) is locally asymptotically stable (LAS) if $R_H < 1$ and unstable if $R_H > 1$.

Proof: To determine the local stability of E_0, the following Jacobian matrix is computed corresponding to equilibrium point E_0. Considering the stability of the disease free equilibrium at the critical point (0,0,0,0,0). Equation (3.115), we have

$$J_H = \begin{pmatrix} -\mu & 0 & 0 & 0 & 0 \\ 0 & -K_1 & 0 & 0 & 0 \\ 0 & K_2 & -K_3 & 0 & 0 \\ 0 & \omega_1 \kappa_H & \gamma_{UH} & -K_4 & 0 \\ 0 & 0 & 0 & \tau_1 & -K_5 \end{pmatrix} \tag{19}$$

Then the characteristics equations are obtained as $|J_H - \lambda I| = 0$ (where I is 5*5 identity matrix).

Where,

$$\lambda I = \begin{bmatrix} \lambda & 0 & 0 & 0 & 0 \\ 0 & \lambda & 0 & 0 & 0 \\ 0 & 0 & \lambda & 0 & 0 \\ 0 & 0 & 0 & \lambda & 0 \\ 0 & 0 & 0 & 0 & \lambda \end{bmatrix}$$

Hence $\left| J_H - \lambda I \right| = 0$ implies that

$$
\begin{pmatrix}
-\mu - \lambda_1 & 0 & 0 & 0 & 0 \\
0 & -K_1 - \lambda_2 & 0 & 0 & 0 \\
0 & K_2 & -K_3 - \lambda_3 & 0 & 0 \\
0 & \omega_1 \kappa_H & \gamma_{UH} & -K_4 - \lambda_4 & 0 \\
0 & 0 & 0 & \tau_1 & -K_5 - \lambda_5
\end{pmatrix} \tag{21}
$$

From equation (21), clearly $\lambda_1 = -\mu$, $\lambda_2 = -K_1$, $\lambda_3 = -K_3$, $\lambda_4 = -K_4$, $\lambda_5 = -K_5$

Hence, the corresponding eigen values of equation (15) are;

$$\lambda_1 = -\mu, \quad \lambda_2 = -(\kappa_H + \mu), \quad \lambda_3 = -(\gamma_{UH} + \mu + \delta_{UH}), \quad \lambda_4 = -(\tau_1 + \mu + \delta_{UH}), \quad \lambda_5 = -(\mu + \delta_{RH})$$

Where,

$$K_1 = (\kappa_H + \mu), \quad K_2 = (1 - \omega_1)\kappa_H, \quad K_3 = (\gamma_{UH} + \mu + \delta_{UH}), \quad K_4 = (\tau_1 + \mu + \delta_{dH}), \quad K_5 = (\mu + \delta_{RH})$$ Since all the real roots are negative, real and distinct. Hence, disease free equilibrium of the HIV only model (15) is locally asymptotically stable (LAS).

3.5. Global stability of disease free equilibrium (hiv)

Here, the global asymptotic stability (GAS) property of the DEF of the HIV model only will be explored.

Theorem 2: The disease free-equilibrium of the system (15) is globally asymptotically stable whenever $R_H < 1$ and unstable if $R_H > 1$.

Proof: It follows that $S = N^* - L_H - H_U - H_D - T_H$ at steady state. The proof is based on using the comparison theorem (Lakshmkantham et al, 1989) to prove the global stability. The rate of change of the variables representing the infected component of the system can be written as follows.

$$\frac{dL_H}{dt} = \varepsilon_1 \lambda_H (N^* - L_H - H_U - H_D - H_W) - K_1 L_H$$

$$\frac{dH_U}{dt} = (1 - \varepsilon_1)\lambda_H (N^* - L_H - H_U - H_D - H_W) - K_2 L_H - K_3 H_U$$

$$\frac{dH_D}{dt} = \omega_1 K_H L_H + \gamma_{UH} H_U - K_4 H_D \tag{22}$$

$$\frac{dT_H}{dt} = \tau_1 H_D - K_5 T_H$$

$$D^* = \left\{ L_H, H_U, H_D, T_H \right) \in R_+^4 : L_H + H_U + H_D + T_H \leq N^* \right\}$$

For the model (15), the associated reproduction number, denoted by R_H where

$$
R_H = \left\{
\begin{aligned}
&\frac{1}{K_4 K_5 K_1 K_3} \Big(\big(\big(\big(K_4 \eta_U + \gamma_{UH} \eta_{dH}\big)K_5 + \gamma_{UH}\eta_T \tau_1\big)K_1\big(1 - \varepsilon_1\big) + \\
&\big(\big(K_2 \gamma_{UH}\eta_{dH} + \big(\eta_{dH}\omega_1 \kappa_H + K_4\big)K_3 + K_4 K_2 \eta_U\big)K_5 + \eta_T \tau_1\big(\omega_1 \kappa_H K_3 + K_2 \gamma_{UH}\big)\big)\varepsilon_1\big)\beta_H\big)
\end{aligned}
\right\}
$$

The DFE of the model (15) is GAS in D^* if $R_H < 1$.

Using comparison method, we have,

$$
\begin{pmatrix} \dfrac{dL_H}{dt} \\[2ex] \dfrac{dH_U}{dt} \\[2ex] \dfrac{dH_D}{dt} \\[2ex] \dfrac{dT_H}{dt} \end{pmatrix} = (F - V) \begin{pmatrix} L_H \\[2ex] H_U \\[2ex] H_D \\[2ex] T_H \end{pmatrix} - Fi \begin{pmatrix} L_H \\[2ex] H_U \\[2ex] H_D \\[2ex] T_H \end{pmatrix}
$$

According to (Castillo Chavez *et al* 2002) and (Driessche and Watmough 2002), all eigenvalues of the matrix (F - V) have negative real parts.

$$
\begin{pmatrix}
(\varepsilon_1 \beta_H - K_1) - \lambda & \varepsilon_1 \beta_H \eta_U & \varepsilon_1 \beta_H \eta_{dH} & \varepsilon_1 \beta_H \eta_T \\
(1 - \varepsilon_1)\beta_H + K_2 & ((1-\varepsilon_1)\beta_H \eta_U - K_3) - \lambda & (1-\varepsilon_1)\beta_H \eta_{dH} & (1-\varepsilon_1)\beta_H \eta_T \\
\omega_1 \kappa_H & \gamma_{UH} & -K_4 - \lambda & 0 \\
0 & 0 & \tau_1 & -K_5 - \lambda
\end{pmatrix} = 0 \quad (23)
$$

From equation (23), we have

$$
\begin{bmatrix}
((\varepsilon_1 \beta_H - K_1) - \lambda)((1-\varepsilon_1)\beta_H \eta_U - K_3 - \lambda)(-K_4 - \lambda)(-K_5 - \lambda) \\
-(\varepsilon_1 \beta_H \eta_U)((1-\varepsilon_1)\beta_H + K_2)(-K_4 - \lambda)(-K_5 - \lambda) + (\varepsilon_1 \beta_H \eta_{dH})((1-\varepsilon_1)\beta_H + K_2)(\gamma_{UH}(-K_5 - \lambda)) \\
-(\varepsilon_1 \beta_H \eta_T)((1-\varepsilon_1)\beta_H + K_2)(\gamma_{UH} + \tau_1)
\end{bmatrix} = 0 \quad (24)
$$

Thus, from equation (24), the characteristic equation is given by

$$
\lambda^4 + a_4 \lambda^3 + a_3 \lambda^2 + a_2 \lambda + a_1
$$

Where

$$
a_4 = (((\eta_U - 1)\varepsilon_1 - \eta_U)\beta_H + K_4 K_5 K_1 K_3)
$$

$$
a_3 = ((((\eta_U - 1)K_5 + K_1 \eta_U + (\eta_U - 1)K_4 - \eta_{dH}\omega_1 \kappa_H - K_2 \eta_U + \gamma_{UH}\eta_{dH} - K_3)\varepsilon_1 - K_1 \eta_U - K_4 \eta_U \\
\qquad - K_5 \eta_U - \gamma_{UH}\eta_{dH})\beta_H + (K_4 + K_1 + K_3)K_5 + (K_4 + K_3)K_1 + K_4 K_3)
$$

$$
a_2 = ((((K_1 \eta_U + (\eta_U - 1)K_4 - \eta_{dH}\omega_1 \kappa_H - K_2 \eta_U + \gamma_{UH}\eta_{dH} - K_3)K_5 + (K_4 \eta_U + \gamma_{UH}\eta_{dH})K_1 + (-K_2 \eta_U - K_3)K_4 \\
\qquad + (-K_2 \eta_{dH} + + \tau_1 \eta_T)\gamma_{UH} - \kappa_H \omega_1 (K_3 \eta_{dH} + +\tau_1 \eta_T))\varepsilon_1 + (-K_1 \eta_U - K_4 \eta_U - \gamma_{UH}\eta_{dH})K_5 + (-K_4 \eta_U - \gamma_{UH}\eta_{dH})K_1 \\
\qquad - \gamma_{UH}\eta_T \tau_1)\beta_H + ((K_4 + K_3)K_1 + K_4 K_3)K_5 + K_1 K_4 K_3)
$$

$$
a_1 = K_4 K_5 K_1 K_3 - ((((K_4 \eta_U + \gamma_{UH}\eta_{dH})K_5 + \gamma_{UH}\eta_T \tau_1)K_1(1 - \varepsilon_1) + \\
((K_2 \gamma_{UH}\eta_{dH} + (\eta_{dH}\omega_1 \kappa_H + K_4)K_3 + K_4 K_2 \eta_U)K_5 + \eta_T \tau_1(\omega_1 \kappa_H K_3 + K_2 \gamma_{UH}))\varepsilon_1)\beta_H)
$$

Thus according to Routh Hurwitz Criteria of order four (4),

$$
n = 4 : a_1 > 0, a_3 > 0, a_4 > 0, and\ a_1 a_2 a_3 > a_3^2 + a_1^2 a_4.
$$

Then for $a_1 > 0$ we have

$$
\frac{(((K_4 \eta_U + \gamma_{UH}\eta_{dH})K_5 + \gamma_{UH}\eta_T \tau_1)K_1(1 - \varepsilon_1) + ((K_2 \gamma_{UH}\eta_{dH} + (\eta_{dH}\omega_1 \kappa_H + K_4)K_3 + K_4 K_2 \eta_U)K_5 + \eta_T \tau_1(\omega_1 \kappa_H K_3 + K_2 \gamma_{UH}))\varepsilon_1)\beta_H)}{K_4 K_5 K_1 K_3} < 1,
$$

Implying that

$$R_H < 1$$

According to (Castillo-Chavez et al. 2002) and (Driessche and Watmough 2002), all eigenvalues of the matrix F – V have negative real parts. It follows that the linearized differential inequality above is stable whenever $R_H < 1$. Consequently $S = (L = H_U = H_D = H_W = 0) \rightarrow (0, 0, 0, 0) \ at \ t \rightarrow \infty$. Substituting $L = H_U = H_D = H_W = 0$ in (R_H) gives $S(t) \rightarrow S(0) \ as \ t \rightarrow \infty$. Hence, we have established that the disease free equilibrium is globally asymptotically stable whenever $R_H < 1$ and unstable $R_H > 1$.

3.6. Hiv sensitivity analysis

It is useful to conduct an investigation to determine how sensitive the threshold quantity basic reproduction number is with respect to its parameters, this will help us to know which of the parameters causes most reduction in R_o and parameters that have high impact on R_o and these should be targeted by intervention strategies in order to have most effective control of the disease. This analysis tells us how crucial and important each parameter is to disease transmission. We compute the normalized forward sensitivity index of the reproduction number with respect to its parameters.

Definition: If a variable 'c' depends differentiably on a parameter 'w', then, the normalized forward sensitivity index of 'c' with respect to 'w' is denoted by Xc, which is defined as $X_c = \dfrac{c}{w}\dfrac{\partial w}{\partial c}$

As we have explicit formula for R_o, we derive an analytical expression for the sensitive of R_o as

$$X_w^{R_o} = \frac{dR_o}{dw} \times \frac{w}{R_o} \tag{25}$$

Sensitivity analysis for each parameter involved in R_H, is therefore calculated and show in the table below.

Table 2. VALUES OF NUMERICAL SENSITIVITY OF HIV

PARAMETER	SENSITIVITY VALUE
τ_1	0.0000000
μ	-0.0777526
δ_{dH}	-0.0061828
δ_{UH}	-0.0080448
γ_{UH}	0.0000000
δ_{TH}	-0.0106258
ε_1	0.9685616
β_H	1.000000
κ_H	-0.9431861

3.7. *TB -only model.* The TB only model is given by

$$\frac{dS}{dt} = \pi - \lambda_T S - \mu S$$

$$\frac{dL_T}{dt} = \varepsilon_2 \lambda_T S - K_6 L_T$$

$$\frac{dT_U}{dt} = (1 - \varepsilon_2)\lambda_T S + K_7 L_T - K_8 T_U \tag{26}$$

$$\frac{dT_D}{dt} = \omega_2 \kappa_T L_T + \gamma_{UT} T_U - K_9 T_D$$

$$\frac{dR_T}{dt} = \tau_2 T_D - K_{10} T_D$$

Where,

$$\lambda_T = \beta_T \frac{(L_T + \eta_U T_U + \eta_{dT} T_D + \eta_{RT} R_T)}{N} \tag{27}$$

For this model, it can be shown that the region,

$$D_1 = \{ (S + L_T + \eta_U T_U + \eta_{dT} T_D + \eta_{RT} R_T) \in R^5_+ : N \leq \pi / \mu \tag{28}$$

3.8 Stability of the disease free equilibrium (dfe)

Disease free equilibrium

For critical points, we set

$$\frac{dS}{dt} = \frac{dL_T}{dt} = \frac{dT_U}{dt} = \frac{dT_D}{dt} = \frac{dR_T}{dt} = 0$$

At disease free equilibrium, it is assumed that there is no infection, and then we set $\lambda_T = 0$

So, $L_T = 0, T_U = 0, T_D = 0, R_T = 0$

Disease free equilibrium of TB model only is given by

$$\varepsilon_0 = \left\{ \frac{\pi}{\mu}, \, 0, \, 0, \, 0, \, 0 \right\} \tag{29}$$

3.9 Derivation of basic reproduction number (R$_o$) for TB-only

the basic reproduction number R_T of the model (26) is calculated by using the next generation matrix (driessche and watmough, 2002). using their approach (driessche and watmough, 2002), we have,

$$Fi = \begin{pmatrix} F1 \\ F2 \\ F3 \\ F4 \end{pmatrix} = \begin{pmatrix} \varepsilon_2 \lambda_T S \\ (1 - \varepsilon_2)\lambda_T S \\ 0 \\ 0 \end{pmatrix}$$

$$Vi = \begin{pmatrix} V1 \\ V2 \\ V3 \\ V4 \end{pmatrix} = \begin{pmatrix} -K_6 L_T \\ K_7 L_T - K_8 T_U \\ \omega_2 \kappa_T L_T + \gamma_{UT} T_U - K_9 T_D \\ \tau_2 T_D - K_{10} T_D \end{pmatrix}$$

where

$$F = \begin{pmatrix} \varepsilon_2 \beta_T & \varepsilon_2 \beta_T \eta_U & \varepsilon_2 \beta_H \eta_{dT} & \varepsilon_2 \beta_T \eta_{RT} \\ (1-\varepsilon_2)\beta_T & (1-\varepsilon_2)\beta_T \eta_U & (1-\varepsilon_2)\beta_T \eta_{dT} & (1-\varepsilon_1)\beta_T \eta_{RT} \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{pmatrix}$$

and

$$V = \begin{pmatrix} K_6 & 0 & 0 & 0 \\ -K_7 & K_8 & 0 & 0 \\ -\omega_2 \kappa_T & -\gamma_{UT} & K_9 & 0 \\ 0 & 0 & -\tau_2 & K_{10} \end{pmatrix}$$

the reproduction number is the dominant eigen values of $F \times V^{-1}$. thus,

$$R_T = \left\{ \begin{array}{l} \frac{1}{K_9 K_{10} K_6 K_8}\left(\left(\left(\left(K_9 \eta_U + \gamma_{UT} \eta_{dT}\right)K_{10} + \gamma_{UT} \eta_{RT} \tau_2\right)K_6\left(1-\varepsilon_2\right)+ \right.\right. \\ \left.\left.\left(\left(K_7 \gamma_{UT} \eta_{dT} + \left(\eta_{dT} \omega_2 \kappa_T + K_9\right)K_8 + K_9 K_7 \eta_U\right)K_{10} + \eta_{RT} \tau_2 \left(\omega_2 \kappa_T K_8 + K_7 \gamma_{UT}\right)\right)\varepsilon_2\right)\beta_T\right) \end{array} \right\} \qquad (30)$$

lemma 3. the dfe of the tb-only model (26), given by (30), is locally asymptotically stable (las) if $R_T < 1$, and unstable if $R_T > 1$.

the threshold quantity R_T is the basic reproduction number of the normalized model system

(26) for tb infection in a population. it measures the average number of new secondary infections generated by a single infected individual in his or her infectious period in a susceptible

population [1].

3.10. Local stability of disease free equilibrium (dfe) TB-only

Theorem 3.: The disease free equilibrium of the system (26) is locally asymptotically stable (LAS) if $R_T < 1$ and unstable if $R_T > 1$.

Proof: To determine the local stability of E_0, the following Jacobian matrix is computed corresponding to equilibrium point E_0. Considering the stability of the disease free equilibrium at the critical point (0,0,0,0,0). Equation 26), we have

$$J_T = \begin{pmatrix} -\mu & 0 & 0 & 0 & 0 \\ 0 & -K_6 & 0 & 0 & 0 \\ 0 & K_7 & -K_8 & 0 & 0 \\ 0 & \omega_2 \kappa_T & \gamma_{UT} & -K_9 & 0 \\ 0 & 0 & 0 & \tau_2 & -K_{10} \end{pmatrix} \qquad (31)$$

Then the characteristics equations are obtained as $\left|J_T - \lambda I\right| = 0$ (where I is 5*5 identity matrix).

Where,

$$\lambda I = \begin{bmatrix} \lambda & 0 & 0 & 0 & 0 \\ 0 & \lambda & 0 & 0 & 0 \\ 0 & 0 & \lambda & 0 & 0 \\ 0 & 0 & 0 & \lambda & 0 \\ 0 & 0 & 0 & 0 & \lambda \end{bmatrix}$$

Hence $\left| J_H - \lambda I \right| = 0$ implies that

$$\begin{pmatrix} -\mu - \lambda_1 & 0 & 0 & 0 & 0 \\ 0 & -K_6 - \lambda_2 & 0 & 0 & 0 \\ 0 & K_7 & -K_8 - \lambda_3 & 0 & 0 \\ 0 & \omega_2 \kappa_T & \gamma_{UT} & -K_9 - \lambda_4 & 0 \\ 0 & 0 & 0 & \tau_2 & -K_{10} - \lambda_5 \end{pmatrix} \qquad (32)$$

From equation (32), clearly $\lambda_1 = -\mu$, $\lambda_2 = -K_6$, $\lambda_3 = -K_8$, $\lambda_4 = -K_9$, $\lambda_5 = -K_{10}$

Hence, the corresponding eigen values of equation (26) are;

$$\lambda_1 = -\mu, \quad \lambda_2 = -(\kappa_T + \mu), \quad \lambda_3 = -(\gamma_{UT} + \mu + \delta_{UT}), \quad \lambda_4 = -(\tau_1 + \mu + \delta_{UH}), \quad \lambda_5 = -(\mu + \delta_{RH})$$

Where,

$K_6 = (\kappa_T + \mu)$, $K_7 = (1 - \omega_2)\kappa_T$, $K_8 = (\gamma_{UT} + \mu + \delta_{UT})$, $K_9 = (\tau_2 + \mu + \delta_{d\,dT})$, $K_{10} = (\mu + \delta_{RT})$ Sin ce all the real roots are negative, real and distinct. Hence, disease free equilibrium of the TB only model (26) is locally asymptotically stable (LAS).

3.11. Global stability of disease free equilibrium (TB)

Here, the global asymptotic stability (GAS) property of the DEF of the TB model only will be explored.

Theorem 4: The disease free-equilibrium of the system (26) is globally asymptotically stable whenever $R_T < 1$ and unstable if $R_T > 1$.

Proof: It follows that $S = N^* - L_T - T_U - T_D - R_T$ at steady state. The proof is based on using the comparison theorem (Lakshmkantham et al, 1989) to prove the global stability. The rate of change of the variables representing the infected component of the system can be written as follows.

$$\frac{dL_T}{dt} = \varepsilon_2 \lambda_T (N^* - L_T - T_U - T_D - H \setminus R_T) - K_6 L_T$$

$$\frac{dT_U}{dt} = (1 - \varepsilon_2)\lambda_T (N^* - L_T - T_U - T_D - R_T) - K_7 L_T - K_8 T_U$$

$$\frac{dT_D}{dt} = \omega_2 \kappa_T L_T + \gamma_{UT} T_U - K_9 T_D \qquad (33)$$

$$\frac{dR_T}{dt} = \tau_2 T_D - K_{10} R_T$$

$$D^* = \left\{ L_T, T_U, T_D, R_T) \in R_+^4 : L_T + T_U + T_D + R_T \le N^* \right\}$$

For the model (26), the associated reproduction number, denoted by R_T where

$$R_T = \left\{ \frac{1}{K_9 K_{10} K_6 K_8} \left(\left(\left((K_9 \eta_U + \gamma_{UT} \eta_{dT}) K_{10} + \gamma_{UT} \eta_{RT} \tau_2 \right) K_6 (1 - \varepsilon_2) + \right. \right. \right.$$
$$\left. \left. \left. \left((K_7 \gamma_{UT} \eta_{dT} + (\eta_{dT} \omega_2 \kappa_T + K_9) K_8 + K_9 K_7 \eta_U) K_{10} + \eta_{RT} \tau_2 (\omega_2 \kappa_T K_8 + K_7 \gamma_{UT}) \right) \varepsilon_2 \right) \beta_T \right) \right\}$$

The DFE of the model (26) given by disease free (), is GAS in D* if $R_T < 1$.

Using comparison method, we have,

$$\begin{pmatrix} \dfrac{dL_H}{dt} \\ \dfrac{dH_U}{dt} \\ \dfrac{dH_D}{dt} \\ \dfrac{dT_H}{dt} \end{pmatrix} = (F - V) \begin{pmatrix} L_H \\ H_U \\ H_D \\ T_H \end{pmatrix} - Fi \begin{pmatrix} L_H \\ H_U \\ H_D \\ T_H \end{pmatrix}$$

According to (Castillo Chavez *et al* 2002) and (Driessche and Watmough 2002), all eigenvalues of the matrix (F - V) have negative real parts.

$$\begin{pmatrix} (\varepsilon_1\beta_H - K_1) - \lambda & \varepsilon_1\beta_H\eta_U & \varepsilon_1\beta_H\eta_{dH} & \varepsilon_1\beta_H\eta_T \\ (1-\varepsilon_1)\beta_H + K_2 & ((1-\varepsilon_1)\beta_H\eta_U - K_3) - \lambda & (1-\varepsilon_1)\beta_H\eta_{dH} & (1-\varepsilon_1)\beta_H\eta_T \\ \omega_1\kappa_H & \gamma_{UH} & -K_4 - \lambda & 0 \\ 0 & 0 & \tau_1 & -K_5 - \lambda \end{pmatrix} = 0 \qquad (34)$$

From equation (3.153), we have

$$\begin{bmatrix} ((\varepsilon_2\beta_T - K_6) - \lambda)((1-\varepsilon_2)\beta_T\eta_U - K_8 - \lambda)(-K_9 - \lambda)(-K_{10} - \lambda) \\ -(\varepsilon_2\beta_T\eta_U)((1-\varepsilon_2)\beta_T + K_7)(-K_9 - \lambda)(-K_{10} - \lambda) + (\varepsilon_2\beta_T\eta_{dT})((1-\varepsilon_2)\beta_T + K_7)(\gamma_{UT}(-K_{10} - \lambda)) \\ -(\varepsilon_2\beta_T\eta_{RT})((1-\varepsilon_2)\beta_T + K_7)(\gamma_{UT} + \tau_2) \end{bmatrix} = 0 \quad (35)$$

Thus, from equation (35), the characteristic equation is given by

$$\lambda^4 + b_4\lambda^3 + b_3\lambda^2 + b_2\lambda + b_1$$

Where

$$b_4 = (((\eta_U - 1)\varepsilon_2 - \eta_U)\beta_t + K_9 K_{10} K_6 K_8)$$

$$b_3 = (((((\eta_U - 1)K_{10} + K_6\eta_U + (\eta_U - 1)K_9 - \eta_{dT}\omega_2\kappa_T - K_7\eta_U + \gamma_{UT}\eta_{dT} - K_8)\varepsilon_2 - K_6\eta_U - K_9\eta_U \\ - K_{10}\eta_U - \gamma_{UT}\eta_{dT})\beta_T + (K_9 + K_6 + K_8)K_{10} + (K_9 + K_8)K_6 + K_9K_8)$$

$$b_2 = ((((K_6\eta_U + (\eta_U - 1)K_9 - \eta_{dT}\omega_2\kappa_T - K_7\eta_U + \gamma_{UT}\eta_{dT} - K_8)K_{10} + (K_9\eta_U + \gamma_{UT}\eta_{dT})K_6 + (-K_7\eta_U - K_8)K_9 \\ + (-K_7\eta_{dT} + +\tau_2\eta_{RT})\gamma_{UT} - \kappa_T\omega_2(K_8\eta_{dT} + +\tau_2\eta_{RT}))\varepsilon_2 + (-K_6\eta_U - K_9\eta_U - \gamma_{UT}\eta_{dT})K_{10} + (-K_9\eta_U - \gamma_{UT}\eta_{dT})K_6 \\ - \gamma_{UT}\eta_{RT}\tau_2)\beta_T + ((K_9 + K_8)K_6 + K_9K_8)K_{10} + K_6K_9K_8)$$

$$b_1 = K_9K_{10}K_6K_8 - ((((K_9\eta_U + \gamma_{UT}\eta_{dT})K_{10} + \gamma_{UT}\eta_{RT}\tau_2)K_6(1 - \varepsilon_2) + \\ ((K_7\gamma_{UT}\eta_{dT} + (\eta_{dT}\omega_2\kappa_T + K_9)K_8 + K_9K_7\eta_U)K_{10} + \eta_{RT}\tau_2(\omega_2\kappa_T K_8 + K_7\gamma_{UT}))\varepsilon_2)\beta_T)$$

Thus according to Routh Hurwitz Criteria of order four (4),

$$n = 4 : b_1 > 0, b_3 > 0, b_4 > 0, \text{and } b_1 b_2 b_3 > b_3^2 + b_1^2 b_4.$$

Then for $b_1 > 0$ we have

$$\frac{\left((((K_9\eta_U + \gamma_{UT}\eta_{dT})K_{10} + \gamma_{UT}\eta_{RT}\tau_2)K_6(1 - \varepsilon_2) + ((K_7\gamma_{UT}\eta_{dT} + (\eta_{dT}\omega_2\kappa_T + K_9)K_8 + K_9K_7\eta_U)K_{10} + \eta_{RT}\tau_2(\omega_2\kappa_T K_8 + K_7\gamma_{UT}))\varepsilon_2)\beta_T\right)}{K_9K_{10}K_6K_8} < 1,$$

Implying that

$$R_T < 1$$

According to (Castillo-Chavez et al. 2002) and (Driessche and Watmough 2002), all eigenvalues of the matrix F – V have negative real parts. It follows that the linearized differential inequality above is stable whenever $R_T < 1$. Consequently $S = (L_T = T_U = T_D = R_T = 0) \rightarrow (0,\ 0,\ 0,\ 0)\ at\ t \quad \rightarrow \infty$. Substituting $L_T = T_U = T_D = R_T = 0$ in (R_T) gives $S(t) \rightarrow S(0)\ as\ t \rightarrow \infty$. Hence, we have established that the disease free equilibrium is globally asymptotically stable whenever $R_T < 1$ and unstable $R_T > 1$.

3.12. TB Sensitivity analysis

Also to each parameters involved in R_T, the sensitivity indices of R_T with respect to each parameter is calculated below,

Results obtained were tabulated below as follows:

Table 3. Values of numerical sensitivity of tb

PARAMETERS	SENSITIVITY VALUES
β_T	0.9999999
γ_{UT}	-0.0000000
μ	-0.0598660
ε_2	0.9575027
δ_{dT}	-0.0064931
δ_{UT}	-0.0110215
δ_{RT}	-0.0165677
κ_T	-1.0089064
τ_2	$-4*10^{-10}$

3.13 Analysis of the full model

Consider now the Co-infection model (14) of HIV-TB

Disease free equilibrium of the full model is given by

$$\varepsilon_1 = \left(S^*, L_H{}^*, H_U{}^*, H_D{}^*, T_H{}^*, L_T{}^*, T_U{}^*, T_D{}^*, R_T{}^*\right)$$

$$\varepsilon_1 = \left(\frac{\pi}{\mu}, 0,0,0,0,0,0,0,0\right) \tag{34}$$

3.14 Derivation of basic reproduction number (R₀) for HIV-TB co-infection

The Next Generation Matrix (F.V¹) Method

The basic reproduction number of the model (16) R_{TH} is calculated by using the next generation matrix (Driessche and Watmough, 2002). Using their approach (Driessche and Watmough, 2002).

The associated matrices F and V, are given, respectively,

$$
F = \begin{pmatrix}
\varepsilon_1\beta_H & \varepsilon_1\beta_H\eta_U & \varepsilon_1\beta_H\eta_{dH} & \varepsilon_1\beta_H\eta_T & 0 & 0 & 0 & 0 & 0 \\
(1-\varepsilon_1)\beta_H & (1-\varepsilon_1)\beta_H\eta_U & (1-\varepsilon_1)\beta_H\eta_{dH} & (1-\varepsilon_1)\beta_H\eta_T & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
\varepsilon_2\beta_T & \varepsilon_2\beta_T\eta_U & \varepsilon_2\beta_T\eta_{dT} & \varepsilon_2\beta_T\eta_{RT} & 0 & 0 & 0 & 0 & 0 \\
(1-\varepsilon_2)\beta_T & (1-\varepsilon_2)\beta_T\eta_U & (1-\varepsilon_2)\beta_T\eta_{dT} & (1-\varepsilon_2)\beta_T\eta_{RT} & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0
\end{pmatrix}
$$

and

$$
V = \begin{pmatrix}
K_1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
-K_2 & K_3 & 0 & 0 & 0 & 0 & 0 & 0 \\
-\omega_1\kappa_H & -\gamma_{UH} & K_4 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & -\tau_1 & K_5 & 0 & 0 & 0 & 0 \\
K_6 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
-K_7 & K_8 & 0 & 0 & 0 & 0 & 0 & 0 \\
-\omega_2\kappa_T & -\gamma_{UT} & K_9 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & -\tau_2 & K_{10} & 0 & 0 & 0 & 0
\end{pmatrix}
$$

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

$$
R = \left\{ \begin{aligned}
&\frac{1}{K_4 K_5 K_1 K_3 K_9 K_{10} K_6 K_8}\big(((-K_8 K_9 \varepsilon_2 \beta_H (K_4 \eta_U + \gamma_{UH}\eta_{dH})K_1^2 + (((-\beta_H(-1+\varepsilon_1)(K_4\eta_U + \gamma_{UH}\eta_{dH})K_8 \\
&- K_3 K_4 \eta_U \beta_T(-1+\varepsilon_2))K_6 + K_3 K_4 \varepsilon_2 \beta_T(K_7\eta_U + K_8))K_9 - K_4\eta_{dT}(\gamma_{UH}(-1+\varepsilon_2)K_6 - \\
&\varepsilon_2(K_8\kappa_T\omega_2 + K_7\gamma_{UT})K_3\beta_T)K_1 + K_9 K_6((K_2\eta_U + K_3)K_4 + \eta_{dH}(K_3\kappa_H\omega_1 + K_2\gamma_{UH}))K_8\varepsilon_1\beta_H)K_5 \\
&-(K_1^2\gamma_{UH}\varepsilon_2 + K_6\gamma_{UH}(-1+\varepsilon_1)K_1 - K_6\varepsilon_1(K_3\kappa_H\omega_1 + K_2\gamma_{UH}))K_9 K_8\eta_{TH}\beta_H\tau_1)K_{10} - K_4\eta_{RT}\tau_2 \\
&(\gamma_{UT}(-1+\varepsilon_2)K_6 - \varepsilon_2(K_8\kappa_T\omega_2 + K_7\gamma_{UT}))K_3 K_1 K_5\beta_T
\end{aligned} \right\} \quad (35)
$$

3.15   Local stability of disease free equilibrium (dfe) of HIV-TB model

Theorem 5: The disease free equilibrium of the system (16) is locally asymptotically stable (LAS) if $R_{HT} < 1$ and unstable if $R_{HT} > 1$.

Proof: Thus, to   determine the local stability of E_0, the following matrix is computed corresponding to equilibrium point E_0. considering the stability of the disease free equilibrium at the critical point (0,0,0,0,0,0,0,0,0). Then we have,

The jacobian matrix of equation (16) is

$$J_{HT} = \begin{pmatrix} -\mu & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & -K_1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & K_2 & -K_3 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & \omega_1 \kappa_H & \gamma_{UH} & -K_4 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & \tau 1 & -K_5 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & -K_6 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & K_7 & -K_8 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & \kappa_T \omega_2 & \gamma_{UT} & -K_9 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & \tau_2 & -K_{10} \end{pmatrix} \quad (36)^{\mathsf{T}}$$

hen the characteristics equation is obtained as $\left| J_{HT} - \lambda I \right| = 0$ (where I is 9*9 identity matrix). Where,

$$\lambda I = \begin{bmatrix} \lambda & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & \lambda & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & \lambda & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & \lambda & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & \lambda & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & \lambda & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & \lambda & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & \lambda & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & \lambda \end{bmatrix}$$

Hence $\left| J_{HT} - \lambda I \right| = 0$ implies that

$$\begin{pmatrix} -\mu - \lambda_1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & -K_1 - \lambda_2 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & K_2 & -K_3 - \lambda_3 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & \omega_1 \kappa_H & \gamma_{UH} & -K_4 - \lambda_4 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & \tau 1 & -K_5 - \lambda_5 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & -K_6 - \lambda_6 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & K_7 & -K_8 - \lambda_7 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & \kappa_T \omega_2 & \gamma_{UT} & -K_9 - \lambda_8 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & \tau_2 & -K_{10} - \lambda_9 \end{pmatrix} \quad (37)$$

From equation (37), we have

$$\lambda_1 = -\mu, \ \lambda_2 = -K_1, \lambda_3 = -K_3, \ \lambda_4 = -K_4, \ \lambda_5 = -K_5, \ \lambda_6 = -K_6, \ \lambda_7 = -K_7, \ \lambda_8 = -K_9$$

$$\lambda_9 = -K_{10}$$

Since all the real roots are negative, real and distinct. Hence, disease free equilibrium of the HIV-TB model (16) is locally asymptotically stable (LAS).

3.16   Global stability of disease free equilibrium (HIV-TB)

Theorem 6: The disease free-equilibrium of the system (16) is globally asymptotically stable whenever $R_{HT} < 1$ and unstable if $R_{HT} > 1$.

Proof: It follows that at steady state. The proof is based on using the comparison theorem (Lakshmkantham et al, 1989), to prove the global stability.

The DFE of the model (1) given by disease free, is GAS in D* if $R_{HT} < 1$.

$$
\begin{pmatrix}
\dfrac{dL_H}{dt} \\[4pt]
\dfrac{dH_U}{dt} \\[4pt]
\dfrac{dH_D}{dt} \\[4pt]
\dfrac{dT_H}{dt} \\[4pt]
\dfrac{dL_T}{dt} \\[4pt]
\dfrac{dT_U}{dt} \\[4pt]
\dfrac{dT_D}{dt} \\[4pt]
\dfrac{dR_T}{dt}
\end{pmatrix}
= (F - V)
\begin{pmatrix}
L_H \\ H_U \\ H_D \\ T_H \\ L_T \\ T_U \\ T_D \\ R_T
\end{pmatrix}
- Fi
\begin{pmatrix}
L_H \\ H_U \\ H_D \\ T_H \\ L_T \\ T_U \\ T_D \\ R_T
\end{pmatrix}
$$

Where

$$
F = \begin{pmatrix}
\varepsilon_1\beta_H & \varepsilon_1\beta_H\eta_U & \varepsilon_1\beta_H\eta_{dH} & \varepsilon_1\beta_H\eta_T & 0 & 0 & 0 & 0 & 0 \\
(1-\varepsilon_1)\beta_H & (1-\varepsilon_1)\beta_H\eta_U & (1-\varepsilon_1)\beta_H\eta_{dH} & (1-\varepsilon_1)\beta_H\eta_T & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
\varepsilon_2\beta_T & \varepsilon_2\beta_T\eta_U & \varepsilon_2\beta_T\eta_{dT} & \varepsilon_2\beta_T\eta_{RT} & 0 & 0 & 0 & 0 & 0 \\
(1-\varepsilon_2)\beta_T & (1-\varepsilon_2)\beta_T\eta_U & (1-\varepsilon_2)\beta_T\eta_{dT} & (1-\varepsilon_2)\beta_T\eta_{RT} & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0
\end{pmatrix}
$$

and

$$V = \begin{pmatrix} K_1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ -K_2 & K_3 & 0 & 0 & 0 & 0 & 0 & 0 \\ -\omega_1\kappa_H & -\gamma_{UH} & K_4 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & -\tau_1 & K_5 & 0 & 0 & 0 & 0 \\ K_6 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ -K_7 & K_8 & 0 & 0 & 0 & 0 & 0 & 0 \\ -\omega_2\kappa_T & -\gamma_{UT} & K_9 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & -\tau_2 & K_{10} & 0 & 0 & 0 & 0 \end{pmatrix}$$

According to (Castillo-Chavez et al. 2002) and (Driessche and Watmough 2002), all eigenvalues of the matrix F − V have negative real parts. It follows that the linearized differential inequality above is stable whenever $R_{HT} < 1$.

Consequently,

$$S = (L_H = H_U = H_D = H_W = L_{TH} = A_{TH} = L_{TH} = L_{HT} = A_{HT} = L_T = T_U = T_D = F_T = R_T = R_{TH} = 0) \rightarrow$$
$$(0,\ 0,\ 0,\ 0,\ 0)\ at\ t \rightarrow \infty$$

Hence, we have established that the disease free equilibrium is globally asymptotically stable whenever $R_{HT} < 1$ and unstable $R_{HT} > 1$.

3.17. HIV-TB Sensitivity analysis

Also to each parameters involved in R_{TH}, the sensitivity indices of R_{TH} with respect to each parameter is calculated below,

Results obtained were tabulated below as follows:

Table 4.   Values of numerical sensitivity of HIV/TB

PARAMETERS	SENSITIVITY VALUES
β_T	0.6005990
β_H	0.3994010
κ_H	-0.9588586
ω_2	$5.8991105*10^{-13}$
ε_1	0.3931723
κ_T	-0.5379916
γ_{UH}	-0.000567
γ_{UT}	$-3.0628670*10^{-10}$
μ	-0.0665580
ε_2	0.5685420
δ_{UH}	-0.0012241
δ_{TH}	-0.0141147
δ_{dH}	-0.0012580
δ_{UT}	-0.0066195

δ_{dT}	-0.0038995
δ_{RT}	-0.0099506
τ_1	-0.0476514
τ_2	-0.0057460

4.0.   Numerical simulation. The full model is simulated to access the impact of each parameter in the dynamical spread of HIV-TB co-infection.

Table 5. Parameter Values used in Numerical Simulations

Parameters	Value	Sources
π	2000	Okuonghae etal.,(2007)
μ	0.02	Becerra et al., (2005)
τ_1, τ_2	0.20619, 0.30619	Assumed
$\varepsilon_1, \varepsilon_2$	0.7, 0.7	Sharomi et al., (2008)
κ_H	0.2522	Daniel et al., (2007)
κ_T	0.3522	Assumed
ω_1, ω_2	0.2, 0.2	Sharomi et al., (2008)
γ_{UH}, γ_{UT}	0.2, 0.3	Assumed
$\beta_H \beta_T$	0.1, 0.2	Colijn et al., (2007)
δ_{UH}, δ_{dH}	0.3, 0.1	Colijn et al., (2007)
$\eta_U, \eta_{dH}, \eta_T$	0.001, 0.001, 0.001	Sharomi et al., (2008)
$\delta_{UT}, \delta_{dT}, \delta_{RT}$	0.3, 0.1, 0.1	Daniel & Andrei(2007)
η_{dT}, η_{RT}	0.001, 0.001,	Sharomi et al., (2008)

Graph of total population when $\beta_H = 0.3$ Graph of total population when $\beta_H = 0.6$
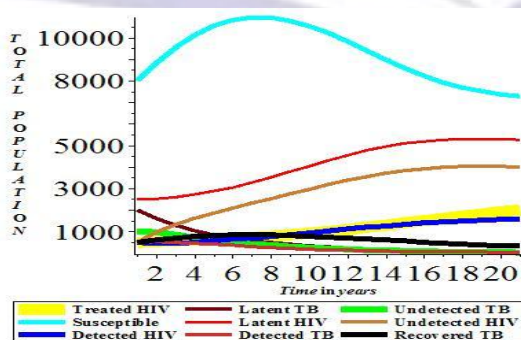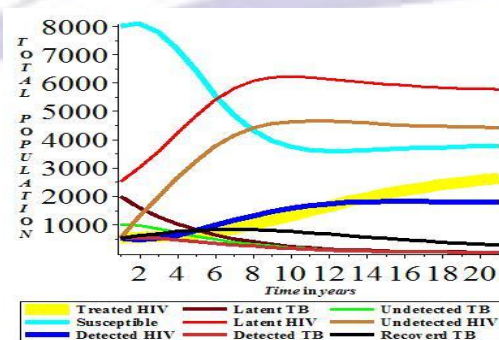
Fig. 1.   **Fig. 2.**

Graph of total population when $\beta_H = 0.9$ Graph of total population when $\beta_T = 0.3$
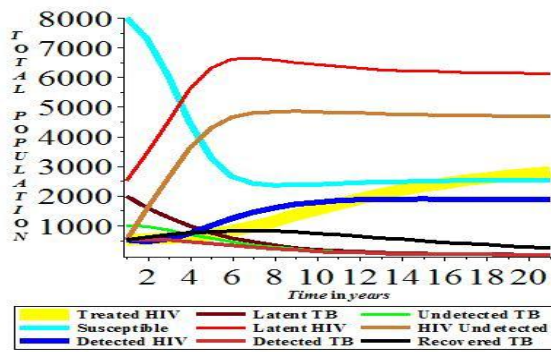
Fig.3.

Graph of total population when $\beta_T = 0.6$
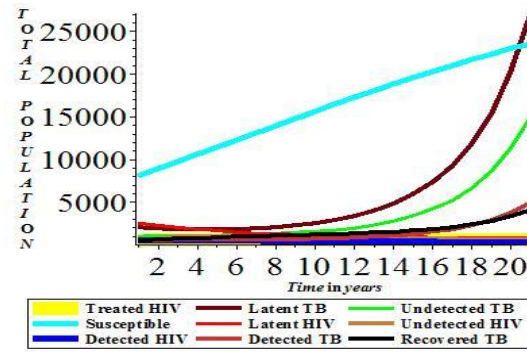
Fig. 4.

Graph of total population when $\beta_T = 0.9$
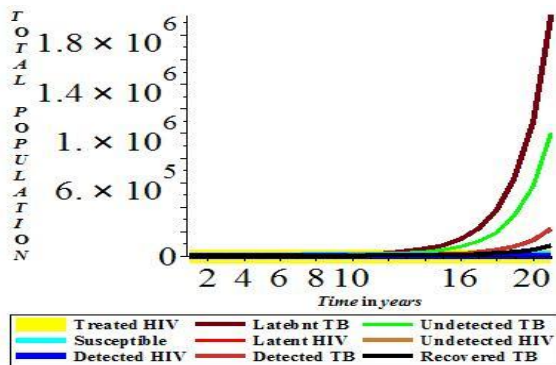
Fig. 5.

Graph of total population when $\varepsilon_1 = 0.2$
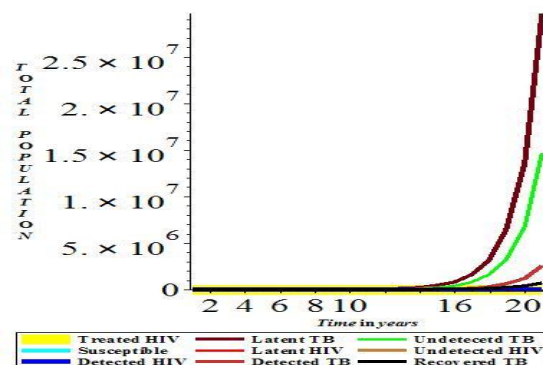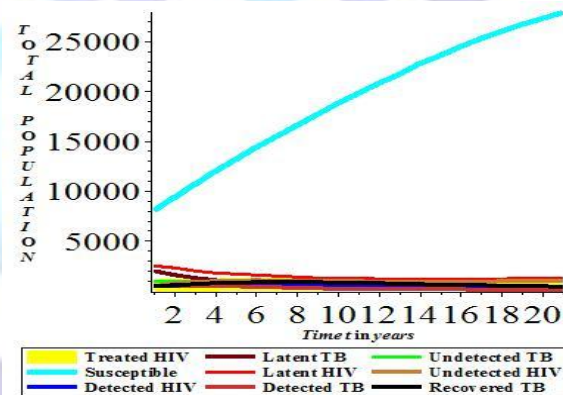

Fig. 6.

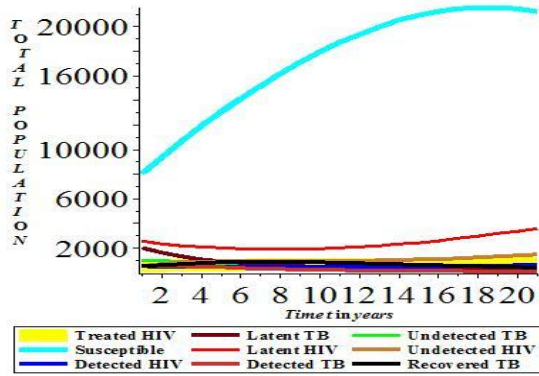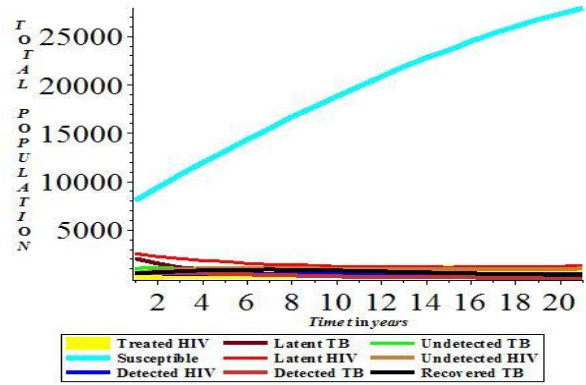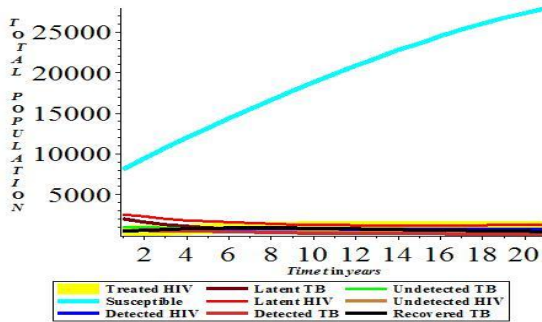Graph of total population when $\varepsilon_1 = 0.6$
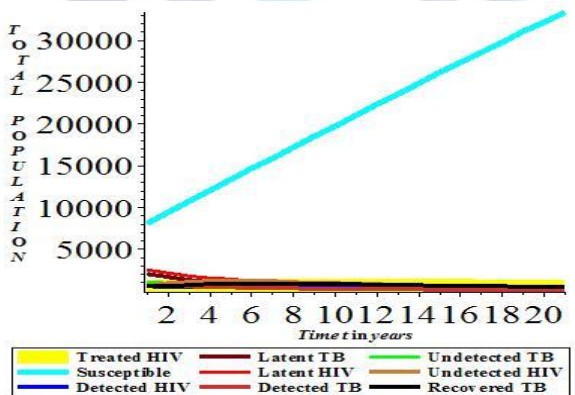
Fig. 7.

Fig. 8.

Graph of total population when $\varepsilon_1 = 0.9$

Graph of total population when $\varepsilon_2 = 0.2$

Fig. 9.

Graph of total population when $\varepsilon_2 = 0.7$

Fig. 10.

Graph of total population when $\varepsilon_2 = 0.9$

Fig. 11.

Graph of total population when $\gamma_{UH} = 0.4$
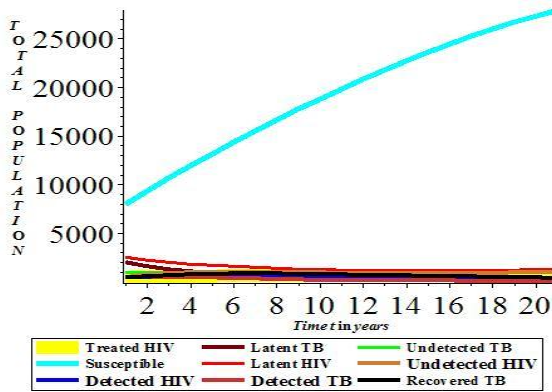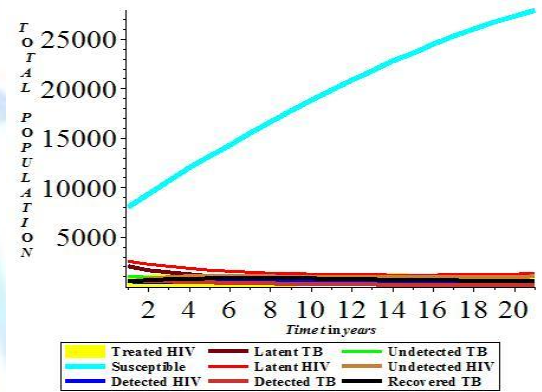
Fig. 12.

Graph of total population when $\gamma_{UH} = 0.7$

Fig. 13.
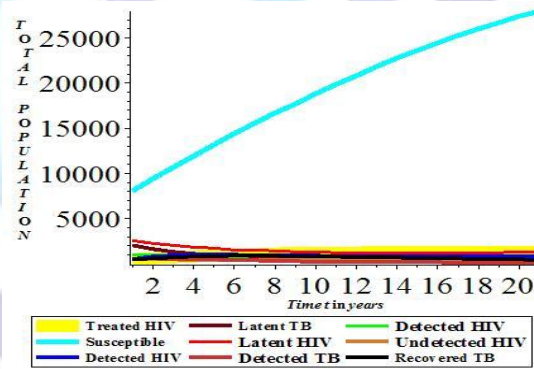
Graph of total population when $\gamma_{UH} = 0.9$

Fig. 14.

Graph of total population when $\gamma_{UT} = 0.4$
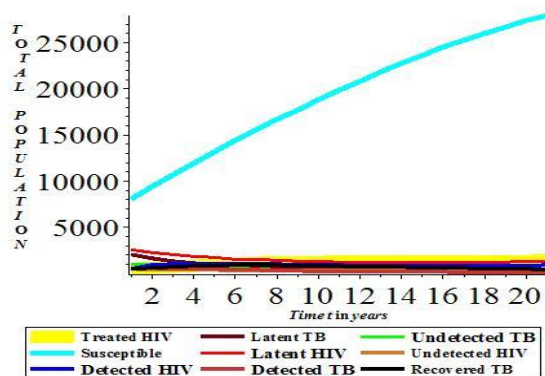
Fig. 15.
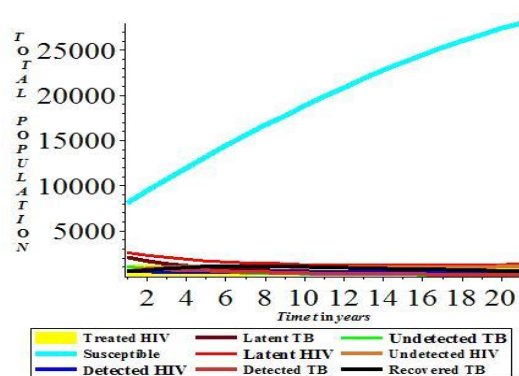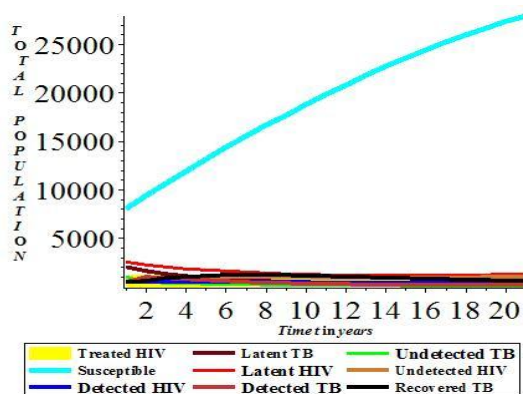

Fig. 16.

Graph of total population when $\gamma_{UT} = 0.7$

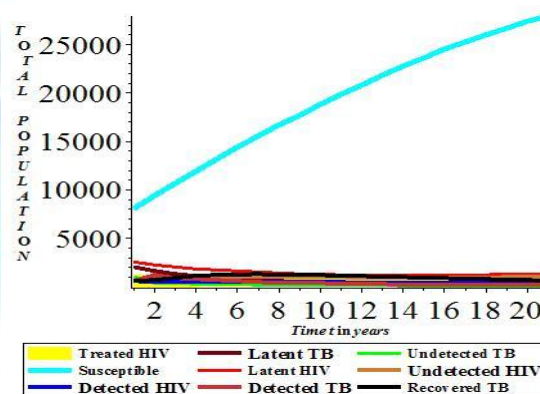**Graph of total population when $\gamma_{UT} = 0.9$**

Fig.17.

Fig. 18.

5.0   Discussion of results

We analyzed a HIV-TB mathematical model, by evaluating the sensitivity indices of parameters involved in the basic reproduction number to know the parameters that need more attention. It is used to discover parameters that have a high impact on basic reproduction number and should be targeted by intervention strategies.

It is observed from the **table 2, 3 and 4.** that when the parameters with positive sensitivity values increase while the remaining parameters remain constant, the value of basic reproduction number increases, and this increase the endemicity of the disease in the population. The increment in basic reproduction number makes it more difficult to have disease free environment .Parameters with negative sensitivity values have less effect in the dynamical spread of HIV-TB co-infection.

Transmission rate β_H, β_T and Fast progresser $\varepsilon_1, \varepsilon_2$ are the most sensitive parameters in the analysis. Medical practitioners need to work on positive indices parameters most especially parameters that have pronounced effect on the basic reproduction number (R_0) i.e. transmission rates β_H and β_T in order to have stable free disease environment.

Using the data in table 5.1, fig. 1, 2, 3, 4, 5 and 6 shows that effective contact rate β_H and β_T decreases the susceptible individuals and increases the latent, infected undetected and infected detected individuals. Fig 7, 8, 9, 10, 11 and 12 shows the effect of progresser on latent and infected undetected individuals. When ε_1 increases from 0.2 to 0.9, it increases latent infected individuals from 2122 to 2297. However, when progresser of TB increases from 0.2 to 0.9, it increases TB latent infected individuals from 1502 to 1640. Fig. 13, 14, 15, 16, 17 and 18 shows that detection of infected undetected individuals has a pronounced effect on infected detected and undetected individuals. When the detection of HIV infected undetected individuals increases from 0.4 to 0.9, it reduces infected undetected individuals from 608 to 369 but increases infected detected individuals from 594 to 832. Also, when the detection of TB infected undetected individuals increases from 0.4 to 0.9 it reduces infected undetected individuals from 767 to 302 but increases infected detected individuals from 706 to 1166.

6.0 Conclusion

In this paper, a deterministic model for the dynamical transmission of HIV-TB co-infection is presented. The objective is to determine the parameters that influence the dynamical spread of the diseases; the model includes Nine (9) compartmental differential equations.

A threshold parameter R_0 is defined and is shown that the disease will spread only if its value exceeds unity, i.e. $R_0 > 1$.

Sensitivity analysis of basic reproduction number R_0 to all the parameters tell us how crucial and important each parameter is to the disease spread in the environment. It showed that parameters representing the transmission rate of HIV and TB have a large impact on the dynamics of the diseases, and which should be targeted by medical practitioners to forestall the spread of the diseases. Also, fast progressor rate of HIV and TB needs to be checked, effort should be put in place medically to improve immunity of susceptible individuals, from the mathematical analysis, we discovered that people with weak immunity are more prone to the two diseases. It also has great significant effect when the two diseases co-exist in a particular patient.

Numerical simulation shows effects of parameters on the dynamical spread of HIV-TB co-infection and this tells us that a change in these parameters can significantly reduce the spread of HIV-TB co-infection disease in the population over time.

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