Mathematical model of HIV/AIDS, tuberculosis and their co-evolution with optimal control: A case study in Ethiopia

by

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Abstract

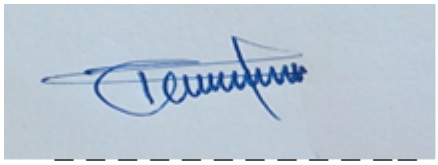
The communicable disease tuberculosis (TB), human immunodeficiency virus/acquired immune deficiency syndrome (HIV/AIDS) disease, and their co-infection are the most serious public health issues in the world. In this thesis, three population level mathematical models of the three infections in Ethiopia are developed and analyzed. The first model considers the dynamics of HIV/AIDS, which comprise the following exclusive classes of individuals, the aware and unaware susceptibles, undiagnosed HIV infectious, diagnosed HIV infectious with and without AIDS symptoms, and those under HIV treatment. This model considers the rate of becoming aware and unaware as a function of media campaigns, whereas screening and treatment rates are constant. The effective reproduction number, equilibria, and nature of stability were formulated. The bifurcation occurs when the effective reproduction number is equal to unity. This model is extended to a new model which incorporates interventions such as preventive, screening, and treatment strategies. In this model, the optimal control problem is formulated and solved analytically. In addition to this, the optimality system is derived and solved numerically using the forward-backward sweep method (FBSM). Finally, the cost-effectiveness of some combined control strategies is derived. The second model reflects the TB transmission dynamics with drug resistance TB (DR-TB). The two infectious TB stages, namely drug-sensitive TB and drug-resistant TB, are considered in the model. Assuming that drug-sensitive TB can be cured by first-line anti-TB drugs. In fact, once the Tubercle Bacilli become resistant to one or more anti-TB drugs, the drug-resistance TB occurs. The model is analyzed analytically and extended to an optimal control problem via incorporating preventive efforts, case finding, and case holding. In the study, four different strategies are introduced based on different combination of measures. The optimal control problem is examined both analytically and numerically. The third model describes a new mathematical model of human immunodeficiency virus (HIV) associated with tuberculosis (TB). This full TB-HIV co-infection model is analyzed analytically. Which is extended to an optimal control problem by using controlling variables such as preventive efforts, case finding effort for TB, and HIV treatment. We proposed four strategies, which are combinations of two or more control measures at a time. The model with controls is analyzed both analytically and numerically. The numerical results are derived using the classical Runge-Kutta method of order four (RK4-method). The finding suggests that optimal combination

strategies are used to reduce both the disease burden and the cost of intervention. Further, the cost- effectiveness of each strategy is assessed to identify the best cost-effective approach the fight against TB-HIV co-infection in Ethiopia.

Keywords*: HIV/AIDS, TB, co-dynamics, RK4-method, Equilibrium, Stability, Bifurcations, Optimal control, FBSM, Cost-effective analysis.*

Declaration Student number: 67122884

I declare that ***"Mathematical model of HIV/AIDS, tuberculosis and their co-evolution with optimal control: A case study in Ethiopia"*** is my own work, that it has not been submitted before for any degree or examination at any other university, and that all sources I have used or quoted have been indicated and acknowledged by complete references.



Tigabu Kasia Ayele

$----3/30/2023--$

Date

Dedication

I sentimentally would like to dedicate this work to the memories of my Mother. I pray that God gives her eternal life. May her soul rest in peace. Amen.

List of Acronyms

Abbreviation	Meaning
AIDS	Acquired Immunodeficiency Syndrome
ART	Antiretroviral Therapy
CD4	Cluster of Differentiation 4
CDC	Center for Disease Control and prevention
DE	Differential Equation
DEP	Disease-free Equilibrium Point
DR-TB	Drug-resistance tuberculosis
EEP	Endemic Equilibrium Point
EPHI	Ethiopian Public Health Institute
EPHIA	Ethiopia Population-based HIV Impact Assessment
HCT	HIV Counseling and Testing
HIV	Human Immunodeficiency Virus
HMFDRE	Healty Minister of Federal Democratic Republic of Ethiopia
ICER	Incremental Cost -Effectiveness Ratio
IPT	Isoniazid Preventive Therapy
MATLAB	Matrix Laboratory
MDR-TB	Multidrug-resistant tuberculosis
ODE	Ordinary Differential Equation
PLH	People Living with HIV
PMP	Pontryagin's Maximum Principle
SSA	Sub-Saharan Africa
TB	Tuberculosis
UNAIDS	Joint United Nations Programme on HIV/AIDS
WHO	World Healthy Organization
XDR-TB	Extensively drug resistant tuberculosis

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List of Publications

The following research papers from this thesis have been published to accredited journals.

1. Tigabu Kasia Ayele, Emile Franc Doungmo Goufo, and Stella Mugisha. Mathematical modeling of hiv/aids with optimal control: A case study in Ethiopia. Elsevier Journal, Results in Physics, 26:104263, 2021.

2. Tigabu Kasia Ayele, Emile Franc Doungmo Goufo, and Stella Mugisha. Mathematical modelling of tuberculosis with drug resistance in the presence of optimal control: A case study in Ethiopia. Elsevier Journal, Mathematics and Computers in Simulation (Under review and close to completion).

3. Tigabu Kasia Ayele, Emile Franc Doungmo Goufo, and Stella Mugisha. Co-Epidemics of HIV/AIDS and tuberculosis model with optimal control: A case study in Ethiopia. International Journal of Dynamics and Control, Springer Journal (Revised submitted and close to completion).

Contents

Chapter 1

General introduction

1.1 Background information on HIV/AIDS

The Human Immunodeficiency Virus (HIV) is the causative agent for Acquired Immunodeficiency Syndrome (AIDS) and has become one of the major global health challenges [fdr13, VTC+14, O+12]. This virus was identified in 1983, two years later the AIDS cases were reported [cdc20]. HIV infects cells in the central nervous system and the immune system. The main type of cell that HIV infects is T-helper lymphocytes. These cells are in the immune system whose role is to organize the actions of other cells in the system. The weak immune system is the result of a high number of reductions of these cells. T-helper cells have a protein called CD4+ on their surface. This CD4+ layer can retain the HIV virus before entering the cells. A reader can see the books Ronald [RJ96] and Brauer [BVdDWA08] for further information. Once HIV enters into this cell, it produces new copies that are able to infect other cells. Thus, T-helper cells are responsible for fighting against the diseases, but their numbers are reducing gradually when HIV infection increases continuously. This disease has been killing people and will continue to do so unless a breakthrough is made. According to the UNAIDS 2021 report, the total number of people living with HIV worldwide is estimated to be 37.7 million, with 36.0 million adults and 1.7 million children under the age of 15. In this report, the number of newly infected people with HIV and the number of people who died with AIDS in 2020 are estimated at 1.5 million and 680 000, respectively. The data statistics show that, in Eastern and Southern Africa, there are 20.6 million people living with HIV, 670 000 people newly infected with HIV and 310 000 people dead due to AIDS. In Western and Central Africa, approximately 4.7 million people are infected with HIV, 200 000 people are newly infected with HIV, and 150 000 people die as a result of AIDS. In the year 2020, there will be 4 000 new HIV infections every day in the world, of which 60% are in Sub-Saharan Africa.

As one of Sub-Saharan Africa country, Ethiopia in 2019, there were around 1 207 826 people living

with HIV, 22 000 new infected individuals with HIV, and 10 543 people died from an AIDS-related disease [(EP20]. Of these overall infected individuals, 613 500 are women aged $15 - 49$, 470 326 are men aged $15 - 49$, 51 000 are children aged 0 to 14. The HIV prevalence rate of adults aged 15 to 49 in Ethiopia is 0.897. Here, the HIV prevalence rates of men and women in this range are 0.51 and 0.39 respectively.
So, we should take remedial action towards controlling this endemic disease seriously at a national level and need more effort than before. To control the burden of this disease, there are different self-protective measures of HIV/AIDS (absenteeism, faithfulness, and using condom). Till now, there is no cure or vaccine for this global pandemic. However, there is a treatment called antiretroviral therapy (ART). ART comprises taking a combination of HIV doses daily. ART is recommended for every person who is HIV-infected. It cannot cure the HIV virus, but HIV medicines help HIV-infected individuals prolong their life.

1.1.1 Modes of transmission

HIV transmission is the spread of the HIV virus from person-to-person. Previously, it was spread accidentally via blood transfusion. Many individuals in the world were infected through this pathway. However, nowadays the blood supply is more severely tested and controlled. A person can't get HIV from donating blood if a new sterile (clean) needle is used for each donation [cx113]. The HIV transmission risk can also be increased by unsafe sex (sex without condoms), because of the semen and vaginal secretion. In addition to this, individuals can be infected with HIV when using injection drugs through sharing needles. Thus, cleaning the needles with a bleach solution before reusing them is the best way. Experts recommend that using fresh needles at any time can remove any risk of infection. Moreover, there is also vertical transmission, where pregnant mothers are HIV positive. The virus can be transferred from an infected mother to her infant during pregnancy or breast feeding. Given that medical care and HIV drugs for HIV-infected pregnant women are essential to remove the risk of infants getting the virus. mothers who are HIV+ should not breastfeed their babies.

1.1.2 How HIV is not transmitted

The HIV virus cannot be transmitted unless certain body fluids are interchanged. Everyone can significantly reduce the HIV transmission risk when injecting drugs through new or clean needles. These measures are vital to protecting a person from the virus. HIV is not transmitted by kissing and sharing exercise equipment. It can't be transmitted when a person is sharing food or drinks, a shower, bath, or bed used by an HIV-positive person [cx113]. Through time, the HIV virus can weaken the immune system so it is unable to resist opportunistic infections. Usually, a person who

has a healthy immune system can control opportunistic infections. However, a person with AIDS has a weakened immune system. Thus, urgent medical intervention is necessary to prevent certain opportunistic infections or treat severe diseases.

1.1.3 Stages of HIV/AIDS

The WHO HIV/AIDS department stated the following four distinct stages of HIV/AIDS [Org10]. These are

1. **Primary infection stage**

   This is the first stage of HIV infection. It begins almost immediately after a person first contracts HIV. This stage is also called acute stage and which takes 2 to 4 weeks. During this time, some people experience flu-like symptoms such as headaches, rashes, and fever. At this stage, HIV duplicates quickly and spreads throughout the human body. During the first few weeks, infected people are highly infectious [xc121, GGD$^+$09]. This phase helps physicians decide whether the patient is eligible for treatment or not. Often, if an HIV test is done, it will come back to negative. This is because HIV antibodies are not yet being produced, but HIV continues to duplicate in the body [Eji11]. Gradually, the antibodies are starting to be produced in the immune system in response to the virus. This situation is known as sero-conversion. When this occurs, about 20% of HIV-infected people show symptoms that is not mild. Nevertheless, HIV diagnosis is missed at this phase [xc121]. Individuals should repeat the HIV test after six months if they believe they have been exposed to HIV.

2. **Asymptomatic stage**

   This is the second stage. Some individuals may have symptoms within a few years, but others can go on average 8 years without symptoms. The infectious period is based on a person characterized by a CD4+ count nearby 500 cells per μl [dcb]. There are no major AIDS-related symptom at this stage, even if there may be swollen glands. The antibody test will display a HIV+ result, due to antibodies being differentiable in the blood. This test is a viral load test which plays a vital role in HIV treatment [xc121].

3. **Symptomatic stage**

   This is the third stage, where the immune system is damaged by HIV and symptoms begin to appear. This leads to a high level of CD4+ cell destruction, and the immune system cannot replace the CD4+ cells that are lost. HIV symptoms appear when the immune system fails to perform its functions. Initially, the symptoms are mild in stage and gradually grow into a severe stage. Opportunistic infections are also beginning to appear. These can affect just

about all parts of the body. For instance, tuberculosis, human papillomavirus, shingles, and cytomegalovirus are known opportunistic infections that appear in HIV-infected individuals. At this stage, HIV treatment helps HIV-infected people to decrease their viral load. However, if they are not starting or delaying the treatment, their immune systems will deteriorate, resulting in the worst HIV symptom [xc121].

4. **Advanced AIDS stage**

   This is the final stage when a person is having AIDS that is diagnosed from a class of similar HIV symptoms caused by severe infection [xc121] . At this stage HIV+ people can die due to the cause of these severe infections. A person infected with HIV progressed to AIDS is having a CD4+ count of 200 per ml or lower. However, a person is having around 1000 per ml in normal situations [Mur01]. Moreover, at this phase opportunistic infections can develop in an infected individual body parts, such as gastro-intestinal system, respiratory system, central nervous system, and on the skin also.

1.1.4 Treatment

HIV treatment is crucial for HIV-infected people to reduce the viral load in their body [cdc20]. HIV medicine is known as ART, which can control HIV. However, taking this medicine does not protect the transmission of sexual transmitted diseases, including HIV.
There is no realistic evidence at which stage HIV treatment should start. The death rates are increasing high when ART treatment is delayed. There was a debate regarding this issue. There was a panel discussion on ART guidelines for adults and adolescents in 2009. The participants suggested that ART should be given to HIV-infected people with a CD4 count of between 350 – 500 and no lower than 350 cells per μl [STU$^+$10]. They emphasized that every patient starting ART should be ready for continuing ART as well as they had to understand the benefit and risk of the treatment [GGD$^+$09]. However, the CDC recommends that all HIV patients can take HIV medicine irrespective of their health status and how long the virus is in their body. Moreover, if HIV treatment is delayed, HIV will continue to damage the patient's immune system. This result means HIV can progress to the AIDS stage and the occurrence of opportunistic infections can increase [cdc20].

1.2 Background information on tuberculosis

Tuberculosis (TB) is a contagious disease caused by the Mycobacterium tuberculosis (a tubercle bacilli) bacteria. It is spread through the air by people who have active tuberculosis. When infectious individuals are coughing, tiny droplets in the air are duplicated. TB infects millions of people

every year and it is one of the ten deadliest diseases on the globe. It is also the principal cause of death, ranking above the Human immunodeficiency Virus (HIV) [MZ18].

When TB disease affects the lungs, it is called pulmonary TB. When it affects other body part such as brain, glands, kidney, and bones is called extra-pulmonary TB [MGM06, Ade08]. There are two stages of TB. One is active TB which covers 10% of the total infected people. The remaining 90% is classified as latent infection (a person has TB but does not have any symptoms). People who develop active TB are infectious; they transmit the virus to others; whereas people in latent infected stage are not infectious that could not transmit the virus to others.

People who have been in contact for a long time with TB infectious individuals, they have a chance of being infected by TB [JKW19]. According to a WHO report, it is estimated that about one third of the world‘s population is infected with TB [cgt21a]. In this report, globally around 8.7-11 million people develop active TB and around 1.1-1.3 million people die with TB annually. In 2019, the burden of TB disease was high in Africa which takes 25% from the total TB cases in the world [cgt21b]. In Africa, Ethiopia is one of the 30 high TB burden countries globally. In this year Ethiopia had 147 168 notified TB cases, TB incidence rate of 140 per 100 000 populations, and mortality rate of 21 per 100 000 populations [cgt21b].

TB infected people can remain latent for a long period of time [Dav15]. Exposed or latent TB periods can stay from years to decades based on the immune system of infected individuals [BT10]. People with healthy immune system may not fall with latent TB, but people with feeble immune system can progress to active stage due to the occurrence of HIV with low CD4 count, underfeeding, diabetes, smoking and alcohol consumption. If HIV-infected people are ill with TB, they have a chance of dying with the primary agent of overpowering infection [SN08]. The dual infections of TB and HIV are one of the main worldwide health challenges of the 21^{st} century. In 2016, universal TB/HIV co-infection statistics discovered that number of deaths happened. These were 374 000 by HIV, 826 000 by TB and 1 300 000 by co-infection of the two diseases. Even though death related to HIV is less than TB infection. The two (TB and HIV) diseases are overwhelming the patient's immunity and curtail the life span if there is no primal diagnosis and treatment [TAG$^+$18].

WHO approximated that 20 times at higher risk of capturing TB on HIV people than counterparts [YZN16]. This report shows a small fraction (5–15%) of the expected 1.7 billion people infected with tubercle bacilli will progress to TB disease during their lifespan.

TB infections can also develop to drug sensitive TB (active TB) and drug resistance TB which is multidrug-resistant strains (MDR-TB) or extensive drug-resistant TB (XDR TB) [RJF$^+$16,cgt21b]. MDR-TB is resistant to at least two of the five first–line antibiotic, namely isoniazid (INH) and rifampicin (RIF), whereas XDR-TB is a rare type of MDR TB plus extra resist to one fluoroquinolone and one of injectable second-line drugs. These serious drug resistance strains occur when patients

lack adherence to TB medications.
MDR-TB is an emerging problem of TB worldwide. Ethiopia is one of these nations, as of 2019, an estimated prevalence rate was 2.7% and new as well as re-treated cases was 14% from total TB cases [cgt21b]. As of 2020, 1 110 DR-TB patients were under treatment in Ethiopia. Among them 123 patients have died, 17 defaulted from treatment, and the majority are in isolation with treatment [vvv22]. Thus, the most common controlling mechanism is isolating infectious individuals and applying effective treatment.

1.2.1 Symptoms of tuberculosis

If infected people do not show TB symptoms, then they are under latent TB stage. However, if they can show TB symptoms, they are under active TB stage [CPJGS$^+$07]. The symptoms are fever, night sweats, weight loss, chills, loss of appetite, and fatigue [MBR$^+$05]. A person may not show any symptoms of the disease until the infection is severely advanced. Sometimes the symptoms can be blaming for other virus.

1.2.2 Treatment of tuberculosis

A person infected with TB can be treated and cured. The primary effort of TB preventive and controlling measures is vaccination of newborns and detection of active cases to take appropriate treatment. If left untreated he or she becomes ill and the situation may be leading to life risking conditions. Thus, the TB disease can be treated by the most powerful first-line anti-TB drugs such as Isoniazid, rifampin, ethambutol, and pyrazinamide. There are also second and third-line anti-TB drugs such as streptomycin, cycloserine, para-aminosalicylic acid, and fluoroquinolones. If the TB treatment is not managed appropriately until completed, the disease may progress to drug resistance TB (DR-TB) like MDR-TB. It is difficult to treat MDR-TB when an old person is infected by this DR-TB. Moreover, there is also a disease called XDR-TB which comes after MDR-TB. This occurs when the TB disease resists both first and second-line drugs. Almost MDR-TB is incurable by normal first-line treatment and this applies to XDR-TB as well. The best anti-TB drugs in an MDR-TB program are fluoroquinolones. The WHO recommend that treatment of MDR-TB and XDR-TB need long duration of time, approximately from 18 to 24 months [O$^+$19].

1.3 Background information on TB-HIV/AIDS co-infection

The two infectious agents HIV and Mtb (the causal agent of TB) co-exist in humans for decades. We have enough evidence that one of these infections accelerates the progression of the other [AKNG$^+$10, KE11, PJS$^+$12, DAMPDC99]. The prevalence rate of TB in HIV+ people is increasing

because of exogenous re-infection and endogenous re-activation [SPGS08]. Individuals infected by HIV lead to a haggled immune system, subsequently rising susceptibility to Mtb infections. It is difficult to diagnose TB in HIV infected people [MLV16]. The two pathogens Mtb and HIV may come either by co-infection or super-infection. One can increase the effect of the other and they can accelerate the deterioration of immune system function. People living with HIV are 20 up to 30 times at a higher risk of developing active TB disease than their counterparts [ccc20, cgt20]. TB also remains the primary agent of death in HIV infected people, counting for around 1 in 3 deaths associated with AIDS [buy21].

The statistics regarding the burden of this disease is available. As of 2017, globally around 16 million people were HIV-TB co-infected [Glo17]. Recently, WHO 2020 report showed that an estimated number of over 14 million people can be co-infected [cgt21a]. The report stated that South-East-Asia and Sub-Saharan Africa were taking the highest portion. More than 90% of TB deaths occurred in these two regions [WHO20]. TB is also the highest cause of death from TB–AIDS related deaths, of which 95% of this happened in developing nations [RFCC09, LPNS17].

The burden of TB-HIV co-infection is high in Sub-Saharan Africa (SSA) [Gro15]. As stated by WHO report of 2019, about 84% of the total number of TB-HIV co-infection cases occurred in the region. SSA has 12% of the global population, it has accounted for 30% of the 9 million TB incidence cases and more than 270 000 deaths related to TB [TANO$^+$20]. In this region the HIV prevalence is high which grips to over 50% of the patients were dually infected.

As one of the Sub-Saharan Africa countries, Ethiopia is severely affected by the TB-HIV co-epidemics. As of 2019, an incidence rate of TB was 345 per 100 000 of which 33 % are living with HIV [vvv22]. Moreover, the WHO 2020 report stated that Ethiopia is one of the high TB and TB-HIV burden countries in the globe [cgt21b]. In 2019, over 23% of people are HIV+ from active TB individuals in Ethiopia [vvv22]. Co-infection of TB with HIV accelerates the possibility of progressing from latent to active stage [GGGN10].

We have been working together with the HMFDRE staffs to find the data prepared. The information in Table (1.1) shows the overall data of the diseases in Ethiopia in the years 2018-2021.

1.3.1 TB-HIV/AIDS co-infection treatment

HIV and TB have different nature and diverse treatment outcomes. Thus an integrative treatment program is urgently needed for TB-HIV co-infection [AKNG$^+$10, BSL$^+$11]. The well-known international institutions, such as the UNAIDS and WHO agreed that an integrated approach is very important to dealing the dual epidemics including preventive measure, diagnosis, and treatment [DUD$^+$14]. Since TB can be cured with appropriate treatment for a period of six up to nine month, the recommendation for people infected by this co-infection disease is to begin TB treat-

ment immediately. Thereafter, they can start ART treatment on the appropriate starting time suggested by physicians. Initiating ART at/ or afterwards the start of TB therapy may cause Immune Reconstitution Inflammatory Syndrome (IRIS). This happens when a high pill burden of antibiotics and ART exist. If IRIS occurs, it will worsen TB infection and treatment can be complicated. Moreover, delaying ART until after TB therapy is completed may increase HIV transmission risk and death caused by HIV. Hence, it is serious to differentiate the actual time where dual treatment is given for HIV-TB infected people.

1.4 Literature review

Mathematical models are very important to classify a given sample population in to different sub population groups such as infected with, immune to or recovered to and so on. A. G. McKendrick and W. O. Kermack developed deterministic mathematical model in a paper published in 1927 [Bac11]. Earlier, Daniel Bernoulli developed a mathematical modeling of spread of a smallpox in 1766 [Ber66]. He trained as a physician, but later he studied focusing on mathematics and publishing a book in 1724. He investigated the advantage of prevention and vaccination against smallpox. His model showed that globally inoculate the disease smallpox would raise the lifespan from 26.5 years to 30 years [BB04].
Daley and Gani investigated the transmission dynamics, controlling mechanisms, and prediction upcoming course of an outbreak for infectious diseases using mathematical modeling [DG01].
Many literatures relevant to this research were reviewed, developed and analyzed by different researchers. The next portion gives an outlying on some selected models on TB, HIV and their co-infections.

1.4.1 HIV/AIDS transmission dynamics models

Many authors investigated the application of mathematical modeling on HIV/AIDS. The following are few works related to our study over the last decades.
Garira et al. have developed new mathematical HIV/AIDS model, in which they considered public health educational campaigns as an intervention approach without preventative vaccination [MGT09]. They have classified the total population into four subclasses of populations such as susceptible S, educated E, infected I, and AIDS A cases at a time t. They analyzed the model qualitatively and showed that public health education campaigns can decrease the value of R_0 less than unity as envisioned to controlling the disease. Their numerical results showed the effective control of the disease whenever effective implementation of educational campaign brought R_0 below one.
Tripathi et al. proposed a non-linear HIV/AIDS mathematical model to study the effect of contact

tracing on HIV infectives [NTS11]. They observed that, if HIV+ people detected by screening and contact tracing are withdrawn from any transmission method, the disease burden decreases dramatically. However, the disease spreads because of immigration and the absence of contact tracing. Hence, the contact tracing is an essential practice in reducing the disease prevalence whenever screening is not practiced well. Finally, they concluded that educating HIV/AIDS people from unprotected sex or any risky activities is the best effective way to curtail the disease burden.

Nyabadza and Mukandavire analyzed a deterministic HIV/AIDS model that comprises intervention strategies such as using condom, HIV counseling and testing (HCT) and treatment [NM11]. The model presented that the HCT campaign has very small influence to decreasing the endemicity of HIV. This was happened whenever the effectiveness of its endeavor exceeds a calculated parameter which measure efficiency of screening without backward bifurcation.

Seatlhodi et al. developed a new HIV epidemic model which permits an inflow of infecteds into the population [Sea15]. They investigated the influence of public health education campaigns on prevalence of the disease. They used Pontryagin's maximum principle to describe the control and find out the optimal system. They generalized that optimal education campaign is much more effective for reducing the number of infected individuals.

Kassa et al. investigated an optimal control problem for infectious disease of human population with preventive education and treatment strategies. They found that combination of these interventions minimizes the disease and cost burden [KO15].

Kumar et al. studied an optimal control problem of infectious diseases considering information-induced vaccination and limited treatment [KSDT20]. Numerically they recognized that the comprehensive use of these intervention strategies is most effective and economically viable during entire epidemic.

More recently, Mushanyu, proposed a mathematical model for HIV/AIDS dynamics. He investigated the impact of late diagnosis of HIV on the transmission of the disease. His numerical results suggested that premature motivation for HIV/AIDS treatment and improving HIV self-testing schedules leads to more undiagnosed people to know their status so as to decrease the transmission of HIV [Mus20].

As per the literature, until now no one proposed a model via considered aware and unaware susceptible as well as undiagnosed and diagnosed HIV/AIDS infected individuals with preventive, screening, and treatment controlling mechanisms.This model considers the rate of becoming aware and unaware as a function of media campaign not constant.

The model considers undiagnosed infectious and susceptible individuals who are the total of aware and unaware populations. For the reason that there are numerous individuals in Ethiopia categorized as these two subclasses. We compared this mathematical model with the model formulated on optimal control of HIV/AIDS model with pre-exposure prophylaxis with partial treatment [SS19].

1.4.2 Tuberculosis (TB) transmission dynamics models

Many scholars studied transmission dynamics of TB disease and developed/ improved mathematical modelling with or with out controlling strategies. For instance, the first mathematical model of tuberculosis was developed by Waaler et al. in 1962 [WGA62]. This model has contributed several applications and improved many times by different authors. In this portion, we reviewed some articles and summarized the following points.

Kumar et al. studied an optimal control problem of communicable diseases [KSDT20]. They incorporated vaccination depending on information and inadequate treatment. They analyzed the optimal model both analytically and numerically. The researchers found that the use of two strategies reduce both the disease and the cost burden. Their numerical result suggested that information-dependent vaccination is more efficient against the sever epidemic, while treatment is cost effective strategy for a mild epidemic. Thus, TB is a communicable disease, which is modeled and analyzed in the present work. However, many points of their work are vital for our study.

Choi et al. proposed optimal control problem for TB from mathematical modelling view point in Korea [CJ14]. They also proposed effective government budget plan for TB eradication. The investigators introduced distancing control, case finding, and completing treatment to associate various schemes. They analyzed the model equation numerically and suggested that distancing method is the best effective factor of all because of unique Korean living tradition. When the researchers used these strategies from 2030 plan, the number of high risk latent and infectious people will be almost 0 nearby 2018. This implied that all controls used at a time are pretty well, but the cost needed is slightly more expensive than other strategies. In order to minimize cost burden they suggested that the combination of either distancing and case finding or distancing and case holding strategy is best alternative approach. The scholars also compared their model results from Korean government TB budget elimination plan. However, the Korean government TB budget is based on mostly on the case finding around 41% and case holding around 46.4%. Finally, they recommend that the Korean government should be rearranging the budget and follow their result. we propose in this thesis, a model which is an extension of the model by Choi et al [CJ14], by accounting for drug resistant TB. Moreover, it is the best model to describe the current TB situation in Ethiopia and well extended combination strategies will be presented.

Kelemu et al. modified a TB model [WCJ11] taking into account TB vaccination for newborns [KMW19]. They calculated the equilibrium points and the basic threshold value. Their sensitivity analysis displayed that the TB transmission coefficient is the most influential parameter. Here, it is recommended that reducing the TB transmission coefficient i.e. increasing the isolation of infectious people can be effective strategy to eradicate TB disease in Ethiopia. Moreover, the researchers endorsed that treatment of both high risk latent and active TB with proper follow-up is an effective control strategy.

However, in this thesis the TB model claimed to be an extension of [WCJ11] with drug resistant TB rather than the vaccination strategy proposed in Kelemu et al [KMW19]. Hence, the two extended models and results are totally different. We also explored the emergency of drug resistance TB and how it is controlled. Moreover, we formulated an optimal control problem of our proposed TB model.

Rodrigues et al. studied an optimal control problem of a TB model accounting for treatment of both early latent and persistent latent infected people [RST14]. They considered anti-TB drugs for early latent TB and prophylactic treatment for persistent latent TB infected people. The results of their analysis showed that at a high reinfection rate the transmission increase rapidly because treatment effort of persistent latent people is reduced. They used ICER calculation to analyze the cost-effectiveness of two controlling efforts separately and together at a time. Their result also suggested that at a high transmission rate, the treatment of early latent people is the best cost effective strategy.

Moualeu et al. developed a mathematical model of TB that comprises undiagnosed and lost sight infectious [MWED15]. Here, they used two controlling strategies, such as providing education to individuals about TB and a wide range of diagnosis campaigns. They proposed an optimal control problem and analyzed it numerically based on the data taken in Cameron. Their results showed that TB burden may decrease by 80% within 10 years, if both of education and diagnosis activities through chemoprophylaxis treatment of latently infected people are well implemented.

Asgedom et al. ascertained the existence of MDR-TB and described its related factors in Ethiopia [ATG18]. They found that in Ethiopia, the average rate and presence of the disease in all TB cases are $12.6 \pm 15.9\%$ and 1.4% respectively. The investigators described that the greatest public risk factor for MDR-TB is previous contact to anti-TB treatment. The scholars suggested that critical treatment for both TB and MDR-TB with proper follow-up must be given to control the disease burden. Whereas the study of TB in this thesis is based on the dynamics of the drug sensitive TB and DR-TB diseases and controlling strategy according to mathematical modeling rather than only medical clarification point of view.

Ronoh et al. developed a mathematical model of TB considering DR-TB [RJF$^+$16]. They analyzed the model analytically and numerically and considered constant and time dependent delays in intervention. Their result shows that MDR-TB patients who fail to go for or delay their treatment, will persist in the population. Due to temporary immunity to TB the scholars recognized that drug sensitive TB and MDR- TB will persist at some equilibrium.

Hafidh et.al. studied mathematical model of TB and MDR-TB with optimal control [HAHA18]. They analyzed the model analytically and obtained four equlibra. The researchers also formulated a gradient algorithm to solve the optimal problem. They used BCG vaccination, first and second anti-TB drugs as control approaches. Their numerical result suggested that the given strategies can

effectively reduce the total infected population. However, when the scholars used only one intervention it is recommend that treatment (both first and second anti-TB) will be effective mechanism than BCG vaccination.

WHO 2018 reported that Sub-Saharan Africa countries had the highest estimated TB incidence rate per year [aaa20]. In this region, Ethiopia is one of 22 high TB infected countries in the world and this disease is the leading cause of illness and mortality. Besides, the presence of MDR-TB and HIV-TB cases are high in Ethiopia. The incidence and prevalence of TB are 448 and 422 per 100 000 of the people respectively [aaa20]. From all TB new cases, around 13% are HIV co-infected. The latest national DR-TB surveillance report stated that around 17.8% infected cases have MDR-TB infected individuals who are previously treated and around 2.3% are TB new cases from all TB cases.

All in all, the research works summarized above indicate that the burden of the disease (TB) would be serious not only in Ethiopia but also across the world, unless the current capacity of intervention strategies will be reformed and updated with multidimensional approach. Hence one important approach is investigating this disease burden from the mathematical modelling view point.

Thus, another objective of our thesis is to propose the best optimal intervention strategy of TB control in Ethiopia. To accomplish the goal, we improved the TB mathematical model [WCJ11] by considering drug resistance tuberculosis (DR-TB) transmission dynamics and extended the model via control measures. The intervention strategies are preventive, case finding, and case holding for both drug sensitive tuberculosis (DS-TB) and DR-TB.

1.4.3 Co-infection of TB-HIV disease transmission dynamics models

Mathematical models are also essential to explore the co-dynamics of diseases and to provide insights about preventive and controlling regimes. Existing models on HIV–TB co-infection are reviewed in the following way.

Navjot et al. formulated TB-HIV co-infection model to study the role of screening and treatment [KGB14]. They considered active sexual adult people in the model. Their result showed that increasing the rate of screening TB leads to decreasing TB infectious people. The researchers recommend that strong cooperation between the TB and HIV intervention regime is needed to control the disease.

Fatmawati et al. studied the effect of antibiotics and ART optimally to control the transmission dynamics of HIV-TB co-epidemics [FT16]. Their numerical result showed that coupling of ART and Anti-TB optimal control is the most effective strategy to fight against the disease. However, they suggested that antibiotics are better than ART when only one control is used.

Hadipour et al. investigated TB–HIV co-epidemics with treatment [LMH20]. They used a math-

ematical model along with an optimum sliding mode controller. The researchers applied a multi-objective genetic optimization algorithm to find the optimal values of the control coefficients. Their result showed that when controls are applied, new infections, disease deaths and total burden values are reduced.

Grace et.al explored the impact of HIV on TB infection via considered ART and TB treatment in Kenya [MM18]. Their result suggested that testing and administering latent TB, HIV testing for all TB patients and vice versa, and treatment for patients are very crucial for Kenyan people.

Cristiana et al. investigated optimal control problem of TB-HIV co-epidemics model [ST15]. They considered two interventions such as the control p representing both HIV and TB treatment at a time and the control q representing only TB treatment. They had taken the value of p and q bounded between 0 and 0.95, because they assumed that there are some budgetary constraints or some resistance from patients in making the treatments. In other words, they assume that one cannot treat all the people for both diseases or even just for tuberculosis. This is more than reasonable from biological side. They had tried these controlling strategies optimally in subclasses of infectious individuals. They conclude that applied both TB and HIV/AIDS treatment at a time is the best option to reduce both the HIV/AIDS and co-infection disease burden.

Roeger et al. introduced a deterministic model of TB - HIV co-infection [RFCC09]. They analyzed the model and their numerical result suggested that the presence of HIV leads to increased cases of co-infectious individuals even if TB reproduction is less than unity. The authors suggested that, to control TB infection in co-infection individuals, more effort should be given in reducing HIV prevalence.

Awoke et al. proposed TB-HIV/AIDS co-epidemics model with behavioural modification [AK18]. They extended the model into an optimal control problem by considering behavioural modification as preventive measures and treatment efforts as controlling strategies. Their numerical result showed that applying both preventive and control measures can reduce the disease and cost burden. The authors declared that the cost of applying preventive effort is very small as compared to treatment, but the cost of administering the infection is huge when the rate of disease transmission is high. They conclude that applying both prevention and treatment efforts at a time is a best effective strategy.

However, none of these authors have studied the extension of model [WCJ11] via HIV/AIDS cohorts and incorporating optimal control efforts. This means none of them explored only high risk (exposed stage) and low risk latent by treatment of co-infected with HIV in Ethiopia. Hence, in this thesis we developed a new TB-HIV co-infected model and extended it into an optimal control problem. The optimal control problem can segregate the possible intervention strategies that minimize both the disease and the cost burden.

1.5 Research aim and objectives

The main aim of the thesis is to apply the optimal control theory on tuberculosis, HIV/AIDS and their co-epidemics using mathematical modelling, with the focus in Ethiopia. To achieve this, the following objectives are set.

- Propose new mathematical models that describe the dynamics of TB, HIV/AIDS and their co-infection in Ethiopia.
- Incorporate the controls to the new models and solved targeted control problems whose aims are to reduce or regulate the transmission of the diseases with the minimum cost possible.

1.6 Limitation of the study

In this thesis, there are some aspects which constrained our investigation. We addressed the limitation of the study as follows.

- Due to lack of real data, the values of some parameters are taken from other related literatures.
- The thesis result did not commented by stakeholders, like health professionals, governmental organizations, and policy makers.
- As COVID-19 is the current emerging infectious disease, the impact of this global pandemic is not incorporated in the thesis.

1.7 Organization of the thesis

Rest of the thesis has been organized as follows. Chapter 2 describes some key mathematical tools and ideas. In chapter 3 the HIV/AIDS disease mathematical model with optimal control is analyzed while in chapter 4 a comprehensive model of TB disease with optimal control is also analyzed. Chapter 5 shows the exploration of other deterministic model of TB-HIV/AIDS co-epidemics with optimal control. In chapter 6 the conclusions outlined from the study, future research, and recommendations are presented.

Data name	In 2018	In 2019	In 2020	In 2021
HIV disease resulting in infectious and parasitic diseases	4 213	5 072	16 122	12 799
HIV disease resulting in mycobacterial infection	146	284	2 004	925
HIV disease resulting in other bacterial infections	368	751	2 923	2 117
HIV disease resulting in multiple infections	453	361	790	811
HIV disease resulting in unspecified infectious	762	657	3 087	1 294
HIV disease resulting in wasting syndrome	198	200	364	621
HIV disease resulting in other conditions	3 521	2 270	9 626	5 937
Acute HIV infection syndrome	646	113	1 700	775
Unspecified HIV disease	2 342	1 802	14 490	8 137
HIV Positivity rate per 100 000	401.3	308.4	706.8	2 184.1
Number of PLHIV ever started on ART	3 293	2 459	7 342	31 572.5
Percentage of STI cases tested for HIV	2 509	4 371.8	1 021.3	24 704
Percentage of adults living with HIV receiving ART	2 186.8	2 278.6	17 243.1	23 799.3
Percentage of children living with HIV receiving ART	3 287.4	1 549.3	7 890.3	9 382.2
Proportion of ART for HIV-positive TB patients	1 004.8	1 088	4 290.3	6 170.9
Proportion of TB patients enrolled in DOTS who have documented HIV result	2 096.3	3 036	9 067.4	15 983.7
Children of PLHIV - received result	4 870	6 772	21 716	23 388
Clients receiving HIV test results	4 091	2 328 462	7 586 286	7 513 723
Clients testing positive for HIV	1 066	11 518	37 580	37 738
DR- TB cases put on second line treatment	203	122	551	548
Estimated number of adult population living with HIV	690 000	825 678	1 045 123	1 576 799
DR TB cases put on second line treatment by diagnosis type	147	121	552	582
DR TB cases put on second line treatment by registration group	119	124	558	548
Estimated number of all forms of TB cases in the population	135 090	147 168	145 179	144 003
HIV-infected clients who screen negative receive IPT per national guidelines for active TB	1 101	960	4 479	6 029

Data name	In 2018	In 2019	In 2020	In 2021
All HIV-infected clients who screen negative for active TB receive per national guidelines	850	969	4 415	6 045
TB patients who are completed and accurate standardized medical record	3 245	2 454	10 024	14 427
Number of relapse (bacteriological confirmed and clinically diagnosed) TB cases detected in the quarter	746	661	3 402	3 111
Number of bacteriology confirmed New Pulmonary TB cases detected in the quarter	11 245	10 589	42 100	45 125
Number of children < 15 year contacts with index of pulmonary TB cases screened negative result for TB	8 254	9 903	21 927	39 690
Number of children < 15 year contact TB screening negative and put on LTBI treatment (IPT)	8 790	7 322	10 252	27 340
Number of children <15 year contacts with index of drug susceptible pulmonary TB cases	5 980	10 983	25 343	43 242
Number of children < 15 year contracts with index of pulmonary TB cases screened for TB	7 610	10 549	24 247	42 034
Number of clients enrolled in HIV care who were screened for TB	610 789	571 353	2 939 368	2 027 265
Number of clinically diagnosed new pulmonary TB cases detected in the quarter	4 984	5 140	26 982	25 632
Number of clinically diagnosed and bacteriology confirmed new EPTB cases detected in the quarter	7 740	5 947	32 052	31 789
Number of clinically diagnosed and bacteriology confirmed new EPTB cases enrolled in the cohort (EPTB)	6 711	3 412	17 463	17 512

Table 1.1: Trend the number of notified people for the last 4 years, Ethiopia. The sources are [vvv22, WHO20, aaa20, cdc22].

Chapter 2

Mathematical preliminaries

This chapter introduces several mathematical terminologies and theorems that will be used in the thesis. Nowadays, the two approaches (stochastic and non-stochastic) are used to investigate infectious diseases transmission dynamics. In the non-stochastic approach the idea of differential equations is widely used in the process of mathematical modeling of infectious diseases. This model development entails different variables, assumptions, and parameters. We introduce the following mathematical preliminaries in terms of definitions and theorems that are crucial to analyze the model and interrelate to dynamical systems.

Definition 1 Dynamical system is a means of describing how one state develops into another state over the course of time. [Per01].

It arises in many fields particularly in the sciences focused on describing the behaviour of a system at a time in space.
A dynamical system on $\mathbb{R}^n$ has a general form $f_t : \mathbb{R}^n \longrightarrow \mathbb{R}^n$, where f_t is continuously differentiable, $\mathbb{R}^n$ is n dimensional real space and $t \in \mathbb{R}$ is a time.

2.1 Differential Equations (DE)

Definition 2 *A* DE is an equation that involves one or more derivatives of a quantity with respect to some independent variable(s).

Differential equations can be classified in to two types. These are ordinary DE and partial DE. An ordinary DE is one that involves the derivatives of a quantity depending on only one variable, whereas partial DE is one that involves the derivatives of a quantity depending on more than one variable. The most part of this thesis will use ordinary DE.

Let x be the state of a dynamical system. Then a general non-linear function f containing x is expressed by

$$\frac{dx}{dt} = f(x, t, \lambda), \tag{2.1}$$

where $x \in \mathbb{R}^n$ and $\lambda \in \mathbb{R}$ is a parameter.
Equation (2.1) is known as an Ordinary Differential Equation (ODE). If the time t explicitly appears in the expression, then the ODE is said to be non-autonomous. However, if t does not appear explicitly in the right hand side of (2.1), then the equation becomes autonomous ODE. Most mathematical models of diseases inclusive the models in the thesis are autonomous systems that can be expressed like

$$x^{'} = f(x), \tag{2.2}$$

where $x^{'} = \frac{dx}{dt}$ is the time-derivative of state variable x and $x = (x_1, x_2, x_3, ..., x_n)$.
If equation (2.2) expressed together with state initial conditions, then the new expression is named as an Initial-Value Problem (IVP), given below:

$$x^{'} = f(x), \text{with } x(t_0) = x_0 \in \mathbb{R}. \tag{2.3}$$

However, when the DE (2.2) is appended with the given data about the initial and final time state, the expression becomes a Boundary-Value Problem (BVP). In this thesis the proposed models are compartmental models that comprise the rate of change of population sizes of different compartments. Let say in a particular system with n compartments, the dynamical system which express the transition of the system can be written as:

$$\begin{cases} \frac{dx_1}{dt} = f_1(x_1, x_2, x_3, ..., x_n), \\ \frac{dx_2}{dt} = f_2(x_1, x_2, x_3, ..., x_n), \\ \qquad\qquad . \\ \qquad\qquad . \\ \qquad\qquad . \\ \frac{dx_{n-1}}{dt} = f_{n-1}(x_1, x_2, x_3, ..., x_n), \\ \frac{dx_n}{dt} = f_n(x_1, x_2, x_3, ..., x_n). \end{cases} \tag{2.4}$$

Lemma 1 *Let $f : \mho \to \mathbb{R}^n$, where $\mho$ is an open subset of $\mathbb{R}^n$. If $f \in C^1(\mho)$, then f is locally Lipschitz on $\mho$ [HSD12].*

The general representation $f \in C^k(\mho)$ denotes the k^{th} order derivative of f exist and continuous on the given set $\mho$.

Theorem 1 *(Existence-Uniqueness Theorem [HSD12]). Let f is C^1 and consider IVP (2.3). Then there exist a solutions of (2.3) which is unique. Indeed $\exists\ a > 0$, a unique solution of (2.3) on the interval $[-a, a]$ satisfying $x(t_0) = x_0$.*

2.2 Invariant sets and stability analysis

Definition 3 *A set V is an invariant set with respect to the flow of (2.2) if $x(0) \in V \Longrightarrow x(t) \in V$, $\forall t \in \mathbb{R}$, provided the solution of (2.2) exists $\forall t \in \mathbb{R}$. However, if this condition holds for $\forall t > 0$, then V is said to be positive invariant set.*

Definition 4 Given a system of DEs (2.2), a state x^* is called an equilibrium point of the model if $f(x^*) = 0$ [All08].

These points are also known as critical points. They are found by making the left hand side of the equations to zero and calculating the value of state variable x.
One important description is also the upcoming evolution of the dynamical system close to the critical point or not if the system starts initially near to equilibrium.

Definition 5 *[All08]*

A. An equilibrium point, x^*, of (2.2) is said to be locally stable if $\forall \epsilon > 0, \exists \delta > 0$ such that $\|x_0 - x^*\| < \delta \Longrightarrow \|x(t) - x^*\| < \epsilon, \forall t > 0$, provided $x(t)$ exists for all $t \geq 0$.
If the equilibrium is not locally stable it is said to be unstable.

B. An equilibrium point , x^*, of (2.2) is said to be locally asymptotically stable if it is locally stable and additionally every solutions starting nearby x^* move towards x^* as $t \to \infty$.
In other words $\exists \delta > 0$ such that $\|x_0 - x^*\| < \delta \Longrightarrow \lim_{x\to\infty} \|x(t) - x^*\| = x^*$.

Proposition 1 A critical point x^* of (2.2) is locally stable if all eigenvalues of the Jacobian evaluated at x^* have negative real parts.

Definition 6 The Jacobian of the system (2.2) is expressed by:

$$J = Df(x) = \begin{bmatrix} \frac{\partial f_1}{\partial x_1} & \frac{\partial f_1}{\partial x_2} & \cdots & \frac{\partial f_1}{\partial x_{n-1}} & \frac{\partial f_1}{\partial x_n} \\ \frac{\partial f_2}{\partial x_1} & \frac{\partial f_2}{\partial x_2} & \cdots & \frac{\partial f_2}{\partial x_{n-1}} & \frac{\partial f_2}{\partial x_n} \\ \vdots & \vdots & \cdots & \vdots & \vdots \\ \frac{\partial f_{n-1}}{\partial x_1} & \frac{\partial f_{n-1}}{\partial x_2} & \cdots & \frac{\partial f_{n-1}}{\partial x_{n-1}} & \frac{\partial f_{n-1}}{\partial x_n} \\ \frac{\partial f_n}{\partial x_1} & \frac{\partial f_n}{\partial x_2} & \cdots & \frac{\partial f_n}{\partial x_{n-1}} & \frac{\partial f_n}{\partial x_n} \end{bmatrix}.$$

Definition 7 A critical point x^* of (2.2) is said to be hyperbolic critical point if all eigenvalues of the jacobian evaluated at x^* have non zero real parts, otherwise x^* is non-hyperbolic.

Proposition 2 ***(Routh-Hurwitz criteria)***
Let the characteristic polynomial of the Jacobian matrix J of the equilibrium x^* of (2.2) be given by:
$\lambda^n + A_1\lambda^{n-1} + A_2\lambda^{n-2} + A_3\lambda^{n-3} + ... + A_{n-1}\lambda + A_n = 0.$
If $\Delta_1 = A_1 > 0, \Delta_2 = \begin{vmatrix} A_1 & A_0 \\ A_3 & A_2 \end{vmatrix} = A_1A_2 - A_0A_3 > 0,$

$$\Delta_3 = \begin{vmatrix} A_1 & A_0 & 0 \\ A_3 & A_2 & A_1 \\ 0 & A_4 & A_3 \end{vmatrix} = A_1A_2A_3 - A_1^2A_4 - A_0A_3^2 > 0, ... , \quad \Delta_n = \begin{vmatrix} A_1 & A_0 & \dots & 0 \\ A_3 & A_2 & \vdots & 0 \\ \vdots & \vdots & \vdots & \vdots \\ 0 & 0 & 0 & A_n \end{vmatrix} > 0.$$

Then, the equilibrium point x^* is stable. Otherwise it is unstable.
***Proof**: see [All08].*

Theorem 2 *(Linearization theorem) [HSD12]. Let x^* be the hyperbolic equilibrium point of the non-linear system (2.2). Then, in a neighbourhood of x^*, then the non-linear flow and its linearization are conjugate to each other.*

This theorem declares that the linearization of (2.2) is enough to assess the local behaviour of a hyperbolic equilibrium point.

2.3 Global stability analysis

We have two approaches, which are direct and indirect method of Lyapunov. The indirect method has some limitations to determine the local stability of the equilibrium points. No information is presented for the level of the basin of attraction (the domain such that all trajectories starting anywhere towards the equilibrium point). However, this problem can be resolved by the direct Lyapunov method.

Definition 8 An equilibrium point x^* is said to be globally asymptotically stable if it is asymptotically stable for all initial condition $x_0 \in \mathbb{R}^n$.

Lyapunov theory is used to determine the global stability of the critical points beyond compute the trajectories of a system (2.2). One critical point about the clue of Lyapunov direct method is how carefully chosen scalar functions. This procedure comprises formulating a differentiable scalar function say $V(x)$ satisfies the following:

A. $V(x)$ is positive definite: $V(0) = 0; V(x) > 0 \, \forall x \neq 0$ and,

B. $\nabla V(x).f(x) < 0 \, \forall x$,

where ∇ represent the gradient vector function and "." denotes the dot product.

Definition 9 Let $V(x)$ be a continuously differentiable function such that $V(x) : U \subseteq \mathbb{R}^n \longrightarrow \mathbb{R}$, where the set U contains the origin.

A. $V(x)$ is positive definite (pd) in U if

a. $V(0) = 0$, *and*

b. $V(x) > 0, \forall x \neq 0 \in U$.

B. $V(x)$ is positive semi-definite (psd) in U if $V(x) \geq 0, \forall x \in U$.

C. Conversely, $V(x)$ is negative definite in U if $V(x) < 0, \forall x \in U$ or $-V(x)$ is pd, and

D. $V(x)$ is negative semi-definite in U if $V(x) \leq 0, \forall x \in U$ or $-V(x)$ is psd.

E. $V(x)$ is Lyapunov function on the region U if $V(x)$ is positive definite and has continuous first-order partial derivatives at every point of U.

Theorem 3 *[JYJS11] Let $x^* = 0$ be an equilibrium point of the system (2.2), where $f : U \longrightarrow \mathbb{R}^n$ is locally Lipschitz and $U \subset \mathbb{R}^n$ is a domain that contains the origin. Let $V : U \longrightarrow \mathbb{R}$ be a continuously differentiable, positive definite function in U.*

a. If $V^{'}(x) \leq 0$, then x^* is globally stable.

b. If $V^{'}(x) < 0$, then x^* is globally asymptotically stable.

Lyapunov functions have great application to proof the global stability of an equilibrium point, but selecting these functions is somehow difficult. Because of there is no common technique for formulating the Lyapunov functions.

2.4 Bifurcation analysis

Definition 10 Bifurcation is defined as a change in the qualitative behaviour of a given dynamical system when an associated parameter varies. The change happens at the points of the parameter which is known as bifurcation points (values).

Let

$$x^{'} = f(x, \mu), x \in \mathbb{R}^n, \mu \in \mathbb{R}, n \in \mathbb{N} \tag{2.5}$$

be family of ODEs with a parameter μ. A critical point of (2.5) given by: $(x, \mu) = (0, 0)$ is undergoes a bifurcation at $\mu = 0$ if the flow of phase portrait near to $\mu = 0$ and $x = 0$ is not qualitatively the same as the flow near x = 0 at $\mu = 0$ [Kie11].
The study of bifurcations for epidemic models is sometime challenging. To solve this challenge, the center manifold theory stated in [CCS04] is an alternative technique. The theorem is presented below.

Theorem 4 *[CCS04] Consider the following general system of ODEs with a parameter ϕ.*

$$\frac{dx}{dt} = f(x, \phi), f : \mathbb{R}^n \times \mathbb{R} \longrightarrow \mathbb{R} \ \ and \ \ f \in C^2(\mathbb{R}^n \times \mathbb{R}), \tag{2.6}$$

where 0 is an equilibrium point of the system (that is, $f(0, \phi) = 0 \ \forall \phi$) and assume

A1. $A = D_x f(0, 0) = \frac{\partial f_i}{\partial x_i}$ is the linearization matrix of (2.6) around the equilibrium point 0 with ϕ evaluated at 0. Zero is a simple eigenvalue of A and other eigenvalues of A have negative real parts;

A2. Matrix A has a right eigenvector w and a left eigenvector v (each corresponding to the zero eigenvalue).
Let f_k be the k^{th} component of f and

$$a = \sum_{k,i,j=1}^{n} v_k w_i w_j \frac{\partial^2 f_k}{\partial x_i \partial x_j}(0, 0), \tag{2.7}$$

$$b \ = \sum_{k,i,j=1}^{n} v_k w_i \frac{\partial^2 f_k}{\partial x_i \partial x_\phi}(0, 0). \tag{2.8}$$

The local dynamics of the system (2.6) around 0 is totally determined by the signs of a and b:

I. $a > 0, b > 0$. When $\phi < 0$ with $\phi \ll 1$, 0 is locally asymptotically stable, and there exists a positive unstable equilibrium; when $0 < \phi \ll 1$, 0 is unstable and there exists a negative and locally asymptotically stable equilibrium.

II. $a < 0, b < 0$. When $\phi < 0$ with $\phi \ll 1$, 0 is unstable; when $0 < \phi \ll 1$, 0 is locally asymptotically stable, and there exists a positive unstable equilibrium.

III. $a > 0, b < 0$. When $\phi < 0$ with $\phi \ll 1$, 0 is unstable, and there exists a locally asymptotically stable negative equilibrium; when $0 < \phi \ll 1$, 0 is stable, and a positive unstable equilibrium appears.

IV. $a > 0, b < 0$. *when* $\phi < 0$ *changes from negative to positive, 0 changes its stability from stable to unstable. Corresponding to a negative unstable equilibrium becomes positive and locally asymptotically stable.*
Particularly if $a > 0$ *and* $b > 0$ *then a backward bifurcation occurs at* $\phi = 0$.

2.5 Compartmental modelling

Compartmental models are a very broad modeling system. Mostly, they are functional to the mathematical modelling of communicable diseases. In this model formulation the population is subdivided into epidemiological classes (compartments). These compartments are described based on the disease condition of the people. They can be labeled as Susceptible (S), Infectious (I), or Recovered/Removed (R). The number of individuals in these classes is expressed via a function of time, by S(t), I(t) and R(t). Individuals can progress from one compartment to the other.

- Susceptible: Individuals who are healthy, but once they have contracted with infectious people or object; they can catch by the disease and move to infected class.
- Infected: Individuals that can transmit the disease.
- Recoverd/Removed: Individuals who recover from the disease or remove by obtaining immunity / progressed to advanced stage and died by the disease.

If more new people are recruited, then the number of susceptible people can increase. However, they can decrease due to new infected people through interaction from individuals in $I(t)$ class and by natural death rate. Infected people who entered in $I(t)$ class can progress to R(t) or may die naturally. The individuals in $R(t)$ class are recovered or removed by the disease or naturally.
Thus, the total population at a given time is given by:

$$N(t) = S(t) + I(t) + R(t).$$

There are different parameters that generate formulation of this type of compartmental model and its extension. Some of them are: the recruitment rate, progression rate, recovery rate, and death rate etc...

2.6 The basic reproduction number, R_0

One of the main outcome in mathematical modeling of infectious diseases is the notion of the basic reproduction number. Finding a publication on a mathematical model of disease dynamic without describing this number is very difficult. Because of this number gives an indication concerning the

upcoming trend of the infection. Moreover, the number tells us whether the disease will persist or be eradicated in the specified time.

Definition 11 *[DHM90]* The basic reproduction number or basic reproduction ratio R_0 is defined as the average number of secondary infections generated by a single infected individual in a completely susceptible population.

When $R_0 > 1$, it means that on average, an infected person infects more than one susceptible person over his/her infectious period. This condition tells us the disease will persist in the community. However, if $R_0 < 1$, then an infected person infects less than one susceptible over his/her infectious period. This condition tells us the disease cannot grow in the community. Calculating R_0 is very simple for simple models (smaller number of compartments), but it becomes complicated for models that have several infected compartments. Driessche et al. gave a method of calculating R_0 for any epidemic model based on the so-called "next generation matrix" [VdDW02].

2.7 The next generation matrix approach

This method was discovered by Van den Driessche and Watmough [VdDW02]. This is the general technique of calculating R_0 for a model that has over one infected compartment.
Consider a system (2.2), where $x = (x_1, x_2, x_3, ..., x_n)$, with x_i representing the proportion of people in compartment i. Define F_i as the rate of appearance of new infections in class i; V_i^- is the rate of transfer of the infected individuals out of class i; and V_i^+ is the rate of infection transfer into class i by all other means.
Then $x_i^{'} = f_i(x) = F_i(x) - V_i(x)$, where $V_i = V_i^- - V_i^+$ and $i = 1, 2, 3, ..., n$.
Let $X_s = \{x \geq 0 | x_i = 0, i = 1, 2, ..., m\}$ be the set of non-infected states.
Thus, the functions described in the system satisfies the assumptions listed as follows (see [VdDW02]).

I. If $x \geq 0$, then $F_i, V^-, V^+ \geq 0$ for all $i = 1, 2, ..., n$.

II. If $x_i = 0$, then $V_i = 0$, In particular if $x \in X_s$, then $V^- = 0$ for all $i = 1, 2, ..., m$.

III. $F_i = 0$ if $i > m$.

IV. If $x \in X_s = 0$, then $F_i(x) = 0$, $V_i^+(x) = 0$, for $i = 1, 2, ..., m$.

V. If $F(x)$ is set to zero, then all eigenvalues of $Df(x_0)$ have negative real parts.
Here, $Df(x_0)$ is the Jacobian matrix derived by $Df(x_0) = \frac{\partial f_i}{\partial x_j}$ at DFE x_0.

Lemma 2 *[VdDW02] If x_0 is a DFE point of (2.2) and $f_i(x)$ satisfies (I)-(V), then the Jacobian matrices $DF(x_0)$ and $DV(x_0)$ are partitioned as*

$DF(x_0) = \begin{pmatrix} M & 0 \\ 0 & 0 \end{pmatrix}$, $DV(x_0) = \begin{pmatrix} N & 0 \\ J_3 & J_4 \end{pmatrix}$, *where* M *and* N *are the* $m \times m$ *matrices defined by*
$M = [\frac{\partial F_i}{\partial x_j}(x_0)]$ *and* $N = [\frac{\partial V_i}{\partial x_j}(x_0)]$ *with* $1 \leq i, j \leq m$. *Further,* F *is non-negative,* V *is a non-singular M-matrix and all eigenvalues of* J_4 *have positive real part.*

The next theorem is used to calculate the quantity R_0.

Theorem 5 *[VdDW02] Consider the disease transmission model given by (2.2) with* $f(x)$ *satisfying conditions (I)–(V). If* x_0 *is a DFE of the model, then* x_0 *is locally asymptotically stable if* $R_0 < 1$*, but unstable if* $R_0 > 1$*, where* R_0 *is defined by*

$R_0 = \rho(FV^{-1})$*, where* $\rho(A)$ *denotes the spectral radius of the matrix* A.

If $R_0 = 1$, then two equlibra exchange their stability. This phenomenon of changing of stability is called forward bifurcation and has been seen in various epidemiological models [KM27, HVA87, CCCHL89, Het00]. The diagram (2.1) shows the description of forward bifurcation. When forward bifurcation happens, then $R_0 \leq 1$ is a necessary and sufficient condition for disease elimination.

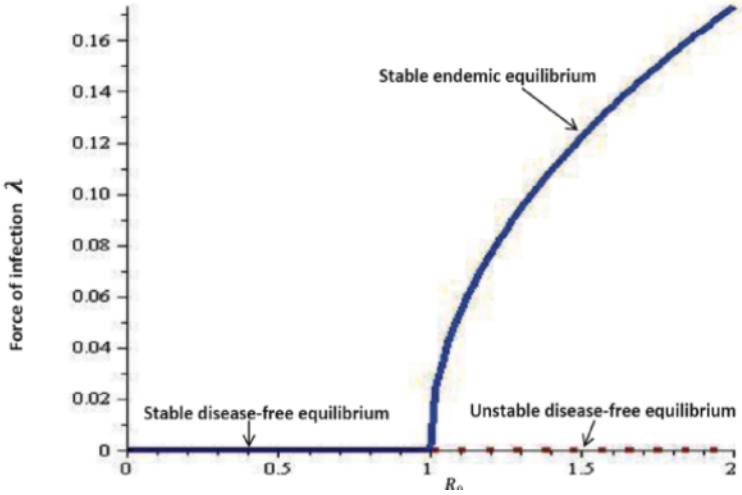

Figure 2.1: Forward bifurcation diagram.

Another type of bifurcation called backward bifurcation may also happen. When this occurs a stable endemic equilibrium co-exists with a stable DFE. As R_0 approaches one, the number of disease cases increases rapidly. This shows that $R_0 \leq 1$ is only a necessary but not sufficient condition for disease elimination and hence disease eradication cannot just be achieved by making $R_0 < 1$. Such conditions occurred in [FCCC00, EG06, CCCHL89, DHCC98]. The diagram is as shown in the Figure (2.2).

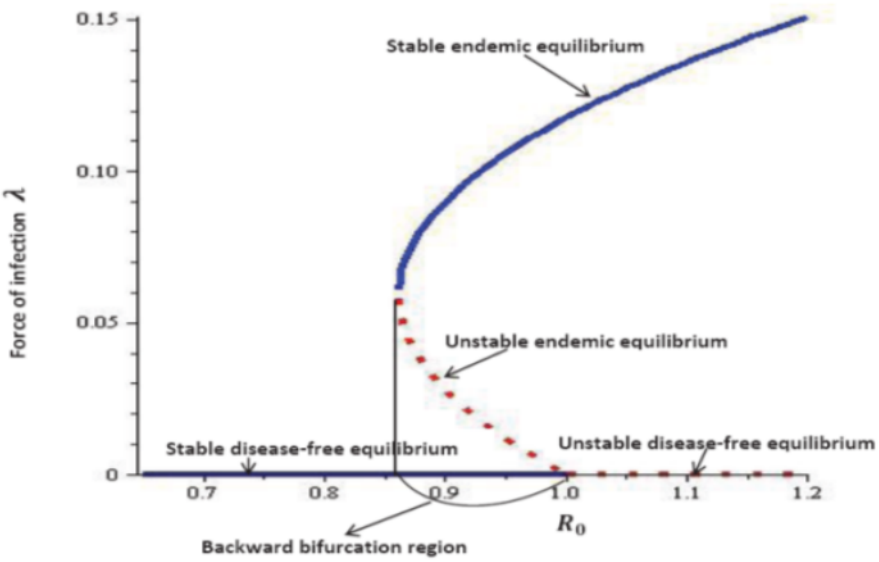

Figure 2.2: Backward bifurcation diagram.

2.8 Optimal control theory

This theory is also the main part of the thesis, which is used to investigate the best method of controlling HIV/AIDS, TB, and their co-epidemics in Ethiopia. In this part, some terminologies of this theory are presented. Optimal control problem is an optimization problem that optimizes an objective function subject to a dynamical system with initial or boundary conditions. For further development, refer to [Ars11, KDM$^+$22, KMO21, SMB21, OMT20, BM20].
The form of an optimal control problem is given by:

$$\begin{cases} \text{Maximize} \quad \int_0^{t_f} g(t,x,u)dt, \\ \quad \text{subject to} \quad \frac{dx}{dt} = f(t,x,u), x(t_0) = x_0, x(t_f) \text{is free and} \\ \quad u(t) \in U, \forall t \in [0,t_f], \end{cases} \tag{2.9}$$

where U is Lebesgue measurable set, $u(t)$ is the optimal command, and t_f is the length of time for the control.
The optimal state $x(t)$ can be formed after substituting $u(t)$ in the given state system. Thus, we say $(u(t), x(t))$ is an optimal pair. There is a necessary condition for an optimal pair that was developed in 1950 by Pontryagin and his students. They introduced adjoint (co-state) variables that link the differential equation to the objective function. The variables are vital for finding optimal control solutions. This clue is related to Lagrange multipliers in multi-dimensional calculus.
Pontryagin's maximum principle is stated in the following theorem.

Theorem 6 *[PM86] Let $u(t)$ be a time optimal control and $x(t)$ be the corresponding response of the system. Then there exists a function $\lambda(t) : [0, t_f] \longrightarrow \mathbb{R}^n$, such that:*

$$x^{'} = \frac{dH}{d\lambda}(x, \lambda, u), x(t_0) = x_0 \quad (\textit{State Equation}), \tag{2.10}$$

$$\lambda^{'} = -\frac{dH}{dx}(x, \lambda, u) \qquad (\textit{Co-state Equation}), \tag{2.11}$$

$$\lambda(t_f) = 0 \qquad (\textit{Transversality condition}), \tag{2.12}$$

$$H(x^*, \lambda, u^*) = \max_{u \in U} H(x, \lambda, u) \ \ (\textit{or } \frac{\partial H}{\partial u} = 0), \tag{2.13}$$

where $H = g(t, x, u) + \lambda(t) f(t, x, u)$ is called the Hamiltonian of the optimal control problem.

2.9 Sensitivity analysis

The sensitivity analysis is used to assess the model robustness to parameter values, because errors may occur in pre-assumed values and data collection. This analysis can identify which parameters have high impact on R_0 [CCH06, BD94]. It also allow to measure the relative change in a state variable when a parameter changes [CCH06]. The sensitivity of each parameter of the model will be analyzed using normalized forward sensitivity index [CHC08]. The idea can be stated in the following way.

Definition 12 Let the variable M be differentiable function of the parameter p, then the normalized forward sensitivity index of a variable M with respect to the parameter p is defined as $\Lambda_p^M = \frac{\partial M}{\partial p} \frac{p}{M}$.

2.10 Numerical solutions

Most mathematical models with or without optimal control arising in biology or engineering cannot be solved analytically. Thus numerical methods are very useful to addressing these problems. The technique may require iterative calculations to obtain good results. In today's world, such problems cannot be an issue due to the high speed computers and softwares available. The softwares are regularly updated and sophisticated to meet the growing demand. The numerical manipulations of a disease model can give better understanding about the behavior of disease transmission dynamics. Thus, a researcher can easily interpret the result of the study after the simulation are performed. The numerical technique used in this thesis is Forward-Backward fourth order Runge- Kutta method in MATLAB [LW07]. The technique will be used to solve the mathematical model of TB, HIV/AIDS, and their co-infection with or without optimal control. Solving optimal control problems in the

thesis numerically one can find piecewise continuous functions $u_i(t)$ that optimize the objective functional. Keep in mind that any solution of the problem must satisfy the state, co-state equations, and the optimality conditions. The rough outline of the algorithm is presented below.

Step 1. Make an initial guess for u over the interval. Store the initial guess as u.

Step 2. Using the initial condition $x(t_0) = x_0$ and the stored values for u, solve x forward in time according to its differential equation in the state equations (2.10).

Step 3. Using the transversality condition $\lambda(t_f) = 0$ and the stored values for x and u, solve λ backward in time according to its differential equation (2.11).

Step 4. Update the control u by entering the new x and λ values into the characterization.

Step 5. Check convergence. If values of the variables in this iteration and the last iteration are negligibly small, output current values as solutions. If values are not small, return to **Step 2.**

While executing the algorithm, in step 1, note that the initial guess $u \equiv 0$ is almost sufficient unless when division by u occurs in the problem, in such case an initial guess must be non-zero. Any ODE solver is applicable for step 2 and step 3, but we applied Runge-kutta 4^{th} order scheme. Explicitly, if $x^{'} = f(t, x(t))$, and $x(t)$ is known, then the approximation of $x(t+h)$, where $h > 0$ is:

$$x(t+h) = x(t) + \frac{h}{6}[k_1 + 2k_2 + 2k_3 + k_4], \tag{2.14}$$

where

$$\begin{aligned} k_1 &= f(t, x(t)), \\ k_2 &= f(t + \tfrac{h}{2}, x(t) + \tfrac{h}{2}k_1), \\ k_3 &= f(t + \tfrac{h}{2}, x(t) + \tfrac{h}{2}k_2), \\ k_4 &= f(t + h, x(t) + hk_3). \end{aligned}$$

Several type of convergence tests exist for step 5. Usually, finding $\sum_{i=1}^{n} |u(i) - u_{old}(i)|$ to be small is sufficient, where $u(i)$ and $u_{old}(i)$ are the vectors of estimated controls for the current and old iterations, respectively. Lenhart and T. Workman proposed for the best convergence criterion (percentage error $= \frac{|u-u_{old}|}{|u|} \leq \delta$ be negligibly small, where δ is the accepted tolerance). With minor adjustments, they allowed the value of $u = 0$ and multiplied both sides by u. Thus, they get simple criteria given by:

$$\delta \sum_{i=1}^{n} |u(i)| - \sum_{i=1}^{n} |u(i) - u_{old}(i)| \geq 0.$$

This criterion is also needed for the variables x and λ. In the Matlab platform taking $n = N + 1$ with usually $N = 1\ 000$ and $\delta = 0.001$ are the best option.

2.11 Cost effective analysis

Cost-effective analysis is used to compare the costs of executing the proposed intervention strategies [ORM13]. Cost effectiveness ratios can be determined by the following three techniques.

A. Average Cost-Effectiveness Ratio (ACER) deals with a single intervention approach and it determines that controlling strategy against its baseline option. The ratio of the net cost of an intervention with the total number of healthy outcomes is used to calculate ACER.

B. Marginal Cost-Effectiveness Ratio (MCER) is used to assess particular changes in cost and effect when a schedule is contracted or prolonged.

C. Incremental Cost-Effectiveness Ratio (ICER) is used to compare the differences between the costs and health outcomes of two optional approaches.

The exact formula of these metrics are given in Table (2.1) below.

$$ACER = \frac{\text{Total cost (Intervension A)}}{\text{Effect (Intervension A)}}$$

$$MCER = \frac{\text{Total cost (Intervension A+1) - Total cost (Intervension A)}}{\text{Total effect (Intervension A+1) - Total effect (Intervension A)}}$$

$$ICER = \frac{\text{Total cost (Intervension A) - Total cost (Intervension B)}}{\text{Total effect (Intervension A) - Total effect (Intervension B)}}$$

Table 2.1: ACER, MCER, and ICER [WFR00].

In this thesis, we used ICER approach due to more than two strategies being proposed to mitigate or eliminate the disease in Ethiopia.

Chapter 3

Modelling of HIV/AIDS disease

3.1 Introduction

Nowadays, there are innovative scientific progression and serious health intervention strategies in the world, but HIV/AIDS disease is until now an overwhelming illness in human history. Many countries are severely affected by this disease. At present widespread of HIV infection has an influence on increasing occurrence of other infectious disease like TB globally [CWW$^+$03].
HIV is the virus that causes HIV infection and it is transmitted by having sex, breast-feeding and sharing injection drug equipments such as needles with HIV positive people. HIV infectious virus progress to AIDS which is the most advanced stage of HIV infection [STW$^+$17]. HIV/AIDS affects many parts of the world, but the disease burden is high in Sub-Saharan Africa [fff21]. Ethiopia is one of the regions which is severely hit by the disease. Whether we know or not different controlling effort mechanisms, very lower control strategies are implemented in Ethiopia. So this epidemic in our country needs critical intervention approaches within a specific period of time through minimal cost possible. Here, we developed and analysed a mathematical model of HIV/AIDS model with optimal control in Ethiopia, which can guide some of the targeted interventions.
Mathematical model is a description of a dynamical system using the language of mathematics. It can play a vital role on HIV/AIDS predict and control. Several assumptions and parameters are key implications to develop a model; whereas a model can be redeveloped using controlling functions. Thus a mathematical model of HIV/AIDS pandemic can be reformulated and the controlling mechanisms of the disease can be investigated through the concept of optimal control theory.

3.2 Mathematical model of HIV/AIDS

Model assumptions

- The population enter into the susceptible class at a constant rate π. They might be infected because of direct contact (free sex), blood transfusion from an infected human, or from the use of a syringe from an infected human.
- The model does not consider HIV infected persons with immigration and vertical transmission.
- The mode of HIV/AIDS transmission is via heterosexual contacts.
- Individuals in class T are screened HIV infectious individuals, but become aware of their infection and enter in to drug therapy.
- Infected population under treatment do not have any contribution in viral transmission.
- Undiagnosed infected individuals become HIV infectious individuals with AIDS symptom's due to lack or delayed screening test.

We used deterministic(compartmental) model as a technique to simplify the mathematical modelling of infectious disease like for HIV/AIDS. Such idea were during in the early twentieth century with the basic SIR (susceptible-infected-removed/recovered) model, developed by Ronald R, et.al. [And91]. In this study, we discussed SIA model for HIV/AIDS, where A represents AIDS class. On the basis of this model, we developed a new model by incorporating the following important points.

- Nowadays, we can divide the given total vulnerable population class into two subclasses depending on the accessibility of pursuing media campaign and take their preventive actions: namely aware and unaware susceptible individuals against HIV/AIDS say S_A and S_U respectively. Here, we emphasis that "aware" does not mean "informed" of the prevalence and existence of the epidemics, but also knowledgeable of disease dynamics and further implementing prevention mechanisms.
- In Ethiopia HIV is often transmitted by unsafe sex with infected individuals. These people may or may not have disease symptoms, but they don't know they have the virus and are therefore categorized as undiagnosed infected people say (L).

Thus, the total population $N(t)$ at time t, is subdivide into the following epidemiological sub-classes.

Aware susceptible individuals ($\mathbf{S_A}$): Healthy people not yet exposed, but have taken awareness from HIV/AIDS as preventive measure.

Unaware susceptible individuals ($\mathbf{S_U}$): Healthy people not yet exposed, but haven't taken awareness from HIV/AIDS as preventive measures.

Undiagnosed infected (L): They have the virus, but they don't know they are infected or they haven't shown HIV symptoms.

Diagnosed HIV infected with-out AIDS symptoms (I): Screened HIV infected individuals who have developed pre-AIDS symptoms.

HIV-infected people under treatment (T): Individuals who take treatment for HIV infection, but can-not recover, because one can not cure HIV/AIDS yet.

Diagnosed HIV infectious with AIDS symptoms (A): Individuals with AIDS symptoms after screening .

Thus, the total population at time t, represented by N(t), is obtained by:

$$N(t) = S_A(t) + S_U(t) + L(t) + I(t) + T(t) + A(t).$$

The aware or unaware susceptible populations are increased due to the recruitment of individuals (assumed susceptible) into the population at a rate π. Let $M(t)$ represents the amount of media campaign measured by time t. This can be done through TV, radio, the latest best way of social media campaign like face-book, telegram, and twitter etc... These media can draw more attention to the overall of the pandemic. As the information disseminates regarding to HIV/AIDS intentionally , people respond to it and eventually modify their behaviour to reduce their vulnerability. Usually, unaware susceptible individuals contract the disease at a higher rate than aware individuals.

Unaware susceptible individuals make sufficient contact with undiagnosed infected, diagnosed infected and AIDS individuals, new infections will occur, and all the newly infected individuals will enter the L and I classes , or progressed to A class after long period of time or they may die due to natural causes at each stage. Hence, these individuals acquire HIV infection at a variable rate (force of infection) is given by $\lambda_1 = \frac{\beta_1(L+\eta_1 I+A\eta_2)}{N}$, where β_1 is the effective contact rate and $\eta_i\{i = 1, 2\}$ measure the relative infectiousness of individuals in classes I, and A when compared to those in L.

The aware population who undergo successful advertisements can adjust their behaviour, however they might fade-away or become careless. They can become infected and leave the susceptible class through direct contact with infected individual, at rate $\lambda_2 = \frac{\beta_2(L+\eta_1 I+A\eta_2)}{N}$, where β_2 is the effective contact rate of aware susceptible and infected HIV/AIDS individuals.

The modelling of the recruitment campaign is expressed by the function $f(M)$ which is a function of M such that $supf(M) = 1$, because the movement from S_U to S_A is proportional to $f(M)$ given by $f(M) = 1 - g(M)$. If no one is joined to I and A sub-classes, then no HIV/AIDS information

Parameter	Discription
π	Recruitment rate
μ	Natural per capita death rate
θ	Rate of unaware susceptible individuals listen to the advertisement campaigns and become aware or response rate of unaware individual‘s to become aware
ϕ	Rate of aware susceptible individuals stop taking preventive measure and become unaware due to memory fading or carelessness.
k	Screening rate from undiagnosed to diagnosed infected stage
σ	Proportion of HIV-infected individuals with no symptom of AIDS after screening
γ	Treatment rate of diagnosed HIV infected persons with no clinical symptom of AIDS
a_1	Progression rate to class A for the diagnosed infectious
ϵ	Rate of treated persons in the class T leave in to the class I
a_2	Progression rate to class A for those under treatment
ρ	Rate of HIV-infected persons with AIDS symptoms are treated for HIV
d	Death rate due HIV/AIDS of people in class A

Table 3.1: Descriptions of the parameters.

campaign. Thus $f(0) = 0$ when $I(t) = 0$ and $A(t) = 0$. Owing to this, one can model $f(M)$ by the following function.

$$f(M) = \frac{p(I+A)}{1+q(I+A)},$$

where p is growth rate of information and q is saturation constant [BB12]. When large number of diagnosed infective individuals are counted, the growth of information will be saturated. Moreover, when aware people stop taking preventive measure due to memory fading or carelessness, the movement from S_A to S_U is proportional to $g(M)$ given by $g(M) = 1 - f(M)$. Thus, the function $g(M)$ is a function of M such that $g(0) = 1$ and $infg(M) = 0$. The $infg(M) = 0$, when the $supf(M) = 1$. The rest of the parameters are described in Table 3.1.

Now depending on the above assumptions and model variables description, the transition diagram of the model is shown in Figure 3.1.

Thus HIV/AIDS transmission flow diagram in Figure 3.1 described by the following deterministic system of non-linear ODE:

$$\begin{cases} \frac{dS_U}{dt} = \pi - \lambda_1 S_U - \theta f(M) S_U + \phi g(M) S_A - \mu S_U, \\ \frac{dS_A}{dt} = \theta f(M) S_U - \phi g(M) S_A - \lambda_2 S_A - \mu S_A, \\ \frac{dL}{dt} = \lambda_1 S_U + \lambda_2 S_A - k\sigma L - (k(1-\sigma) + \mu) L, \\ \frac{dI}{dt} = k\sigma L + \epsilon T - a_1 I - \gamma I - \mu I, \\ \frac{dT}{dt} = \gamma I + \rho A - a_2 T - (\epsilon + \mu) T, \\ \frac{dA}{dt} = k(1-\sigma) L + a_1 I + a_2 T - (d + \rho + \mu) A, \end{cases} \tag{3.1}$$

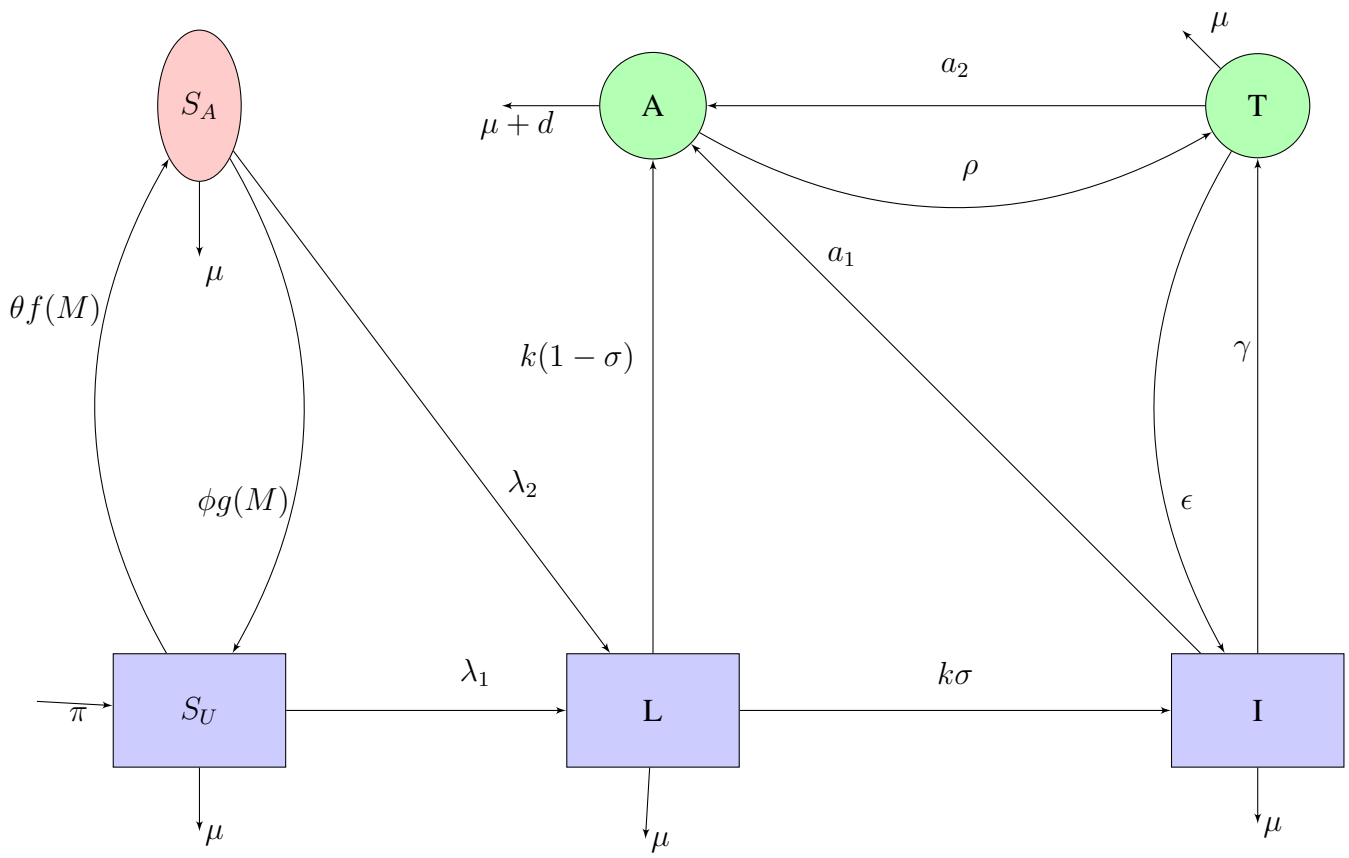

Figure 3.1: HIV/AIDS transmission flow diagram .

with inital conditions

$$S_U(0) > 0, S_A(0) > 0, L(0) > 0, I(0) > 0, T(0) > 0, \text{and } A(0) > 0. \tag{3.2}$$

3.3 Model analysis

3.3.1 Positivity of the solutions

Here, we discussed the condition in which the HIV/AIDS model (3.1) has non-negative solutions. To be exact this epidemiological HIV/AIDS model reflects human population in different compartments.

Theorem 7 *let* $\Omega = \{(S_U, S_A, L, I, T, A) \in \mathbb{R}^6_+ : S_U(0) > 0, S_A(0) > 0, L(0) > 0, I(0) > 0, T(0) > 0, A(0) > 0\}$*, then the solutions* $(S_U(t), S_A(t), L(t), I(t), T(t), A(t))$ *of (3.1) are positive for* $\forall t \geq 0$.

Proof:

Consider the system (3.1) and let us take the first equation:

$$\frac{dS_U(t)}{dt} = \pi - \lambda_1 S_U - \theta f(M) S_U + \phi g(M) S_A - \mu S_U \ .$$
$$\implies \frac{dS_U(t)}{dt} \geq -(\lambda_1 + \theta f(M) + \mu) S_U = -(\frac{\beta_1(L+\eta_1 I + A\eta_2)}{N} + \theta f(M) + \mu) S_U.$$
$$\implies \frac{dS_U(t)}{dt} \geq -(\beta_1(L + \eta_1 I + A\eta_2) + \theta f(M) + \mu) S_U.$$
$$\implies \frac{dS_U}{S_U} \geq -(\beta_1(L + \eta_1 I + A\eta_2) + \theta f(M) + \mu) dt.$$

We solved the above inequality gives:

$$\implies S_U(t) \geq S_U(0) exp^{-\mu t - \int (L(t) + \eta_1 I(t) + A(t)\eta_2 + \theta f(M)) dt} \geq 0.$$

let us take the second equation

$$\frac{dS_A(t)}{dt} = \theta f(M) S_U - \phi g(M) S_A - \lambda_2 S_A - \mu S_A.$$
$$\implies \frac{dS_A(t)}{dt} \geq -(\frac{\beta_2(L+\eta_1 I + A\eta_2)}{N} + \phi g(M) + \mu) S_A.$$
$$\implies \frac{dS_A(t)}{dt} \geq -(\beta_2(L + \eta_1 I + A\eta_2) + \phi g(M) + \mu) S_A.$$
$$\implies \frac{dS_A}{S_A} \geq -(\beta_2(L + \eta_1 I + A\eta_2) + \phi g(M) + \mu) dt.$$
$$\implies S_A(t) \geq S_A(0) exp^{-\mu t - \int (\beta_2(L(t) + \eta_1 I(t) + A(t)\eta_2) + \phi g(M)) dt} \geq 0.$$

Again let us take the third equation

$$\frac{dL}{dt} \geq -(k + \mu) L.$$
$$\implies L(t) \geq L(0) e^{-(k+\mu)t} \geq 0, \forall t \geq 0.$$

The positivity solution of the rest three equations can be shown in the following way.

First $I(t) > 0, \forall t \in [0, \vartheta)$, where $0 < \vartheta \leq +\infty$. If it does not hold, then $\exists\ t_1 \in [0, \vartheta)$ such that $I(t_1) = 0, \frac{dI}{dt}(t_1) \leq 0$ and $I(t) > 0, \forall t \in [0, t_1)$. So there must have $T(t) > 0, \forall t \in [0, t_1)$. If it is not true, $\exists\ t_2 \in (0, t_1)$ such that $T(t_2) = 0, \frac{dT}{dt}(t_2) \leq 0$ and $T(t) > 0, \forall t \in (0, t_2)$. Our claim is $A(t) > 0, \forall t \in [0, t_2)$. If it is not true, then $\exists\ t_3 \in (0, t_2)$ such that $A(t_3) = 0, \frac{dA}{dt}(t_3) \leq 0$ and $A(t) > 0, \forall t \in (0, t_3)$.

From sixth equation of (3.1):

$\frac{dA}{dt}(t_3) = k(1-\sigma)L(t_3) + a_1 I(t_3) + a_2 T(t_3) - (d+\rho+\mu)A(t_3) = k(1-\sigma)L(t_3) + a_1 I(t_3) + a_2 T(t_3) > 0$, which is a contradiction to $\frac{dA}{dt}(t_3) \leq 0$. Thus, $A(t) > 0, \forall t \in [0, t_2)$.

So, fifth equation of (3.1):

$\frac{dT}{dt}(t_2) = \gamma I(t_2) + \rho A(t_2) - (a_2 + \epsilon + \mu) T(t_2) = \gamma I(t_2) + \rho A(t_2) > 0$, which is a contradiction to $\frac{dT}{dt}(t_2) \leq 0$. Thus, $T(t) > 0, \forall t \in [0, t_1)$.

Similarly we have, $A(t) > 0, \forall t \in [0, t_1)$.

Now we claim $I(t) > 0, \forall t \in [0, \vartheta)$. If it is not true, then $\exists\ t_1 \in (0, \vartheta)$ such that $I(t_1) = 0, \frac{dI}{dt}(t_1) \leq 0$ and $I(t) > 0, \forall t \in [0, t_1)$.

From fourth equation of (3.1):

$\frac{dI}{dt}(t_1) = k\sigma L(t_1) + \epsilon T(t_1) - (a_1 + \gamma + \mu) I(t_1) = k\sigma L(t_1) + \epsilon T(t_1) > 0$, which is a contradiction to $\frac{dI}{dt}(t_1) \leq 0$. Thus, $I(t) > 0, \forall t \in [0, \vartheta)$.

This completes the proof.

3.3.2 Invariant region

In this part, we showed the solutions of all state systems are uniformly bounded in the region, as given by the following theorem.

Theorem 8 *The model system (3.1) is biological significance on the region given by* $\Omega \in \mathbb{R}^6_+$ *such that* $\Omega = \{(S_U, S_A, L, I, T, A) \in \mathbb{R}^6_+ : N \leq \frac{\pi}{\mu}\}$.

Proof:
The rate of change of total population $\frac{dN}{dt}$ can be obtained by adding all the equations in (3.1). Hence

$$\begin{aligned}
&\tfrac{dN}{dt} = \tfrac{dS_U}{dt} + \tfrac{dS_A}{dt} + \tfrac{dL}{dt} + \tfrac{dI}{dt} + \tfrac{dT}{dt} + \tfrac{dA}{dt},\\
&\Rightarrow \tfrac{dN}{dt} = \pi - \mu S_U - \mu S_A - \mu L - \mu I - \mu T - (d+\mu)A,\\
&\Rightarrow \tfrac{dN}{dt} = \pi - \mu(S_U + +S_A + L + I + T + A) - dA,\\
&\Rightarrow \frac{dN}{dt} = \pi - \mu N(t) - dA, \qquad (3.3)\\
&\Rightarrow \tfrac{dN}{dt} \leq \pi - \mu N(t).
\end{aligned}$$

Therefore, the solution of this last inequality satisfies the relation.

$$N(t) \leq \tfrac{\pi}{\mu} + e^{-\mu t}(N(0) - \tfrac{\pi}{\mu}).$$

Here, if the initial population $0 < N(0) \leq \frac{\pi}{\mu}$, then we obtain $0 < N(t) \leq \frac{\pi}{\mu}$ for all $t \geq 0$. This shows that Ω is positively invariant. Therefore, for all $t \geq 0$ every solution of the model system (3.1) with initial conditions in Ω remains there and all are bounded.

3.3.3 Disease-free equilibrium (DFE)

The deterministic system of non linear ODE (3.1) has the disease-free equilibrium (DFE). The DFE is obtained by setting the right hand side of the equations (3.1) to zero in the absence of HIV infection, which is

$$\tfrac{dS_U}{dt} = \tfrac{dS_A}{dt} = \tfrac{dL}{dt} = \tfrac{dI}{dt} = \tfrac{dT}{dt} = \tfrac{dA}{dt} = 0.$$

In case of no disease, $S_A = L = I = T = A = 0$ which implies the system (3.1) leads to

$$\tfrac{dS_U}{dt} = \pi - \lambda_1 S_U - \theta f(M) S_U + \phi g(M) S_A - \mu S_U = 0,$$

but $\lambda_1 = \dfrac{\beta_1(L + \eta_1 I + +A\eta_2)}{N} = 0$ and if there is no disease in the community, then there are no aware individuals that make preventive measures.

Thus $\frac{dS_U}{dt} = \pi - \mu S_U = 0 \quad \Rightarrow S_U = \frac{\pi}{\mu}$.

Therefore, the DFE point say $E_{h0} = (\frac{\pi}{\mu}, 0, 0, 0, 0, 0)$.

3.3.4 Control reproduction number

Control reproduction number is the threshold parameter that governs the spread of a disease, which is denoted by say R_e. So to compute R_e simply it is the spectral radius of the next generation matrix [VdDW02]. In this approach it is essential to differentiate new infected peoples from all other class. The infected classes are L, I, T, A. So, we can write system (3.1) as $X = F - V$ and $V = V^- - V^+$, where $X = (S_U, S_A, L, I, T, A)$, F is the rate of appearance of new infections in each class, V^- is the rate of transfer of the infectious individuals out of each class, and V^+ is the rate of transfer into each class by all other means. Hence, the associated matrices F of the new infection terms and V is the remaining transition terms are given by

$$F = \begin{bmatrix} \lambda_1 S_U + \lambda_2 S_A \\ 0 \\ 0 \\ 0 \end{bmatrix} \text{ and } V = \begin{bmatrix} (k+\mu)L \\ (a_1+\gamma+\mu)I - k\sigma L - \epsilon T \\ (a_2+\epsilon+\mu)T - \gamma I - \rho A \\ (d+\rho+\mu)A - k(1-\sigma)L - a_2 T - a_1 I \end{bmatrix},$$

where $\lambda_1 = \frac{\beta_1(L+\eta_1 I + A\eta_2)}{N}$ and $\lambda_2 = \frac{\beta_2(L+\eta_1 I + A\eta_2)}{N}$.

The entries of the matrix F are say f_1, f_2, f_3 and f_4 , where $f_1 = \lambda_1 S_U + \lambda_2 S_A, f_2 = 0, f_3 = 0$ and $f_4 = 0$. We can also write $F = (f_1 \;\; f_2 \;\; f_3 \;\; f_4)^T$, where T is the transpose of 1 row matrix. Also, the entries of the matrix V are say $v_1 = (k+\mu)L, v_2 = (a_1+\gamma+\mu)I - kL - \epsilon T, v_3 = (a_2+\epsilon+\mu)T - \gamma I - \rho A$ and $v_4 = (d+\rho+\mu)A - k(1-\sigma)L - a_2 T - a_1 I$.

The next is obtaining the Jacobian matrix of F and V with respect to L, I, T, and A at the disease free equilibrium $E_{h0} = (\frac{\pi}{\mu}, 0, 0, 0, 0, 0)$. Here, if there is no disease in the community, then the populations are initial unaware susceptible individuals whose assigned to be $S_{U0} = \frac{\pi}{\mu}$.

Let us say the Jacobian matrix of F and V are f and v respectively. Hence, the entry members of f and v are in the following way.

$$f = \begin{bmatrix} \frac{\partial f_1}{\partial L} & \frac{\partial f_1}{\partial I} & \frac{\partial f_1}{\partial T} & \frac{\partial f_1}{\partial A} \\ \frac{\partial f_2}{\partial L} & \frac{\partial f_2}{\partial I} & \frac{\partial f_2}{\partial T} & \frac{\partial f_2}{\partial A} \\ \frac{\partial f_3}{\partial L} & \frac{\partial f_3}{\partial I} & \frac{\partial f_3}{\partial T} & \frac{\partial f_3}{\partial A} \\ \frac{\partial f_4}{\partial L} & \frac{\partial f_4}{\partial I} & \frac{\partial f_4}{\partial T} & \frac{\partial f_4}{\partial A} \end{bmatrix} \text{ and } v = \begin{bmatrix} \frac{\partial v_1}{\partial L} & \frac{\partial v_1}{\partial I} & \frac{\partial v_1}{\partial T} & \frac{\partial v_1}{\partial A} \\ \frac{\partial v_2}{\partial L} & \frac{\partial v_2}{\partial I} & \frac{\partial v_2}{\partial T} & \frac{\partial v_2}{\partial A} \\ \frac{\partial v_3}{\partial L} & \frac{\partial v_3}{\partial I} & \frac{\partial v_3}{\partial T} & \frac{\partial v_3}{\partial A} \\ \frac{\partial v_4}{\partial L} & \frac{\partial v_4}{\partial I} & \frac{\partial v_4}{\partial T} & \frac{\partial v_4}{\partial A} \end{bmatrix}.$$

Thus

$$f = \begin{bmatrix} \beta_1 S_U + \beta_2 S_A & \eta_1(\beta_1 S_U + \beta_2 S_A) & 0 & \eta_2(\beta_1 S_U + \beta_2 S_A) \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{bmatrix}$$

$$= (\beta_1 S_U + \beta_2 S_A) \begin{bmatrix} 1 & \eta_1 & 0 & \eta_2 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{bmatrix} \text{ and}$$

$$v = \begin{bmatrix} k+\mu & 0 & 0 & 0 \\ -\sigma k & (a_1+\gamma+\mu) & -\epsilon & 0 \\ 0 & -\gamma & (a_2+\epsilon+\mu) & -\rho \\ \sigma k - k & -a_1 & -a_2 & (d+\rho+\mu) \end{bmatrix} = \begin{bmatrix} k+\mu & 0 & 0 & 0 \\ -\sigma k & B & -\epsilon & 0 \\ 0 & -\gamma & C & -\rho \\ \sigma k - k & -a_1 & -a_2 & D \end{bmatrix},$$

where

$$B = a_1 + \gamma + \mu, \qquad C = a_2 + \epsilon + \mu, \qquad D = d + \rho + \mu. \tag{3.4}$$

Remark: To simplify our work easily use B, C, and D for the whole work as they are required.
Hereafter find the product of fv^{-1}, where v^{-1} is the inverse matrix of v.
First find v^{-1} which becomes:
$v^{-1} = \frac{1}{det(v)} \times$

$$\begin{bmatrix} B(CD-\rho a_2) - \epsilon(\rho a_1 + D\gamma) & 0 & 0 & 0 \\ k[\sigma(CD - \rho a_2 - \epsilon\rho) + \rho\epsilon] & (k+\mu)(CD-\rho a_2) & (k+\mu)D\epsilon & (k+\mu)\rho\epsilon \\ k[\sigma(a_1\rho + \gamma D - B\rho) + B\rho] & (k+\mu)(a_1\rho + \gamma D) & (k+\mu)BD & (k+\mu)\rho B \\ W & (k+\mu)(Ca_1 + \gamma a_2) & (k+\mu)(\epsilon a_1 + Ba_2) & (k+\mu)(BC - \epsilon\gamma) \end{bmatrix},$$

where $det(v) = (k+\mu)[BCD - B\rho a_2 - D\gamma\epsilon - \epsilon\rho a_1], W = k[\sigma(Ca_1 + \gamma a_2 + \gamma\epsilon - BC) - \gamma\epsilon + BC]$, and $\times$ indicates multiplication.
Thus $fv^{-1} = \frac{(\beta_1 S_U + \beta_2 S_A)}{[BCD - B\rho a_2 - D\gamma\epsilon - \epsilon\rho a_1]} \times$

$$\begin{bmatrix} \frac{\Sigma}{k+\mu} & [C(\eta_1 D + \eta_2 a_1) + a_2(\gamma\eta_2 - \eta_1\rho)] & [\epsilon(\eta_1 D + \eta_2 a_1) + Ba_2\eta_2] & [\epsilon(\eta_1\rho - \gamma\eta_2) + \eta_2 BC] \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{bmatrix},$$

where $\Sigma = (CD - \rho a_2)(B + k\sigma\eta_1) - \epsilon(\rho a_1 + D\gamma) + k[\sigma\eta_2(Ca_1 + \gamma(a_2+\epsilon) - BC) + \epsilon\eta_1\rho(1 - \sigma) + \eta_2(BC - \epsilon\gamma)]$.
Thus, the dominant eigenvalue of the next generation matrix (fv^{-1}) is control reproductive number is given by:

$R_e = \frac{\frac{(\beta_1 S_U + \beta_2 S_A)}{N}}{k+\mu}[1 + \frac{k[\sigma\eta_1(CD-\rho a_2)+\sigma\eta_2(Ca_1+\gamma(a_2+\epsilon)-BC)+\epsilon\eta_1\rho(1-\sigma)+\sigma\eta_2(BC-\epsilon\gamma)]}{[BCD-B\rho a_2-D\gamma\epsilon-\epsilon\rho a_1]}]$.

Therefore, $R_e = \frac{\beta_1}{k+\mu}[1 + \frac{\eta_1 k(CD\sigma-\sigma\rho a_2+\rho\epsilon-\sigma\rho\epsilon)+k\eta_2(\gamma\sigma a_2+Ca_1\sigma+BC+\sigma\epsilon\gamma-\epsilon\gamma-BC\sigma)}{BCD-B\rho a_2-\epsilon\gamma D-\epsilon\rho a_1}]$.

3.3.5 Local stability of DFE

Theorem 9 *The DFE point is locally asymptotically stable if* $R_e < 1$ *and unstable if* $R_e > 1$.

Proof

To prove local stability of DFE, we obtained the Jacobian matrix of the system (3.1) at the DFE E_{h0}.

$J(\frac{\pi}{\mu}, 0, 0, 0, 0, 0) =$

$$\begin{bmatrix} -(\theta f(M)+\mu) & \phi g(M) & -\beta_1 & -\eta_1\beta_1-\theta p & 0 & -\eta_2\beta_1-\theta p \\ (\theta f(M)+\mu) & -(\mu+\phi g(M)) & 0 & 0 & 0 & 0 \\ 0 & 0 & \beta_1-(k+\mu) & \eta_1\beta_1 & 0 & \eta_2\beta_1 \\ 0 & 0 & k\sigma & -(a_1+\gamma+\mu) & \epsilon & 0 \\ 0 & 0 & 0 & \gamma & -(a_2+\epsilon+\mu) & \rho \\ 0 & 0 & k(1-\sigma) & a_1 & a_2 & -(d+\rho+\mu) \end{bmatrix}.$$

$$= \begin{bmatrix} -(\theta f(M)+\mu) & \phi g(M) & -\beta_1 & -\eta_1\beta_1-\theta p & 0 & -\eta_2\beta_1-\theta p \\ (\theta f(M)+\mu) & -(\mu+\phi g(M)) & 0 & 0 & 0 & 0 \\ 0 & 0 & \beta_1-(k+\mu) & \eta_1\beta_1 & 0 & \eta_2\beta_1 \\ 0 & 0 & k\sigma & -B & \epsilon & 0 \\ 0 & 0 & 0 & \gamma & -C & \rho \\ 0 & 0 & k(1-\sigma) & a_1 & a_2 & -D \end{bmatrix}.$$

Now find the eigenvalues of this matrix, which becomes

$$\begin{vmatrix} -(\theta f(M)+\mu)-\lambda & \phi g(M) & -\beta_1 & -\eta_1\beta_1-\theta p & 0 & -\eta_2\beta_1-\theta p \\ (\theta f(M)+\mu) & -(\mu+\phi g(M))-\lambda & 0 & 0 & 0 & 0 \\ 0 & 0 & \beta_1-(k+\mu)-\lambda & \eta_1\beta_1 & 0 & \eta_2\beta_1 \\ 0 & 0 & k\sigma & -B-\lambda & \epsilon & 0 \\ 0 & 0 & 0 & \gamma & -C-\lambda & \rho \\ 0 & 0 & k(1-\sigma) & a_1 & a_2 & -D-\lambda \end{vmatrix} =$$

0.

$$\Rightarrow -(\theta f(M)+\mu)-\lambda \begin{vmatrix} -(\mu+\phi g(M))-\lambda & 0 & 0 & 0 & 0 \\ 0 & \beta_1-(k+\mu)-\lambda & \eta_1\beta_1 & 0 & \eta_2\beta_1 \\ 0 & k\sigma & -B-\lambda & \epsilon & 0 \\ 0 & 0 & \gamma & -C-\lambda & \rho \\ 0 & k(1-\sigma) & a_1 & a_2 & -D-\lambda \end{vmatrix} -$$

$$(\theta f(M)+\mu) \begin{vmatrix} \phi g(M) & -\beta_1 & -\eta_1\beta_1-\theta p & 0 & -\eta_2\beta_1-\theta p \\ 0 & \beta_1-(k+\mu)-\lambda & \eta_1\beta_1 & 0 & \eta_2\beta_1 \\ 0 & k\sigma & -B-\lambda & \epsilon & 0 \\ 0 & 0 & \gamma & -C-\lambda & \rho \\ 0 & k(1-\sigma) & a_1 & a_2 & -D-\lambda \end{vmatrix} = 0.$$

$$\Longleftrightarrow [\mu(\theta f(M)+\mu+\lambda)+\lambda(\theta f(M)+\lambda+\mu+\phi g(M))] = 0 \tag{3.5}$$

$$\text{or} \begin{vmatrix} \beta_1-(k+\mu)-\lambda & \eta_1\beta_1 & 0 & \eta_2\beta_1 \\ k\sigma & -B-\lambda & \epsilon & 0 \\ 0 & \gamma & -C-\lambda & \rho \\ k(1-\sigma) & a_1 & a_2 & -D-\lambda \end{vmatrix} = 0.$$

Now $f(M)=0$ and $g(M)=1-f(M)=1$ at DFE E_{h0}.

Hence equation (3.5) becomes: $\lambda^2+(2\mu+\phi)\lambda+\mu^2=0$.

The roots of this quadratic equation are eigenvalues λ_1 and λ_2.

The eigenvalues λ_1 and λ_2 have negative real part, since μ and ϕ are positive.

Again $\begin{vmatrix} \beta_1-(k+\mu)-\lambda & \eta_1\beta_1 & 0 & \eta_2\beta_1 \\ k\sigma & -B-\lambda & \epsilon & 0 \\ 0 & \gamma & -C-\lambda & \rho \\ k(1-\sigma) & a_1 & a_2 & -D-\lambda \end{vmatrix} =$

$$(\beta_1-(k+\mu)-\lambda) \begin{vmatrix} -B-\lambda & \epsilon & 0 \\ \gamma & -C-\lambda & \rho \\ a_1 & a_2 & -D-\lambda \end{vmatrix} \text{-}\eta_1\beta_1 \begin{vmatrix} k\sigma & \epsilon & 0 \\ 0 & -C-\lambda & \rho \\ k(1-\sigma) & a_2 & -D-\lambda \end{vmatrix}$$

$$\text{-}\eta_2\beta_1 \begin{vmatrix} k\sigma & -B-\lambda & \epsilon \\ 0 & \gamma & -C-\lambda \\ k(1-\sigma) & a_1 & a_2 \end{vmatrix} = 0.$$

After long derivation, we simplify the following polynomial expression

$\lambda^4+\lambda^3[k+\mu+B+C+D-\beta_1]+\lambda^2[-\epsilon\gamma-\beta_1(B+C+D+\eta_1 k\sigma)+\eta_2 k(1-\sigma)+(k+\mu)(B+C+D)BC+CD+BD]+\lambda[-\beta_1(BC+CD+BD+\epsilon\gamma)+\eta_1(Ck\sigma+k\sigma D)+\eta_2(K\sigma a_1+BkCk-Bk\sigma-Ck\sigma)+\rho a_2-(k+\mu)\epsilon\gamma-\epsilon\gamma D-\epsilon\rho a_1]+ABCD+(k+\mu)\rho a_2-(k+\mu)\epsilon\gamma D-(k+\mu)\epsilon\rho a_1+\beta_1[-BCD-\rho a_2+\epsilon\gamma D+\epsilon\rho a_1-\eta_1 k(CD\sigma-\sigma\rho a_2+\rho\epsilon-\sigma\rho\rho\epsilon)-$

$$k\eta_2(\gamma\sigma a_2 + Ca_1\sigma + BC + \sigma\epsilon\gamma - \epsilon\gamma - BC\sigma)] = 0. \tag{3.6}$$

Thus, we expressed (3.6) as

$$A_0\lambda^4 + A_1\lambda^3 + A_2\lambda^2 + A_3\lambda + A_4 = 0,$$

where $A_0 = 1, \qquad A_1 = k + \mu + B + C + D - \beta_1,$

$A_2 = -\epsilon\gamma - \beta_1(B + C + D + \eta_1 k\sigma + \eta_2 k(1-\sigma)) + (k+\mu)(B+C+D) - BC + CD + BD$

$A_3 = -\beta_1(BC + CD + BD - \epsilon\gamma - a_2\rho) + A(BC + BD + CD - a_2\rho - \epsilon\gamma) + \eta_1(Ck\sigma + k\sigma D) +$
$\eta_2(K\sigma a_1 + Bk + Ck - Bk\sigma - Ck\sigma) + B(CD - a_2\rho) - \epsilon(\gamma D + a_1\rho),$

$A_4 = (k+\mu)(BCD - B\rho a_2 - \epsilon\gamma D - \epsilon\rho a_1) + \beta_1[-BCD + B\rho a_2 + \epsilon\gamma D + \epsilon\rho a_1 - \eta_1 k(-CD\sigma +$
$\sigma\rho a_2 - \rho\epsilon + \sigma\rho\epsilon) - k\eta_2(-\gamma\sigma a_2 - Ca_1\sigma - BC - \sigma\epsilon\gamma + \epsilon\gamma + BC\sigma)].$
$= (k+\mu)(BCD - B\rho a_2 - \epsilon\gamma D - \epsilon\rho a_1)$
$[1 + \frac{\beta_1}{k+\mu}(-1 - \frac{\eta_1 k(CD\sigma - \sigma\rho a_2 + \rho\epsilon - \sigma\rho\epsilon) + k\eta_2(\gamma\sigma a_2 + Ca_1\sigma + BC + \sigma\epsilon\gamma - \epsilon\gamma - BC\sigma)}{BCD - B\rho a_2 - \epsilon\gamma D - \epsilon\rho a_1})].$
$= (k+\mu)(BCD - B\rho a_2 - \epsilon\gamma D - \epsilon\rho a_1)[1 - R_e].$
$= (k+\mu)(BCD - B\rho a_2 - \epsilon\gamma D - \epsilon\rho a_1)[1 - R_e].$
$= (k+\mu)((d+\mu)(a_2 B + \epsilon a_1) + \mu D(\epsilon + B)[1 - R_e].$

Applying the Routh–Hurwitz criterion [All08], it can be shown that the eigenvalues of the 4×4 Jacobin matrix (the roots of the characteristic polynomial $P(\lambda) = \lambda^4 + A_1\lambda^3 + A_2\lambda^2 + A_3\lambda + A_4$) have negative real parts, if $R_e < 1$. If $R_e > 1$, then $A_3 < 0$, thus the Jacobian matrix has at least one eigenvalue with positive real part. Hence, DFE E_{h0} is locally asymptotically stable if $R_e < 1$ and unstable if $R_e > 1$.

Biologically speaking, this implies that HIV can be eliminated from the community (when $R_e < 1$). When the initial size of the population are in the basin of attraction of E_{h0}.

3.3.6 Global stability of DFE

We used the method which is executed in [CCBVdD$^+$02] to explore the global stability of the DFE point.

First the model (3.1) can be re-written in the form:

$$\begin{cases} \frac{dX}{dt} = F(X, Z), \\ \frac{dZ}{dt} = G(X, Z), G(X, 0) = 0. \end{cases} \tag{3.7}$$

Where the vectors X and Z represents the non-infected and infected compartments. Now $X = (S_A, S_U)$, $Z = (L, I, T, A)$, and the conditions (H_1) and (H_2) are:

(H_1), $\frac{dX}{dt} = F(X, 0)$, X^* is GAS.

(H_2), $\frac{dZ}{dt} = QZ - G^*(X, Z), G^*(X, Z) \geq 0$ for $(X, Z) \in R_6^+$, where Q is a Metzler matrix (the non-diagonal entries of Q are positive.)

Here $Q = \begin{bmatrix} \beta_1 - (k+\mu) & \eta_1\beta_1 & 0 & \eta_2\beta_1 \\ k\sigma & -(a_1+\gamma+\mu) & \epsilon & 0 \\ 0 & \gamma & -(a_2+\epsilon+\mu) & \rho \\ k(1-\sigma) & a_1 & a_2 & -(d+\rho+\mu) \end{bmatrix}$.

Thus, the non diagonal entries of Q, are non-negative.
Again $\frac{dZ}{dt} = G(X,Z) = QZ - G^*(X,Z)$,

where $G^*(X,Z) = \begin{bmatrix} (L+\eta_1 I+\eta_2 A)[\beta_1(1-\frac{S_U}{N}) - \beta_2\frac{S_A}{N}] \\ 0 \\ 0 \\ 0 \end{bmatrix}$

$$= \begin{bmatrix} (L+\eta_1 I+\eta_2 A)[\beta_1 - (\beta_1\frac{S_U}{N} + \beta_2\frac{S_A}{N})] \\ 0 \\ 0 \\ 0 \end{bmatrix} = \begin{bmatrix} G_1^*(X,Z) \\ G_2^*(X,Z) \\ G_3^*(X,Z) \\ G_4^*(X,Z) \end{bmatrix}.$$

In a matrix $G^*(X,Z)$, we can not conclude that $G_1^*(X,Z) = \beta_1 - (\beta_1\frac{S_U}{N} + \beta_2\frac{S_A}{N})$ is positive. This leads to the second condition of (H_2) is not satisfied.
Thus, E_{h0} may not be globally asymptotically stable when $R_e < 1$.

3.3.7 Endemic equilibrium

The endemic equilibrium which means HIV/AIDS is endemic in the community is calculated by after setting to zero each equations of (3.1). Then solve them independently and express all solutions in-terms of diagnosed infected I. Then

$$\frac{dS_U}{dt} = \pi - \lambda_1 S_U - \theta f(M) S_U + \phi g(M) S_A - \mu S_U = 0, \tag{3.8}$$
$$\frac{dS_A}{dt} = \theta f(M) S_U - \phi g(M) S_A - \lambda_2 S_A - \mu S_A = 0, \tag{3.9}$$
$$\frac{dL}{dt} = \lambda_1 S_U + \lambda_2 S_A - kL - \mu L = 0, \tag{3.10}$$
$$\frac{dI}{dt} = kL + \epsilon T - a_1 I - \gamma I - \mu I = 0, \tag{3.11}$$
$$\frac{dT}{dt} = \gamma I + \rho A - a_2 T - (\epsilon+\mu) T = 0, \tag{3.12}$$
$$\frac{dA}{dt} = k(1-\sigma)L + a_1 I + a_2 T - (d+\rho+\mu) A = 0. \tag{3.13}$$

Here, from equation (3.8)– (3.13), we obtain $T = \frac{\gamma I+\rho A}{a_2+\epsilon+\mu}$, $L = \frac{(a_1+\gamma+\mu)I-\epsilon T}{k}$, $A = \frac{a_1 I+a_2 T+k(1-\sigma)L}{d+\rho+\mu}$, $L = \frac{\lambda_1 S_U+\lambda_2 S_A}{k+\mu}$, $S_A = \frac{\theta f(M)S_U}{\phi g(M)+\lambda_2+\mu}$, and $S_U = \frac{\pi+\phi g(M)S_A}{\lambda_1+\theta f(M)+\mu}$.
Then substitute one equation to the other, adding, and subtracting equations simultaneously we obtain the following results.
Therefore, the endemic equilibrium say $E_{h1} = (S_U^*, S_A^*, L^*, I^*, T^*, A^*)$, where

$$S_U^* = \frac{A[B(CD-\rho a_2)-\epsilon(\gamma+\rho a_1)]I^*}{k[(CD-\rho a_2+\epsilon\rho)(1-\sigma)(\lambda_1^*(\lambda_2^*+\phi g(M)+\mu)+\lambda_2^*\theta f(M))]},$$

$$S_A^* = \frac{\theta f(M)A[B(CD-\rho a_2)-\epsilon(\gamma+\rho a1)]I^*}{k(\phi g(M)+\lambda_2^*+\mu)[(CD-\rho a_2+\epsilon\rho)(1-\sigma)(\lambda_1^*(\lambda_2^*+\phi g(M)+\mu)+\lambda_2^*\theta f(M))]},$$

$$L^* = \frac{[B(CD-\rho a_2)-\epsilon(\gamma+\rho a_1)]I^*}{k[(CD-\rho a_2+\epsilon\rho)(1-\sigma)]},$$

$$I^* = \frac{k\pi[(CD-\rho a_2+\epsilon\rho)(1-\sigma)(\lambda_1^*(\lambda_2^*+\phi g(M)+\mu)+\lambda_2^*\theta f(M))(\lambda_2^*+\phi g(M)+\mu)]}{A[(\lambda_2^*+\phi g(M)+\mu)(\lambda_1^*\theta f(M)+\mu)B(CD-\rho a_2)-\epsilon(\gamma+\rho a_1)]},$$

$$T^* = \frac{[B(\rho(1-\sigma)+\gamma+\rho a_1)]I^*}{(CD-\rho a_2+\epsilon\rho)(1-\sigma)}, \quad \text{and} \qquad A^* = [\frac{BC(\rho(1-\sigma)+\gamma+\rho a1)}{(CD-\rho a_2+\epsilon\rho)(1-\sigma)} - \gamma]I^*,$$

where $\lambda_1^* = \frac{\beta_1(L^*+I^*+A^*)}{N}$, $\lambda_2^* = \frac{\beta_2(L^*+I^*+A^*)}{N}$, $f(M) = \frac{p(I^*+A^*)}{1+q(I^*+A^*)}$, and $g(M) = 1 - f(M)$.

Lemma 3 *For $R_e > 1$, a unique endemic equilibrium point E_{h1} exist and no endemic equilibrium otherwise.*

Proof. If the disease is endemic in the community, then $\exists\ t^* > 0$ such that $\frac{dL(t^*)}{dt} > 0$, $\frac{dI(t^*)}{dt} > 0$, $\frac{dT(t^*)}{dt} > 0$, and $\frac{dA(t^*)}{dt} > 0$. Thus, keeping the state variables L, I, T, and A at t^*, we have:

$$\frac{dL}{dt} = \lambda_1 S_U + \lambda_2 S_A - kL - \mu L > 0, \tag{3.14}$$

$$\frac{dI}{dt} = k\sigma L + \epsilon T - a_1 I - \gamma I - \mu I > 0, \tag{3.15}$$

$$\frac{dT}{dt} = \gamma I + \rho A - a_2 T - (\epsilon + \mu)T > 0, \tag{3.16}$$

$$\frac{dA}{dt} = k(1-\sigma)L + a_1 I + a_2 T - (d + \rho + \mu)A > 0. \tag{3.17}$$

Here from (3.14) $\lambda_1 S_U + \lambda_2 S_A > (k+\mu)L$,

$$\Rightarrow (k+\mu)L < \frac{\beta_1(L+\eta_1 I + +A\eta_2)}{N} S_U + \frac{\beta_1(L+\eta_1 I + A\eta_2)}{N} S_A,$$

$$\Rightarrow (k+\mu)L < (L+\eta_1 I + \eta_2 A)\frac{\beta_1 S_U + \beta_2 S_A}{N}.$$

$\Rightarrow (k+\mu)L < \beta_1(L+\eta_1 I+\eta_2 A)\dfrac{S_U+\frac{\beta_2}{\beta_1}S_A}{N}.$

Since from the fact that $\dfrac{S_U+\frac{\beta_2}{\beta_1}S_A}{N} < 1.$

Thus

$$(k+\mu)L < \beta_1(L+\eta_1 I+\eta_2 A). \tag{3.18}$$

Again from (3.15), (3.16), and (3.17), we have the following inequalities.

$(a_1+\gamma+\mu)I < k\sigma L+\epsilon T, \qquad (a_2+\epsilon+\mu)T < \gamma I+\rho A, \qquad (d+\rho+\mu)A < k(1-\sigma)L+a_1 I+a_2 T.$

Use B, C, D representation, we have the following.

$$BI < k\sigma L+\epsilon T, \tag{3.19}$$

$$CT < \gamma I+\rho A, \tag{3.20}$$

$$DA < k(1-\sigma)L+a_1 I+a_2 T. \tag{3.21}$$

Use inequality (3.19) and (3.20), (3.20) and (3.21) simultaneously to eliminate the term T we obtain the following.

$(BC-\epsilon\gamma)I < kC\sigma L+\epsilon\rho A$ and $-(\gamma a_2+a_1 C)I < Ck(1-\sigma)L+(\rho a_2-DC)A.$

Add these inequalities simultaneously and eliminate the term I by multiplying the term $(\gamma a_2+a_1 C)$ to the first and $BC-\epsilon\gamma$ to the second , we obtain

$0 < [kC\sigma(\gamma a_2+a_1 C)+kC(1-\sigma)(BC-\epsilon\gamma)]L+[\epsilon\rho(\gamma a_2+a_1 C)+(a_2\rho-DC)(BC-\epsilon\gamma)]A.$

And also multiply the first by $DC-a_2\rho$ and the second by $\epsilon\rho$, then add simultaneously to eliminate the term A, we obtain the following inequality.

$[(BC-\epsilon\gamma)(DC-a_2\rho)-\epsilon\rho(\gamma a_2+a_1 C)]I < [kC\sigma(DC-\rho a_2)+\epsilon\rho Ck(1-\sigma)]L.$

These two results gives

$$A < \frac{kC[\sigma a_2\gamma+\sigma a_1 C+BC-BC\sigma+\sigma\epsilon\gamma-\epsilon\gamma]L}{[-\epsilon\rho\gamma a_2-\epsilon\rho a_1 C+(DC-a_2\rho)(BC-\epsilon\gamma)]}, \tag{3.22}$$

$$I < \frac{[kC\sigma(DC-\rho a_2)+\epsilon\rho Ck(1-\sigma)]L}{[-\epsilon\rho\gamma a_2-\epsilon\rho a_1 C+(BC-\epsilon\gamma)(DC-a_2\rho)]}. \tag{3.23}$$

After this substitute (3.22) and (3.23) in $(k+\mu)L < \beta_1(L+\eta_1 I+\eta_2 A)$ at (3.18) we obtain,

$$(k+\mu)L < \beta_1[L+\eta_1\tfrac{[kC\sigma(DC-\rho a_2)+\epsilon\rho Ck(1-\sigma)]L}{[-\epsilon\rho\gamma a_2-\epsilon\rho a_1 C+(BC-\epsilon\gamma)(DC-a_2\rho)]}+\eta_2\tfrac{kC[\sigma a_2\gamma+\sigma a_1 C+BC-BC\sigma+\sigma\epsilon\gamma-\epsilon\gamma]L}{[-\epsilon\rho\gamma a_2-\epsilon\rho a_1 C+(DC-a_2\rho)(BC-\epsilon\gamma)]}],$$

$$\Rightarrow \quad (k+\mu)L < \beta_1[1+\tfrac{\eta_1[kC\sigma(DC-\rho a_2)+\epsilon\rho Ck(1-\sigma)]+\eta_2 kC[\sigma a_2\gamma+\sigma a_1 C+BC-BC\sigma+\sigma\epsilon\gamma-\epsilon\gamma]}{[-\epsilon\rho\gamma a_2-\epsilon\rho a_1 C+(BC-\epsilon\gamma)(DC-a_2\rho)]}]L.$$

Divided both sides by $(k+\mu)L$, we have

$$\Rightarrow \quad 1 < \beta_1[\frac{1}{k+\mu} + \frac{\eta_1[kC\sigma(DC-\rho a_2)+\epsilon\rho Ck(1-\sigma)]+\eta_2 kC[\sigma a_2\gamma+\sigma a_1 C+BC-BC\sigma+\sigma\epsilon\gamma-\epsilon\gamma]}{(k+\mu)[-\epsilon\rho\gamma a_2-\epsilon\rho a_1 C+(BC-\epsilon\gamma)(DC-a_2\rho)]}].$$

This reduced to $1 < \beta_1[\frac{1}{k+\mu}+\frac{k[\eta_1(\sigma(DC-\rho a_2)+\epsilon\rho k(1-\sigma))+\eta_2(\sigma a_2\gamma+\sigma a_1 C+BC-BC\sigma+\sigma\epsilon\gamma-\epsilon\gamma)]}{(k+\mu)[-\epsilon\rho a_1+BCD-\epsilon\gamma D-a_2\rho B]}]$,

$$\Rightarrow \quad 1 < \beta_1\frac{\pi}{\mu}[\frac{1}{(k+\mu)} + \frac{k[\eta_1(\sigma(DC-\rho a_2)+\epsilon\rho k(1-\sigma))+\eta_2(\sigma a_2\gamma+\sigma a_1 C+BC-BC\sigma+\sigma\epsilon\gamma-\epsilon\gamma)]}{(k+\mu)[-\epsilon\rho a_1+BCD-\epsilon\gamma D-a_2\rho B]}],$$
$$\Rightarrow \quad 1 < R_e,$$
$$\Rightarrow \quad R_e > 1.$$

This completes the proof.

3.3.8 The global stability of endemic equilibrium

Theorem 10 *If $R_e > 1$, the endemic equilibrium E_{h1} of (3.1) is globally asymptotically stable on $\mathbb{R}^6_{+0}\backslash\varpi$, with solutions in ϖ limiting to E_{h0}, where $\varpi = (S_U, S_A, 0, 0, 0, 0)$.*

Proof.

Consider the Lyapunov function

$G = (S_U - S_U^* - S_U^* \ln \frac{S_U}{S_U^*}) + (S_A - S_A^* - S_A^* \ln \frac{S_A}{S_A^*}) + N_1(L - L^* - L^* \ln \frac{L}{L^*}) + N_2(I - I^* - I^* \ln \frac{I}{I^*}) + (T - T^* - T^* \ln \frac{T}{T^*}) + N_3(A - A^* - A^* \ln \frac{A}{A^*})$, where N_1, N_2, N_3 are positive constants to be determined.

This type of Lyapunov function has been mentioned in [MLL03, Hou18].

Now, we can write the time derivative of G as

$G' = (1 - \frac{S_U^*}{S_U})S_U' + (1 - \frac{S_A^*}{S_A})S_A' + (1 - \frac{T^*}{T})T' + N_1(1 - \frac{L^*}{L})L' + N_2(1 - \frac{I^*}{I})I' + N_3(1 - \frac{A^*}{A})A'$

$= (1 - \frac{S_U^*}{S_U})[(\beta_1(L^* + \eta_1 I^* + \eta_2 A^*) + \theta f(M) + \mu)S_U^* - \phi g(M)S_A^* - (\mu + \beta_1(L + \eta_1 I + \eta_2 A) + \theta f(M))S_U + \phi g(M)S_A] + (1 - \frac{S_A^*}{S_A})[\theta f(M)S_U - (\phi g(M) + \beta_2(L + \eta_1 I + \eta_2 A) + \mu)S_A] + (1 - \frac{T^*}{T})[\gamma I + \rho A - CT] + N_1(1 - \frac{L^*}{L})[\beta_1(L + \eta_1 I + \eta_2 A)S_U + \beta_2(L + \eta_1 I + \eta_2 A)S_A - (k + \mu)L] + N_2(1 - \frac{I^*}{I})[kL + \epsilon T - BI] + N_3(1 - \frac{A^*}{A})[k(1 - \sigma)L + a_1 I + a_2 T - DA].$

$= (1 - \frac{S_U^*}{S_U})[(\beta_1(L^* + \eta_1 I^* + \eta_2 A^*) + \theta f(M) + \mu)S_A^* - \phi g(M)S_A^* + \phi g(M)S_A] - (1 - S_U^*)(\mu + \beta_1(L + \eta_1 I + \eta_2 A) + \theta f(M)) + (1 - \frac{S_A^*}{S_A})\theta f(M)S_U - (\phi g(M) + \beta_2(L + \eta_1 I + \eta_2 A) + \mu)(1 - S_A^*) + (1 - \frac{T^*}{T})[\gamma I + \rho A] - CT + C[T^*]) + N_1(1 - \frac{L^*}{L})[\beta_1(L + \eta_1 I + \eta_2 A)S_U + \beta_2(L + \eta_1 I + \eta_2 A)S_A] - (k + \mu)(1 - \frac{(L^* + \eta_1 I^* + \eta_2 A^*)(\beta_1 S_U^* + \beta_2 S_A^*)}{k+\mu}) + N_2(1 - \frac{I^*}{I})[kL + \epsilon T] - B(1 - [\frac{kL^* + \epsilon T^*}{B}])] + N_3(1 - \frac{A^*}{A})[k(1 - \sigma)L + a_1 I + a_2 T] - D(1 - [\frac{a_1 I^* + a_2 T^* + k(1-\sigma)L^*}{D}]).$

$= -(\theta f(M) + \mu)\frac{(S_U - S_U^*)^2}{S_U} + \phi g(M)(S_A - S_A^*) + (1 - \frac{S_U^*}{S_U})\lambda_1^* S_U^* - \lambda_1(S_U - S_U^*) + (1 - \frac{S_A^*}{S_A})\theta f(M)S_U - (\phi g(M) + \lambda_2 + \mu)(S_A - S_A^*) + (1 - \frac{T^*}{T})[\gamma I + \rho A] - C(T - T^*) + N_1(1 - \frac{L^*}{L})[\lambda_1 S_U + \lambda_2 S_A] - N_1(k + \mu)(L - L^*) + N_2(1 - \frac{I^*}{I})[kL + \epsilon T] - BN_2(I - I^*) + N_3(1 - \frac{A^*}{A})[k(1 - \sigma)L + a_1 I + a_2 T] - DN_3(A - A^*),$

where $\lambda_1 = \beta_1(L + \eta_1 I + \eta_2 A), \lambda_2 = \beta_2(L + \eta_1 I + \eta_2 A), \lambda_1^* = \beta_1(L^* + \eta_1 I^* + \eta_2 A^*), \lambda_2^* = \beta_2(L^* + \eta_1 I^* + \eta_2 A^*)$.

Now, the positive constants N_1, N_2, and N_3 are chosen such that the coefficients of

$S_U L, S_U I, S_U A, S_A L, S_A I, S_A A, L, I$, and A are equal to zero.

First take the coefficient of $S_U L$ gives

$-\beta_1 + N_1(\beta_1) = 0, \Rightarrow N_1 = 1.$

Second take the coefficient of A gives $\rho - DN_3 = 0 \Rightarrow N_3 = \frac{\rho}{D}$.

Third take the coefficient of I gives $-BN_2 + \gamma + a_1 N_3 = 0 \Rightarrow \gamma + a_1 N_3 = BN_2$.

$$\Rightarrow N_2 = \frac{D\gamma + a_1\rho}{BD}.$$

Hence $(N_1, N_2, N_3) = (1, \frac{D\gamma+a_1\rho}{BD}, \frac{\rho}{D})$.

Next substitute the results of N_1, N_2, N_3 in $\frac{dG}{dt}$ and then collect positive and negative terms, we get to

$\frac{dG}{dt} = [2(\theta f(M) + \mu)S_U^* + \phi g(M)S_A + \lambda_1^* S_U^* + \lambda_1 S_U^* + \theta f(M)S_U + S_A^*(\phi g(M) + \lambda_2 + \mu) + \gamma I + \rho A + CT^* + S_U(\lambda_1 + \lambda_2) + L^*(k + \mu) + \frac{(D\gamma+a_1\rho)}{BD}(kL + \epsilon T) + BI^*\frac{(D\gamma+a_1\rho)}{BD} + \frac{\rho}{D}(k(1-\sigma)L + a_1 I + a_2 T) + \rho A^*] - [\phi g(M)S_A^* + (\theta f(M) + \mu)(S_U + \frac{(S_U^*)^2}{S_U}) + \frac{\lambda_1^*(S_U^*)^2}{S_U} + \lambda_1 S_U + \theta f(M)S_U\frac{S_A^*}{S_A} + S_A(\phi g(M) + \lambda_2 + \mu) + \frac{T^*}{T}(\gamma I + \rho A) + CT + \frac{L^*}{L}S_U(\lambda_1 + \lambda_2) + L(k+\mu) + \frac{I^*}{I}\frac{(D\gamma+a_1\rho)}{BD}(kL + \epsilon T) + BI\frac{(D\gamma+a_1\rho)}{BD} + \frac{A^*}{A}\frac{\rho}{D}(k(1-\sigma)L + a_1 I + a_2 T) + \rho A]$.

$\frac{dG}{dt} = P - Q$, where

$P = 2(\theta f(M) + \mu)S_U^* + \phi g(M)S_A + \lambda_1^* S_U^* + \lambda_1 S_U^* + \theta f(M)S_U + S_A^*(\phi g(M) + \lambda_2 + \mu) + \gamma I + \rho A + CT^* + S_U(\lambda_1 + \lambda_2) + L^*(k+\mu) + \frac{(D\gamma+a_1\rho)}{BD}(kL + \epsilon T) + BI^*\frac{(D\gamma+a_1\rho)}{BD} + \frac{\rho}{D}(k(1-\sigma)L + a_1 I + a_2 T) + \rho A^*$

and

$Q = \phi g(M)S_A^* + (\theta f(M) + \mu)(USh + \frac{(S_U^*)^2}{S_U}) + \frac{\lambda_1^*(S_U^*)^2}{S_U} + \lambda_1 S_U + \theta f(M)S_U\frac{S_A^*}{S_A} + S_A(\phi g(M) + \lambda_2 + \mu) + \frac{T^*}{T}(\gamma I + \rho A) + CT + \frac{L^*}{L}S_U(\lambda_1 + \lambda_2) + L(k+\mu) + \frac{I^*}{I}\frac{(D\gamma+a_1\rho)}{BD}(kL + \epsilon T) + BI\frac{(D\gamma+a_1\rho)}{BD} + \frac{A^*}{A}\frac{\rho}{D}(k(1-\sigma)L + a_1 I + a_2 T) + \rho A$.

$\frac{dG}{dt} = 0$ at the endemic equilibrium point $E_{h1} = (S_U^*, S_A^*, L^*, I^*, T^*, A^*)$ and

$\frac{dG}{dt} < 0$ if $P < Q$.

Thus, the largest compact invariant set in $\{(S_U^*, S_A^*, L^*, I^*, T^*, A^*) \in \Omega : \frac{dG}{dt} = 0\}$ is the singleton endemic equilibrium E_{h1}. This implies that each solution which intersects $\mathbb{R}^6_{+0}\backslash\{L = I = T = A = 0\}$ limits to E_{h1}. By LaSalles invariant principle [LaS76], it implies that E_{h1} is globally asymptotically stable on $\mathbb{R}^6_{+0}\backslash\{L = I = T = A = 0\}$ if $P < Q$.

3.3.9 Determination of bifurcation at $R_e = 1$

Here, we used center manifold theory to investigate the possibility of forward and backward bifurcations of (3.1) by renaming the variables as follows.

Let $S_U = x_1, S_A = x_2, L = x_3, I = x_4, T = x_5$, and $A = x_6$ or to express them in vector notation; $x = (x_1, x_2, x_3, x_4, x_5, x_6)^T$, where T is transpose. Thus (3.1) can be written in the form

$\frac{dx}{dt} = F(x)$, where $F(x) = (f_1, f_2, f_3, f_4, f_5, f_6)^T$ likes below.

$$\begin{cases} \frac{dx_1}{dt} = \pi - \lambda_1 x_1 - \theta f(M) x_1 + \phi g(M) x_2 - \mu x_1, \\ \frac{dx_2}{dt} = \theta f(M) x_1 - \phi g(M) x_2 - \lambda_2 x_2 - \mu x_2, \\ \frac{dx_3}{dt} = \lambda_1 x_1 + \lambda_2 x_2 - k\sigma x_3 - (k(1-\sigma) + \mu) x_3, \\ \frac{dx_4}{dt} = k\sigma x_3 + \epsilon x_5 - a_1 x_4 - \gamma x_4 - \mu x_4, \\ \frac{dx_5}{dt} = \gamma x_4 + \rho x_6 - a_2 x_5 - (\epsilon + \mu) x_5, \\ \frac{dx_6}{dt} = k(1-\sigma) x_3 + a_1 x_4 + a_2 x_5 - (d + \rho + \mu) x_6, \end{cases} \tag{3.24}$$

where $\lambda_1 = \frac{\beta_1(x_3+\eta_1 x_4+\eta_2 x_6)}{N}$, $\lambda_2 = \frac{\beta_2(x_3+\eta_1 x_4+\eta_2 x_6)}{N}$, $f(M) = \frac{p(x_4+x_6)}{1+q(x_4+x_6)}$, $g(M) = 1 - f(M)$, and $N = x_1 + x_2 + x_3 + x_4 + x_5 + x_6$.
The Jacobian matrix of this system at the disease free equilibrium (DFE) $E_{h0} = (\frac{\pi}{\mu}, 0, 0, 0, 0, 0)$ is already expressed

$$J(E_{h0}) = \begin{bmatrix} -(\theta f(M) + \mu) & \phi g(M) & -\beta_1 & -\eta_1\beta_1 - \theta p & 0 & -\eta_2\beta_1 - \theta p \\ (\theta f(M) + \mu) & -(\mu + \phi g(M)) & 0 & 0 & 0 & 0 \\ 0 & 0 & \beta_1 - (k + \mu) & \eta_1\beta_1 & 0 & \eta_2\beta_1 \\ 0 & 0 & k\sigma & -B & \epsilon & 0 \\ 0 & 0 & 0 & \gamma & -C & \rho \\ 0 & 0 & k(1-\sigma) & a_1 & a_2 & -D \end{bmatrix}. \tag{3.25}$$

Suppose that $\beta_1 = \beta_1^*$ is a bifurcation parameter of the equation of control reproduction number, $R_e = [\frac{1}{k+\mu} + \frac{k[\sigma\eta_1(CD-\rho a_2)+\sigma\eta_2(Ca_1+\gamma(a_2+\epsilon)-BC)+\epsilon\eta_1\rho(1-\sigma)+\eta_2(BC-\epsilon\gamma)]}{(k+\mu)[BCD-B\rho a_2-D\gamma\epsilon-\epsilon\rho a_1]}]\beta_1^*$.
The center manifold theory can be used to analyse the stability of the endemic equilibrium E_{h1} near $R_e = 1$ or bifurcation point, then we obtained
$1 = [\frac{1}{k+\mu} + \frac{k[\sigma\eta_1(CD-\rho a_2)+\sigma\eta_2(Ca_1+\gamma(a_2+\epsilon)-BC)+\epsilon\eta_1\rho(1-\sigma)+\eta_2(BC-\epsilon\gamma)]}{(k+\mu)[BCD-B\rho a_2-D\gamma\epsilon-\epsilon\rho a_1]}]\beta_1^*$.

$$\Rightarrow \beta_1^* = \frac{(k+\mu)[BCD-B\rho a_2-D\gamma\epsilon-\epsilon\rho a_1]}{[BCD-B\rho a_2-D\gamma\epsilon-\epsilon\rho a_1+k[\sigma\eta_1(CD-\rho a_2)+\sigma\eta_2(Ca_1+\gamma(a_2+\epsilon)-BC)+\epsilon\eta_1\rho(1-\sigma)+\eta_2(BC-\epsilon\gamma)]]}.$$

The Jacobean matrix near $\beta_1^* = \beta_1$, has a right eigenvector $u = (u_1, u_2, u_3, u_4, u_5, u_6)^T$ associated with the zero eigenvalue.

Thus, we have

$$\begin{bmatrix} -(\theta f(M)+\mu) & \phi g(M) & -\beta_1 & -\eta_1\beta_1-\theta p & 0 & -\eta_2\beta_1-\theta p \\ \theta f(M) & -(\mu+\phi g(M)) & 0 & 0 & 0 & 0 \\ 0 & 0 & \beta_1-(k+\mu) & \eta_1\beta_1 & 0 & \eta_2\beta_1 \\ 0 & 0 & k\sigma & -B & \epsilon & 0 \\ 0 & 0 & 0 & \gamma & -C & \rho \\ 0 & 0 & k(1-\sigma) & a_1 & a_2 & -D \end{bmatrix} \begin{pmatrix} u_1 \\ u_2 \\ u_3 \\ u_4 \\ u_5 \\ u_6 \end{pmatrix} = \begin{pmatrix} 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \end{pmatrix}. \tag{3.26}$$

The system of equation becomes;

$$\begin{cases} -(\theta f(M)+\mu)u_1+\phi g(M)u_2-\beta_1u_3-\beta_1\eta_1u_4-\theta pu_4-\beta_1\eta_2u_6-\theta pu_6=0, \\ \theta f(M)u_1-(\mu+\phi g(M))u_2=0, \\ (\beta_1-(k+\mu))u_3+\beta_1\eta_1u_4+\beta_1\eta_2u_6=0, \\ k\sigma u_3-Bu_4+\epsilon u_5=0, \\ \gamma u_4-Cu_5+\rho u_6=0, \\ k(1-\sigma)u_3+a_1u_4+a_2u_5-Du_6=0. \end{cases} \tag{3.27}$$

Solving system (3.27) we obtain
$u_2 = 0$, since the expression $f(M) = 0$ and $g(M) = 1$ at DFE (E_{h0}).

$u_1 = -[\frac{\beta_1(u_3+\eta_1u_4+\eta_2u_6)+\theta p(u_4+u_6)}{\mu}]$, where $u_3 = \frac{\beta_1\eta_1[\frac{\sigma(DC-a_2\rho)+\epsilon\rho(1-\sigma)}{(BC-\epsilon\gamma)(1-\sigma)+\sigma(a_1C+a_2\gamma)}]+\beta_1\eta_2}{k+\mu-\beta_1}$,
$u_4 = \frac{\sigma(DC-a_2\rho)+\epsilon\rho(1-\sigma)}{(BC-\epsilon\gamma)(1-\sigma)+\sigma(a_1C+a_2\gamma)}$, $u_5 = \frac{\gamma[\frac{\sigma(DC-a_2\rho)+\epsilon\rho(1-\sigma)}{(BC-\epsilon\gamma)(1-\sigma)+\sigma(a_1C+a_2\gamma)}]+\rho}{C}$, and $u_6 = 1$.
The left eigenvectors of (3.25) associated with the zero eigenvalue at $\beta_1 = \beta_1^*$ is given by $v = (v_1, v_2, v_3, v_4, v_5, v_6)^T$. Then

$$\begin{bmatrix} -(\theta f(M)+\mu) & \theta f(M) & 0 & 0 & 0 & 0 \\ \phi g(M) & -(\mu+\phi g(M)) & 0 & 0 & 0 & 0 \\ -\beta_1 & 0 & \beta_1-(k+\mu) & k\sigma & 0 & k(1-\sigma) \\ -\eta_1\beta_1-\theta p & 0 & \eta_1\beta_1 & -B & \gamma & a_1 \\ 0 & 0 & 0 & \epsilon & -C & a_2 \\ -\eta_2\beta_1-\theta p & 0 & \eta_2\beta_1 & 0 & \rho & -D \end{bmatrix} \begin{pmatrix} v_1 \\ v_2 \\ v_3 \\ v_4 \\ v_5 \\ v_6 \end{pmatrix} = \begin{pmatrix} 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \end{pmatrix}. \tag{3.28}$$

Hence, we get $v_1 = v_2 = 0, \quad v_3 = \frac{\rho\epsilon k(1-\sigma)+k\sigma(CD+a_2\rho)}{\rho\epsilon(k+\mu)+k\sigma\eta_2 C\beta_1-\rho\epsilon\beta_1}$,
$v_4 = C[\frac{\rho\epsilon k(1-\sigma)+k\sigma(CD+a_2\rho)}{\rho\epsilon(k+\mu)+k\sigma\eta_2 C\beta_1-\rho\epsilon\beta_1}] - \frac{a_2}{\epsilon}$,
$v_5 = \frac{D-\eta_2\beta_1[\frac{\rho\epsilon k(1-\sigma)+k\sigma(CD+a_2\rho)}{\rho\epsilon(k+\mu)+k\sigma\eta_2 C\beta_1-\rho\epsilon\beta_1}]}{\rho}, \quad$ and $v_6 = 1$.
To compute a and b use the formula $a = \sum_{k,i,j=1}^{n} v_k u_i u_j \frac{\partial^2 f_k}{\partial x_i \partial x_j}(E_{h0})$, and
$b = \sum_{k,i=1}^{n} v_k u_i \frac{\partial^2 f_k}{\partial x_i \partial \beta_1}(E_{h0})$ in [CCS04], where $f_1 = \frac{dx_1}{dt}, f_2 = \frac{dx_2}{dt}, f_3 = \frac{dx_3}{dt}, f_4 = \frac{dx_4}{dt}, f_5 = \frac{dx_5}{dt}, f_6 = \frac{dx_6}{dt}$ (3.24). We can consider the left eigenvectors v_3, v_4, v_5 and v_6 , since v_1 and v_2 are zero.
Thus $\frac{\partial^2 f_3}{\partial x_3 \partial x_1} = \beta_1, \quad \frac{\partial^2 f_3}{\partial x_4 \partial x_1} = \beta_1\eta_1, \quad \frac{\partial^2 f_3}{\partial x_6 \partial x_1} = \beta_1\eta_2, \quad \frac{\partial^2 f_3}{\partial x_3 \partial x_2} = \beta_2, \quad \frac{\partial^2 f_3}{\partial x_4 \partial x_2} = \beta_2\eta_1, \quad \frac{\partial^2 f_3}{\partial x_6 \partial x_2} = \beta_2\eta_2, \quad \frac{\partial^2 f_3}{\partial x_3 \partial \beta_1} = 1, \quad \frac{\partial^2 f_3}{\partial x_4 \partial \beta_1} = \eta_1, \quad \frac{\partial^2 f_3}{\partial x_6 \partial \beta_1} = \eta_2.$
Then, the value of $a = v_3 u_1 \beta_1(u_3 + \eta_1 u_4 + \eta_2 u_6)$ and $b = v_3(u_3 + \eta_1 u_4 + \eta_2 u_6)$.
As we have seen from the derivation of eigenvalues, the values of $u_1 < 0, u_3 < 0$ and $v_3 > 0$. However, the value $u_3 + \eta_1 u_4 + \eta_2 u_6$ is positive, since the sum of $\eta_1 u_4 + \eta_2 u_6$ is grater than u_3.
Thus $a < 0$ and $b > 0$.
Hence, applying Theorem 4.1 stated in [CCS04], the model (3.1) undergoes a forward bifurcation at $R_e = 1$.
Therefore, we established the following result.

Theorem 11 *The unique endemic equilibrium E_{h1} of model (3.1) is locally asymptotically stable for $R_e > 1$ but close to 1.*

3.4 Sensitivity analysis of the parameters

The sensitivity analysis is used to govern the model robustness to parameter values. Thus we followed [CCH06, BD94] and we can identify which parameters have high impact on R_e. The sensitivity of each parameter also analyzed using normalized forward sensitivity index ([CHC08]). Thus $\Lambda_{\beta_1}^{R_e} = \frac{\partial R_e}{\partial \beta_1}\frac{\beta_1}{R_e} = +1$, $\Lambda_k^{R_e} = \frac{\partial R_e}{\partial k}\frac{k}{R_e}$, $\Lambda_\sigma^{R_e} = \frac{\partial R_e}{\partial \sigma}\frac{\sigma}{R_e}$, and other indices are $\Lambda_{a_1}^{R_e}$, $\Lambda_{a_2}^{R_e}$, $\Lambda_\mu^{R_e}$, $\Lambda_\epsilon^{R_e}$, $\Lambda_\gamma^{R_e}$, $\Lambda_\rho^{R_e}$, $\Lambda_d^{R_e}$, $\Lambda_{\eta_1}^{R_1}$, and $\Lambda_{\eta_2}^{R_1}$. The sign of sensitivity induces of each parameter involved in (R_e) is expressed in the table (3.2).

3.4.1 Interpretation of sensitivity indices

Table (3.2) shows the sensitivity indices of R_e to the parameters in the HIV/AIDS model (3.1). The sign +ve and -ve denote the positive and negative results of the sensitivity of R_e to the respective parameters. We used the values of the parameters in Table (3.3) to find out the positive and negative indices.

Parameters	Sensitivity indices	Parameters	Sensitivity indices
β_1	+1	a_2	+ve
a_1	+ve	σ	-ve
ϵ	+ve	γ	-ve
ρ	-ve	d	-ve
k	-ve	μ	-ve
η_1	+ve	η_2	+ve

Table 3.2: Indices of sensitivity.

The result shows that when the parameters $\beta_1, a_1, a_2, \epsilon, \eta_1$, and η_2 are increase keeping others constant they increase the values of R_e. This shows us the control reproduction number (R_e) is most sensitive to the parameters $\beta_1, a_1, a_2, \epsilon, \eta_1$, and η_2. Thus, they raise the disease burden as they have positive indices.
However, the parameters $\rho, k, \gamma, \sigma, d$, and μ reduce the values of R_e when keeping others constant. This shows us HIV treatment rate, screening rate, proportion rate to infectious stage, and death rates have an inversely proportional relationship with R_e. This implies that if incrementing those parameters reduces the control reproduction number (R_e) and, consequently, the HIV/AIDS burden would be reduced.

3.5 Extension of the model into an optimal control

In this part, we apply optimal control theory on the model (3.1) which helps to identify the best intervention strategy to eradicate the disease in the specified time. From our sensitivity analysis, we found that R_e is most sensitive to the contact rate β_1, shows the effectiveness of preventive measures in controlling disease transmission. Moreover, the screening and HIV treatment rates have negative induces implies that incrementing them can reduce the disease burden. Therefore, based on the analysis we suggested that the time based preventive, screening, and treatment controlling strategies would be an effective option. This motivates us to incorporate the following three controls defined as:

1. u_1 a preventive effort: HIV/AIDS education campaign through social media and healthy centres, that protect unaware susceptible from contacting HIV.

2. u_2 a screening effort: To help undiagnosed infected individuals to screen themselves.

3. u_3 a treatment effort: To minimize infection by treating individuals who have HIV symptoms.

It is often convenient to consider the proportion of each compartment in model (3.1), explicitly $s_a = \frac{S_A}{N}, s_u = \frac{S_U}{N}, l = \frac{L}{N}, i = \frac{I}{N}, h = \frac{T}{N}, a = \frac{A}{N}$, since the total population $N(t) = S_A(t) +$

$S_U(t) + L(t) + I(t) + T(t) + A(t)$ is not constant. The recruitment rate $\pi = \Pi N$ is not a constant, but the birth rate Π is a constant parameter.

Now, the equation $s_u = \frac{S_U}{N} \Longrightarrow S_U = s_u N$.

$\Longrightarrow \frac{dS_U}{dt} = \frac{ds_u}{dt}N + \frac{dN}{dt}s_u$.

$\Longrightarrow \pi + \phi g(M)S_A - (\lambda_1 + \theta f(M) + \mu)S_U = \frac{ds_u}{dt}N + (\pi - \mu N - dA)s_u$, where $\frac{dN}{dt} = \pi - \mu N - dA$ (3.3).

$\Longrightarrow \frac{\pi}{N} + \phi g(M)\frac{S_A}{N} - (\lambda_1 + \theta f(M) + \mu)\frac{S_U}{N} = \frac{ds_u}{dt} + (\frac{\pi}{N} - \mu - d\frac{A}{N})s_u$, divided both sides by N.

$\Longrightarrow \Pi + \phi g(M)s_a - (\lambda_1 + \theta f(M) + \mu)s_u = \frac{ds_u}{dt} + (\Pi - \mu - da)s_u$.

$\Longrightarrow \frac{ds_u}{dt} = \Pi + \phi g(M)s_a - (\lambda_1 + \theta f(M))s_u - \mu s_u - (\Pi - da)s_u + \mu s_u$.

$\Longrightarrow \frac{ds_u}{dt} = \Pi(1 - s_u) - (\lambda_1 + \theta f(M) - ad)s_u + \phi g(M)s_a$.

Let us take the second equation $s_a = \frac{S_A}{N} \Longrightarrow S_A = s_a N$.

$\Longrightarrow \frac{dS_A}{dt} = \frac{ds_a}{dt}N + \frac{dN}{dt}s_a$.

$\Longrightarrow \theta f(M)S_U - \phi g(M)S_A - \lambda_2 S_A - \mu S_A = \frac{ds_a}{dt}N + (\pi - \mu N - dA)s_a$.

$\Longrightarrow \theta f(M)\frac{S_U}{N} - \phi g(M)\frac{S_A}{N} - \lambda_2\frac{S_A}{N} - \mu\frac{S_A}{N} = \frac{ds_a}{dt} + (\frac{\pi}{N} - \mu - d\frac{A}{N})s_a$, divided both sides by N.

$\Longrightarrow \theta f(M)s_u - (\phi g(M)s_a + \lambda_2 + \mu)s_a = \frac{ds_a}{dt} + (\Pi - \mu - da)s_a$.

$\Longrightarrow \frac{ds_a}{dt} = \theta f(M)s_u - (\Pi + \lambda_2 + \phi g(M) - da)s_a$.

Again let us take the third equation

$l = \frac{L}{N} \Longrightarrow L = lN$.

$\Longrightarrow \frac{dL}{dt} = \frac{dl}{dt}N + \frac{dN}{dt}l$.

$\Longrightarrow \lambda_1 S_U + \lambda_2 S_A - k\sigma L - (k(1-\sigma) + \mu)L = \frac{dl}{dt}N + (\pi - \mu N - dA)l$.

$\Longrightarrow \lambda_1 S_U + \lambda_2 S_A - (k + \mu)L = \frac{dl}{dt}N + (\pi - \mu N - dA)l$.

$\Longrightarrow \lambda_1\frac{S_U}{N} + \lambda_2\frac{S_A}{N} - (k + \mu)\frac{L}{N} = \frac{dl}{dt} + (\frac{\pi}{N} - \mu - d\frac{A}{N})l$, divided both sides by N.

$\Longrightarrow \lambda_1 s_u + \lambda_2 s_a - (k + \mu)l = \frac{dl}{dt} + (\Pi - \mu - da)l$.

$\Longrightarrow \frac{dl}{dt} = \lambda_1 s_u + \lambda_2 s_a - (k + \mu)l - (\Pi - \mu - da)l$.

$\Longrightarrow \frac{dl}{dt} = \lambda_1 s_u + \lambda_2 s_a - (\Pi + k - da)l$.

Similarly, let us take the rest three equations, we have $i = \frac{I}{N}, h = \frac{T}{N}, a = \frac{A}{N} \Longrightarrow I = iN, T = hN, A = aN$.

Applying the same procedure we obtain the following three equations.

$\frac{di}{dt} = k\sigma l + \epsilon h - (a_1 + \gamma + \Pi - ad)i$

$\frac{dh}{dt} = \gamma i + \rho a - (a_2 + \epsilon + \Pi - ad)h$

$\frac{da}{dt} = k(1-\sigma)l + a_1 i + a_2 h - (d + \rho + \Pi - ad)a$.

Thus, incorporating u_1, u_2, u_3 with state variables s_a, s_u, l, i, h, and a , we obtain the following

controlled model of HIV/AIDS.

$$\begin{cases} \frac{ds_u}{dt} = \Pi(1-s_u) - (\lambda_1(1-u_1) + (\theta+u_1)f(M) - ad)s_u + \phi g(M)s_a, \\ \frac{ds_a}{dt} = (\theta+u_1)f(M)s_u - (\Pi + \phi g(M) + \lambda_2 - ad)s_a, \\ \frac{dl}{dt} = \lambda_1(1-u_1)s_u + \lambda_2 s_a - (k+u_2+\Pi - ad)l, \\ \frac{di}{dt} = (k\sigma+u_2)l + \epsilon h - (a_1(1-u_3) + \gamma + u_3 + \Pi - ad)i, \\ \frac{dh}{dt} = (\gamma+u_3)i + (\rho+u_3)a - (a_2+\epsilon+\Pi-ad)h, \\ \frac{da}{dt} = k(1-u_2)(1-\sigma)l + a_1(1-u_3)i + a_2 h - (d+\rho+u_3+\Pi-ad)a. \end{cases} \tag{3.29}$$

Here, we added a variable preventive effort u_1 on θ to increase the aware susceptible individuals in the community, whereas we multiplied the preventive failure $(1-u_1)$ by force of infection λ_1 move to undiagnosed infected class L. Moreover, we added the screening effort u_2 to decrease undiagnosed infected individuals and treatment control to decrease individuals in I and A classes. Thus, increasing the constant screening rate by time-based screening effort u_2 and ρ and γ by time-based treatment control u_3, the disease burden can be minimized.

To study the optimal level of the controls, the control set U is Lebesgue measurable and it is defined as : $U = \{u_1(t), u_2(t), u_3(t) : 0 \leq u_1(t) \leq 1, 0 \leq u_2(t) \leq 1, 0 \leq u_3(t) \leq 1, 0 \leq t \leq T\}$. Here $u_1 = 0$ is no response and $u_1 = 1$ is the full response of unaware susceptible become aware and the justification is the same for the remaining interventions.

Let the objective function be:

$$J(t) = \min_{u_1,u_2,u_3} \int_0^{t_f} [b_1 l(t) + b_2 i(t) + b_3 a(t) + \frac{1}{2}(w_1 u_1^2(t) + w_2 u_2^2(t) + w_3 u_3^2(t))]dt. \tag{3.30}$$

where b_i's are coefficients of state variables and coefficients w_i are the measure of the relative costs of the interventions associated to the controls u_i [SM14]. Our aim is to obtain a control u_i, where $i = 1, 2, 3$ that minimize the number of individuals with unaware susceptible, undiagnosed HIV infected, diagnosed HIV infectious with and without AIDS symptoms alongside with the associated costs. By its nature, costs are not linear, so we choose the cost expression, $\frac{1}{2}w_i u_i^2$ where $i = 1, 2, 3$ is quadratic [GS09, JLLW06].

Existence and characterization of optimal control solution

Theorem 12 *(Existence of optimal solution). There exists an optimal control $u_1^*(t)$, $u_2^*(t)$, $u_3^*(t)$ and corresponding solutions (s_u^*, s_a^*, l^*, i^*, h^*, a^*) to the state initial value problem (3.29) and (3.30) that minimizes $J(u_1, u_2, u_3)$ over U.*

Proof.

The following conditions are verified thanks to Fleming and Rishel's theorem.

1. The set of all solutions to system (3.29) and the corresponding control functions in U is non-empty.

2. The state system can be written as a linear function of the control variables with coefficients dependent on time and the state variables.

3. The integrand L in (3.30) of the objective functional given by $L(x,u,t) = b_1 l + b_2 i + b_3 a + \frac{1}{2}(w_1 u_1^2 + w_2 u_2^2 + w_3 u_3^2)$ is convex on U and it also satisfies $L(x,u,t) \geq \delta_1 \mid (u_1,u_2,u_3) \mid^{\beta} -\delta_2$, where $\delta_1 > 0$ and $\beta > 1$.

To establish condition 1, we refer to [CL55, GCF+08]. In fact, if the state equations are continuous and its solutions are bounded and Lipschitz in the state variables, then there is a unique solution corresponding to every admissible control U.
Again, the total population also bounded below by a positive non-zero number N_0 and above by $\frac{\pi}{\mu}$ and also each of the state variables which is a subset of the total population are bounded. It follows that the state system is continuous and bounded. It is equivalently to show the boundedness of the partial derivatives with respect to the state variables in the state system [Cod12].
This completes the proof that 1 holds.
Condition 2 is verified by observing the linear dependence of the state equations on controls u_1, u_2, u_3.
Lastly, to verify condition 3, by definition from [BP12, Ped06], any constant, linear and quadratic functions are convex. Thus, $L(x,u,t)$ is convex on U.
Now, to prove boundness on the function L, we have the following.
$w_3 u_3^2 \leq w_3$, since $u_3 \in [0,1]$.
$\Rightarrow \frac{1}{2} w_3 u_3^2 \leq \frac{w_3}{2} \Rightarrow \frac{1}{2} w_3 u_3^2 - \frac{w_3}{2} \leq 0.$
Then $L(x,u,t) = b_1 l + b_2 i + b_3 a + \frac{1}{2}[w_1 u_1^2 + w_2 u_2^2 + w_3 u_3^2] \geq \frac{1}{2} w_1 u_1^2 + \frac{1}{2} w_2 u_2^2 + \frac{1}{2} w_3 u_3^2 - \frac{w_3}{2}$,
$\Rightarrow L(x,u,t) \geq \min(\frac{w_1}{2}, \frac{w_2}{2}, \frac{w_3}{2})(u_1^2 + u_2^2 + u_3^2) - \frac{w_3}{2},$
$\Rightarrow L(x,u,t) \geq \min(\frac{w_1}{2}, \frac{w_2}{2}, \frac{w_3}{2}) \mid\mid (u_1,u_2,u_3) \mid\mid^2 - \frac{w_3}{2}.$
Therefore, the function $L(x,u,t) \geq \delta_1 \mid (u_1,u_2,u_3) \mid^{\beta} -\delta_2$, where $\delta_1 = \min(\frac{w_1}{2}, \frac{w_2}{2}, \frac{w_3}{2})$, $\delta_2 = \frac{w_3}{2}$ and $\beta = 2$.
By using Pontryagin's maximum principle (PMP) [PM86], we got the necessary conditions which is satisfied by optimal pair. Thus, by this principle we obtained a Hamiltonian (H) defined as:
$H(s_u, s_a, l, i, h, a, u, t) = L(x,u,t) + \lambda_1 \frac{ds_u}{dt} + \lambda_2 \frac{ds_a}{dt} + \lambda_3 \frac{dl}{dt} + \lambda_4 \frac{di}{dt} + \lambda_5 \frac{dh}{dt} + \lambda_6 \frac{da}{dt},$
where $\lambda_i, i = 1,2,3,4,5,6$ are the adjoint variables to be determined by [PM86] and [FR82] for existence of optimal control pairs.

Theorem 13 *For an optimal control set u_1, u_2, u_3 that minimizes J over U, there is an adjoint*

variable $\lambda_i, i = 1, 2, 3, 4, 5, 6$ *such that,*

$$\begin{cases} \frac{d\lambda_1}{dt} = \lambda_1[\Pi + \beta_1(l + \eta_1 i + \eta_2 a)(1 - u_1) + (\theta + u_1)f(M) - ad] - \lambda_2(\theta + u_1)f(M) - \\ \qquad \lambda_3\beta_1(1 - u_1)(l + \eta_1 i + \eta_2 a), \\ \frac{d\lambda_2}{dt} = -\lambda_1\phi g(M) + \lambda_2[\beta_2(l + \eta_1 i + \eta_2 a) + \Pi + \phi g(M) - ad] - \lambda_3\beta_2(l + \eta_1 i + \eta_2 a), \\ \frac{d\lambda_3}{dt} = -b_1 + \lambda_1\beta_1(1 - u_1)s_u + \lambda_2\beta_2 s_a - \lambda_3[\beta_1(1 - u_1)s_u + \beta_2 s_a - k - u_2 - \Pi + ad] - \\ \qquad \lambda_4(k\sigma + u_2) - \lambda_6 k(1 - u_2)(1 - \sigma), \\ \frac{d\lambda_4}{dt} = -b_2 + [(\beta_1\eta_1(1 - u_1) + \frac{p(\theta+u_1)}{(1+q(i+a))^2})s_u + \frac{p\phi s_a}{(1+q(i+a))^2}]\lambda_1 - \lambda_2[\frac{p(\theta+u_1)}{(1+q(i+a))^2}s_u + (\frac{p\phi}{(1+q(i+a))^2} - \beta_2\eta_1)s_a] \\ \qquad -\lambda_3[(1 - u_1)\beta_1\eta_1 s_u + \beta_2\eta_1 s_a] + \lambda_4[a_1(1 - u_3) + \gamma + u_3 + \Pi - ad] - (\gamma + u_3)\lambda_5 - \lambda_6 a_1(1 - u_3), \\ \frac{d\lambda_5}{dt} = -\epsilon\lambda_4 + \lambda_5[a_2 + \epsilon + \Pi - ad] - \lambda_6 a_2, \\ \frac{d\lambda_6}{dt} = -b_3 + \beta_1\eta_2(1 - u_1)s_u(\lambda_1 - \lambda_3) + \beta_2\eta_2 s_a(\lambda_2 - \lambda_3) + (\lambda_1 - \lambda_2)\frac{(ps_u(\theta+u_1)+p\phi s_a)}{(1+q(i+a))^2} \\ \qquad -d(\lambda_1 s_u + \lambda_2 s_a + \lambda_3 l + \lambda_4 i + \lambda_5 h - \lambda_6 + 2a\lambda_6) + (\rho + u_3)(\lambda_6 - \lambda_5) + \Pi\lambda_6, \end{cases} \tag{3.31}$$

with the transversality conditions $\lambda_i(t_f) = 0, i = 1, 2, 3, ..., 6$. *Furthermore, we obtain the control set* $(u_1^*(t), u_2^*(t), u_3^*(t))$ *characterized by:*

$u_1^*(t) = max\{0, min(1, u_1^*)\}, \quad u_2^*(t) = max\{0, min(1, u_2^*)\}, \quad u_3^*(t) = max\{0, min(1, u_3^*)\},$

where $u_1^* = [\frac{f(M)s_u^*(\lambda_1-\lambda_2)+\beta_1(l+\eta_1 i+\eta_2 a)(\lambda_3-\lambda_1)}{w_1}]$, $u_2^* = \frac{l^*[\lambda_3-\lambda_4+\lambda_6 k(1-\sigma)]}{w_2}$, *and* $u_3^* = \frac{[\lambda_4 i^*(1-a_1)-\lambda_5(a^*+i^*)+\lambda_6(a_1 i^*+a^*)]}{w_3}$.

Proof:

The Hamiltonian H associated to the controlled model is given by:
$H = L(x, u, t) + \lambda_1\frac{ds_u}{dt} + \lambda_2\frac{ds_a}{dt} + \lambda_3\frac{dl}{dt} + \lambda_4\frac{di}{dt} + \lambda_5\frac{dh}{dt} + \lambda_6\frac{da}{dt}$. This can be expressed as:

$H = b_1 l(t) + b_2 i(t) + b_3 a(t) + \frac{1}{2}(w_1 u_1^2(t) + w_2 u_2^2(t) + w_3 u_3^2(t)) + \lambda_1[\Pi(1 - s_u) - (\lambda_1(1 - u_1) + (\theta + u_1)f(M) - ad)s_u + \phi g(M)s_a] + \lambda_2[(\theta + u_1)f(M)s_u - (\Pi + \phi g(M) + \lambda_2 - ad)s_a] + \lambda_3[\lambda_1(1 - u_1)s_u + \lambda_2 s_a - (k + u_2 + \Pi - ad)l] + \lambda_4[(k\sigma + u_2)l + \epsilon h - (a_1(1 - u_3) + \gamma + u_3 + \Pi - ad)i] + \lambda_5[(\gamma + u_3)i + (\rho + u_3)a - (a_2 + \epsilon + \Pi - ad)h] + \lambda_6[k(1 - u_2)(1 - \sigma)l + a_1(1 - u_3)i + a_2 h - (d + \rho + u_3 + \Pi - ad)a].$

From the second condition of the PMP, there exist adjoint variables $\lambda_i, i = 1, 2, ..., 6$ which satisfy the following canonical equations.

$$\frac{d\lambda_1}{dt} = -\frac{dH}{ds_u}, \qquad \frac{d\lambda_2}{dt} = -\frac{dH}{ds_a}, \qquad \frac{d\lambda_3}{dt} = -\frac{dH}{dl},$$
$$\frac{d\lambda_4}{dt} = -\frac{dH}{di}, \qquad \frac{d\lambda_5}{dt} = -\frac{dH}{dh}, \qquad \frac{d\lambda_6}{dt} = -\frac{dH}{da}.$$

So, we have

$$\begin{cases} \frac{d\lambda_1}{dt} = \lambda_1[\Pi + \beta_1(l+\eta_1 i+\eta_2 a)(1-u_1) + (\theta+u_1)f(M) - ad] - \lambda_2(\theta+u_1)f(M) - \\ \qquad \lambda_3\beta_1(1-u_1)(l+\eta_1 i+\eta_2 a), \\ \frac{d\lambda_2}{dt} = -\lambda_1\phi g(M) + \lambda_2[\beta_2(l+\eta_1 i+\eta_2 a) + \Pi + \phi g(M) - ad] - \lambda_3\beta_2(l+\eta_1 i+\eta_2 a), \\ \frac{d\lambda_3}{dt} = -b_1 + \lambda_1\beta_1(1-u_1)s_u + \lambda_2\beta_2 s_a - \lambda_3[\beta_1(1-u_1)s_u + \beta_2 s_a - k - u_2 - \Pi + ad] - \\ \qquad \lambda_4(k\sigma+u_2) - \lambda_6 k(1-u_2)(1-\sigma), \\ \frac{d\lambda_4}{dt} = -b_2 + [(\beta_1\eta_1(1-u_1) + \frac{p(\theta+u_1)}{(1+q(i+a))^2})s_u + \frac{p\phi s_a}{(1+q(i+a))^2}]\lambda_1 - \lambda_2[\frac{p(\theta+u_1)}{(1+q(i+a))^2}s_u + (\frac{p\phi}{(1+q(i+a))^2} - \beta_2\eta_1)s_a] \\ \qquad -\lambda_3[(1-u_1)\beta_1\eta_1 s_u + \beta_2\eta_1 s_a] + \lambda_4[a_1(1-u_3) + \gamma + u_3 + \Pi - ad] - (\gamma+u_3)\lambda_5 - \lambda_6 a_1(1-u_3), \\ \frac{d\lambda_5}{dt} = -\epsilon\lambda_4 + \lambda_5[a_2 + \epsilon + \Pi - ad] - \lambda_6 a_2, \\ \frac{d\lambda_6}{dt} = -b_3 + \beta_1\eta_2(1-u_1)s_u(\lambda_1-\lambda_3) + \beta_2\eta_2 s_a(\lambda_2-\lambda_3) + (\lambda_1-\lambda_2)\frac{(ps_u(\theta+u_1)+p\phi s_a)}{(1+q(i+a))^2} \\ \qquad -d(\lambda_1 s_u + \lambda_2 s_a + \lambda_3 l + \lambda_4 i + \lambda_5 h - \lambda_6 + 2a\lambda_6) + (\rho+u_3)(\lambda_6-\lambda_5) + \Pi\lambda_6, \end{cases} \tag{3.32}$$

with the transversality conditions $\lambda_i(t_f) = 0, i = 1, 2, 3, ..., 6$.
Now, from optimality conditions, $\frac{dH}{du_1}\mid_{u_1=u_1^*} = 0$, $\frac{dH}{du_2}\mid_{u_2=u_2^*} = 0$ $\frac{dH}{du_3}\mid_{u_3=u_3^*} = 0$.

So, $u_1^* = \big[\frac{f(M)s_u^*(\lambda_1-\lambda_2)+\beta_1(l+\eta_1 i+\eta_2 a)(\lambda_3-\lambda_1)}{2w_1}\big]^{\frac{1}{3}}$, $u_2^* = \frac{l^*[\lambda_3-\lambda_4+\lambda_6 k(1-\sigma)]}{w_2}$, and $u_3^* = \frac{[\lambda_4 i^*(1-a_1)-\lambda_5(a^*+i^*)+\lambda_6(a_1 i^*+a^*)]}{w_3}$.
Now, we can write these findings along with the characteristics of control set U, we have

$$u_1^* = \begin{cases} 0, & \text{if } \big[\frac{f(M)s_u^*(\lambda_1-\lambda_2)+\beta_1(l+\eta_1 i+\eta_2 a)(\lambda_3-\lambda_1)}{w_1}\big] \le 0 \\ \big[\frac{f(M)s_u^*(\lambda_1-\lambda_2)+\beta_1(l+\eta_1 i+\eta_2 a)(\lambda_3-\lambda_1)}{w_1}\big], & \text{if } 0 < \big[\frac{f(M)s_u^*(\lambda_1-\lambda_2)+\beta_1(l+\eta_1 i+\eta_2 a)(\lambda_3-\lambda_1)}{w_1}\big] < 1 \\ 1, & \text{if } \big[\frac{f(M)s_u^*(\lambda_1-\lambda_2)+\beta_1(l+\eta_1 i+\eta_2 a)(\lambda_3-\lambda_1)}{w_1}\big] \ge 1 \end{cases},$$

$$u_2^* = \begin{cases} 0, & \text{if } \frac{l^*[\lambda_3-\lambda_4+\lambda_6 k(1-\sigma)]}{w_2} \le 0 \\ \frac{l^*[\lambda_3-\lambda_4+\lambda_6 k(1-\sigma)]}{w_2}, & \text{if } 0 < \frac{l^*[\lambda_3-\lambda_4+\lambda_6 k(1-\sigma)]}{w_2} < 1 \\ 1, & \text{if } \frac{l^*[\lambda_3-\lambda_4+\lambda_6 k(1-\sigma)]}{w_2} \ge 1 \end{cases},$$

$$u_3^* = \begin{cases} 0, & \text{if } \frac{[\lambda_4 i^*(1-a_1)-\lambda_5(a^*+i^*)+\lambda_6(a_1 i^*+a^*)]}{w_3} \le 0 \\ \frac{[\lambda_4 i^*(1-a_1)-\lambda_5(a^*+i^*)+\lambda_6(a_1 i^*+a^*)]}{w_3}, & \text{if } 0 < \frac{[\lambda_4 i^*(1-a_1)-\lambda_5(a^*+i^*)+\lambda_6(a_1 i^*+a^*)]}{w_3} < 1 \\ 1, & \text{if } \frac{[\lambda_4 i^*(1-a_1)-\lambda_5(a^*+i^*)+\lambda_6(a_1 i^*+a^*)]}{w_3} \ge 1 \end{cases}.$$

The above expressions of u_1^*, u_2^*, u_3^* are equivalent to:
$u_1^*(t) = \max\{0, \min(1, u_1^*)\}, \quad u_2^*(t) = \max\{0, \min(1, u_2^*)\}, \quad u_3^*(t) = \max\{0, \min(1, u_3^*)\}.$

3.6 Numerical results and discussion

We have discussed so far for equilibrium points and their stability conditions of a given HIV/AIDS transmission dynamical system and also find the optimal control variables which basically minimize the total cost that has been considered. Here, to validate our analytical findings, we shall make the numerical simulations. We can also find the result of cost function for each strategy.
So, we can solve the control system (3.29) along with (3.30) numerically using the parameter values provided in table (3.3) and the initial size of populations by fixed final time t_f = 10 years. Thus S_{U0}=366 000, S_{A0} =634 000, L(0)=144 900, I(0)=363 400, T(0)=448 500, A(0)=181 700 are approximated data of the year 2019 in Ethiopia [aaa20, fff21, DAA$^+$10]. To represent in proportionality from the total population N=2 138 500, they are S_{U0}=0.17, $S_{A0} = 0.297$, L(0)=0.068, I(0)=0.16993, T(0)=0.21, A(0)=0.08.
Here, we should be underlined that the number of HIV/AIDS infected people are very high in Ethiopia as compared to the total of diagnosed HIV infectious and AIDS symptom's, but they are co-infected with other infectious disease not necessary to this model.
To estimate the constant parameters in model (3.1), we formulate the model as

$$z^{'} = f(t, z, \theta), z(t_0) = z_0. \tag{3.33}$$

Here, z is the state variable and θ is the parameter value to be determined. To measure our fit to the real data, we define a least squares objective function

$$S(\theta) = \sum_{i=1} (z(i) - \bar{z}(i))^2, \tag{3.34}$$

where $z(i)$ the solution of (3.33) and $\bar{z}(i)$ is the real data. We get the optimum parameter values by minimizing the objective function

$$\begin{cases} \min\limits_{\theta} S(\theta) \\ \qquad \text{Subject to } \; z^{'} = f(t, z, \theta), z(t_0) = z_0. \end{cases} \tag{3.35}$$

The algorithm is presented below:

Step 1. Guess initial parameter values a_0. Set $a = a_0$.

Step 2. Using MATLAB version 2013a ode45 routine, solve Eq. (3.33) using a to find the solution $z(i)$.

Step 3. Evaluate error using Eq. (3.34).

Step 4. Use a to minimize Eq.(3.35) using an optimization algorithm nlinfit to find the parameters $\hat{a}$ with 95% confidence interval. Update $a = \hat{a}$.

Step 5. Check for the convergence. If the convergence is not satisfied go to Step 2.

Step 6. On convergence, set $a = \hat{a}$.

Using the above algorithm the estimated parameter values are given in Table (3.3).

Here N is the total population and $N(0)$ is the initial population. We can take the values of some

Parameters	Values	References	Parameters	Values	References
η_1	0.8	[KO11]	k	0.1	estimated
η_2	1.05	[KO11]	σ	0.88	estimated
β_1	0.18	estimated	γ	0.25	[ddd21]
β_2	0.00014	estimated	a_1	0.07	[SS19]
π	0.06	estimated	a_2	0.01	[SS19]
p	0.01	[BdL12]	ϵ	0.35	estimated
q	1	[BdL12]	ρ	0.25	estimated
μ	0.07	[zzz22]	ϕ	0.3	estimated
θ	2.5	estimated	d	0.016	[ddd21]

Table 3.3: Symbols and values of parameters.

parameters from [ST17] and the reference cited therein. We have taken some of the following data from [GS09, KO15] and we have assumed some of them just for numerical purpose as below. Unfortunately, we don't have good data on coefficients of costs associated with the control variables and infected persons.

Coefficient for cost of infected individuals	$b_1 = 1.2$	$b_2 = 1.64$	$b_3 = 1.8$
Coefficient for cost of production and administering the control efforts	$w_1 = 10$	$w_2 = 10$	$w_3 = 20$

We can assume that the weight factor w_3 associated with control u_3 is higher than w_1 and w_2 because of the following reasons:

1. The cost associated with u_1 will include the cost of education on different media and healthy centres.

2. The cost associated with u_2 will include the cost of screening infected individuals.

3. The cost associated with u_3 will include the cost of drugs, medical tests and hospitalization.

We used MATLAB software to show the graphical scenarios of state system with or without optimal control and adjoint system for various cases. The optimal control profiles for each strategy and state system are plotted together as shown in all graphs. It can be noted that the preventive effort can work with in a specified period of time to alert unaware susceptible individuals; the screening effort can work within a specified period of time to decrease undiagnosed infectious individuals; and the treatment effort can work within a specified period of time to decrease diagnosed infectious individuals with and without AIDS symptoms. Here, we have used three intervention strategies to analysis our optimal control model, but Sangeeta Saha and G.P. Samanta have proposed a mathematical model for the transmission of HIV/AIDS including treatment and Pre-exposure prophylaxis (PrEP) [SS19]. They showed that both interventions are effective to control the disease and reduce economic burden also. Thus, we used the three intervention approaches with combination of two or three controls at a time to eliminate or minimize the burden of the disease in our country Ethiopia, as only single intervention is not effective [KO11, SS19, TMM17]. Thus applying those coupling two or three control strategies in the state system at a time we interpreted the graphical solutions of sub-class of populations in the next section. Such ideas and analysis are also confirmed by current findings of other infectious diseases like Hepatitis C virus and pneumonia [TMM17, ASD$^+$20].

3.6.1 Control with prevention and treatment

We used optimal control of prevention coupled with treatment as an alternative intervention strategy (i.e.,$u_1 \neq 0, u_3 \neq 0$, and $u_2 = 0$). The graphs (A-D) of figure (3.2) illustrate the graphical impact of this strategy on HIV/AIDS dynamics. Thus, this combination strategy helps to bring down undiagnosed HIV infections and overthrow unaware susceptible. It also helps to decrease diagnosed HIV infectious with and without AIDS symptoms dramatically in the specified period of time in comparison with no control. Figure (3.6)(A) shows the corresponding control profile of the current strategy. It shows that, the joint application of u_1 and u_3 is useful and can be used to minimize the disease from the community. Both controls are dropped to the lower bound at the final time. The cost function corresponding to the current strategy is as shown in the figure (3.6) (B). Here, the overall total cost or cost burden reduced dramatically due to smaller number of unaware susceptible and HIV/AIDS infected individuals which lead to increase productivity.

3.6.2 Control with prevention and screening

We used optimal control of prevention coupled with screening as an alternative intervention strategy (i.e.,$u_1 \neq 0, u_2 \neq 0$, and $u_3 = 0$). The graphs (A-D) of figure (3.3) clarify the graphical

impact of this strategy on HIV/AIDS dynamics. This coupled strategy helps to bring down undiagnosed HIV infections and overthrow unaware susceptible. It also helps to decrease diagnosed HIV infectious with and with-out AIDS symptoms dramatically. However, there are more individuals in AIDS class as compared from the first strategy (due to lack of treatment). The corresponding control profile has been given in Fig (3.7) (A). It shows that the joint application of u_1 and u_2 is useful and can be used to minimize the disease from the community. The control u_1 grows up to 0.0146 and then slows down to 0 at the final time, whereas the control u_2 decreases dramatically up to 7 years and then sit on the lower bound 0 up to 3 years. The cost function corresponding to the current strategy is as shown in the figure (3.7) (B). Here, the cost burden rises to 0.0146 for the first consecutive months. However, the implementation of this control strategy results to smaller number of unaware susceptible and HIV/AIDS infected individuals which lead to increase productive people. Owing to this, the economic burden decreases dramatically for the remaining years.

3.6.3 Control with screening and treatment

In this alternative approach, we set the preventive control equals to zero i.e.,$u_1 = 0$ and consider the screening coupled with the treatment control to demonstrate the dynamics of the HIV/AIDS infection. Fig. (3.4)(A-D) shows the effect of this mechanism graphically, whereas the sub-plot (3.8)(A) shows that the corresponding control profile of this case. In comparison with the first strategy, screening effort helps to slow down new infectious, and then unaware susceptible decreases (i.e., individuals are not vulnerable to the disease). The treatment effort also decreases diagnosed infectious people dramatically as shown in the figure. The cost function corresponding to the current strategy is as shown in the figure (3.8) (B). Here both control policies are used, the number of unaware susceptible and HIV/AIDS infected individuals will be minimized lead to increase productive labors. Owing to this, the cost burden decreases dramatically.

3.6.4 Control with prevention, screening, and treatment

In the preceding three cases, we discussed the effect of different sets of controls and provided the dynamics of each subclasses of population graphically. Here, in this case, we consider all the three interventions at a time, that is, $u_1 \neq 0, u_2 \neq 0$ and $u_3 \neq 0$. Fig (3.5)(A-D) shows the graphical solutions of this strategy, whereas the corresponding control outline is as shown in the sub-plot (3.9)(A). As we observed from the analysis, the unaware susceptible and undiagnosed infectious throw down for the entire period of time. The diagnosed infectious individuals with and without AIDS symptoms are also decreased dramatically. The control function u_1 rises to 0.0140 for the first 3 years and then decreases slowly to lower bound 0 at the final time. The control u_2 dropped

to 0 gradually up to 7.2 years, but it sit on the lower bound 0 for the remaining years. The third control u_3 is maximum at the beginning compare from others. This strategy is dropped radically to the lower bound 0 at the final time. The cost function corresponding to the current strategy is as shown in the figure (3.9) (B). Here all control policies are used, the number of unaware susceptible and HIV/AIDS infected individuals will be minimized lead to increase productive labors. Owing to this, the cost burden decreases dramatically.

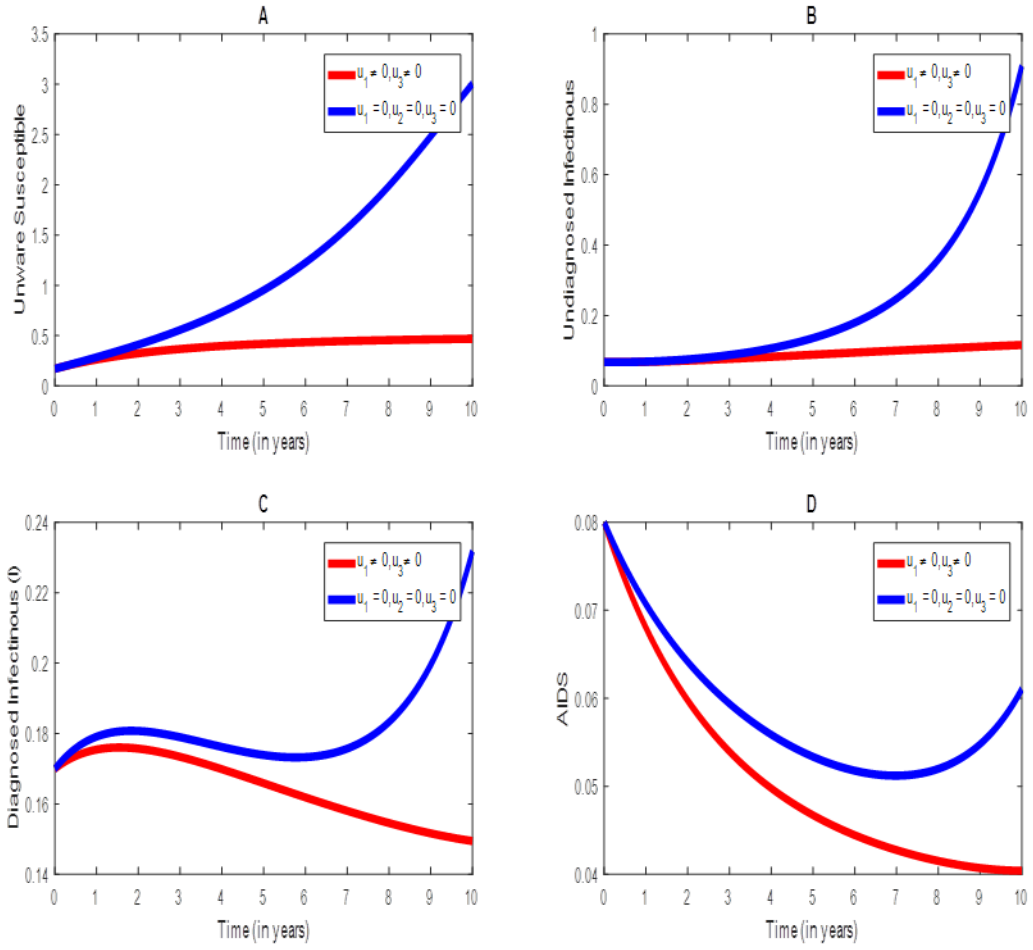

Figure 3.2: Simulations of optimal control with prevention and treatment interventions.

3.7 Cost-effectiveness analysis

Here, we discussed the rank of more than one intervention strategies at a time in-terms of their cost. We can achieve this by (Baba and Makinde, 2014); they had stated that

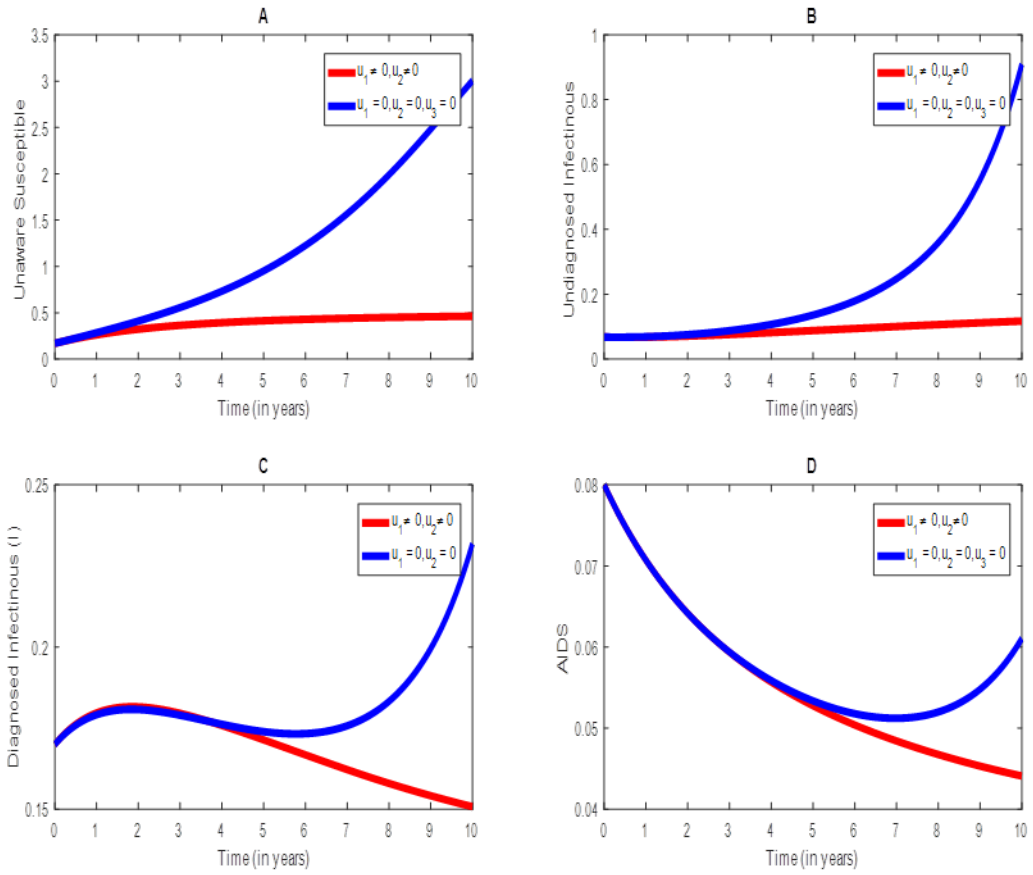

Figure 3.3: Simulations of optimal control with prevention and screening interventions.

Incremental Cost-Effectiveness Ratio (ICER)= $\frac{\text{Difference in costs between strategies}}{\text{Difference in health effects between strategies}}$.

To implement the intervention strategies mentioned above, we get the total number of infectious averted and total cost in (3.4), where the total number of infectious averted is the difference between the total infectious persons without and with control.

Strategies	Description	Total infectious averted	Total cost (USD)
A	Prevention and screening	1 904 762	1 080 584.05
B	Screening and treatment	1 908 611	1 105 818.35
C	Prevention and treatment	1 917 593	1 109 667.65
D	Prevention, screening and treatment	1 920 801	1 109 239.95

Table 3.4: Number of infectious averted and total cost of each strategy.

We compare the cost effectiveness of strategy A and B by computing the $ICER$:

$$ICER(A) = \frac{1\,080\,584.05}{1\,904\,762} = 0.5673 \quad \text{and} \quad ICER(B) = \frac{1\,105\,818.35\text{-}1\,080\,584.05}{1\,908\,611\text{-}1\,904\,762} =$$

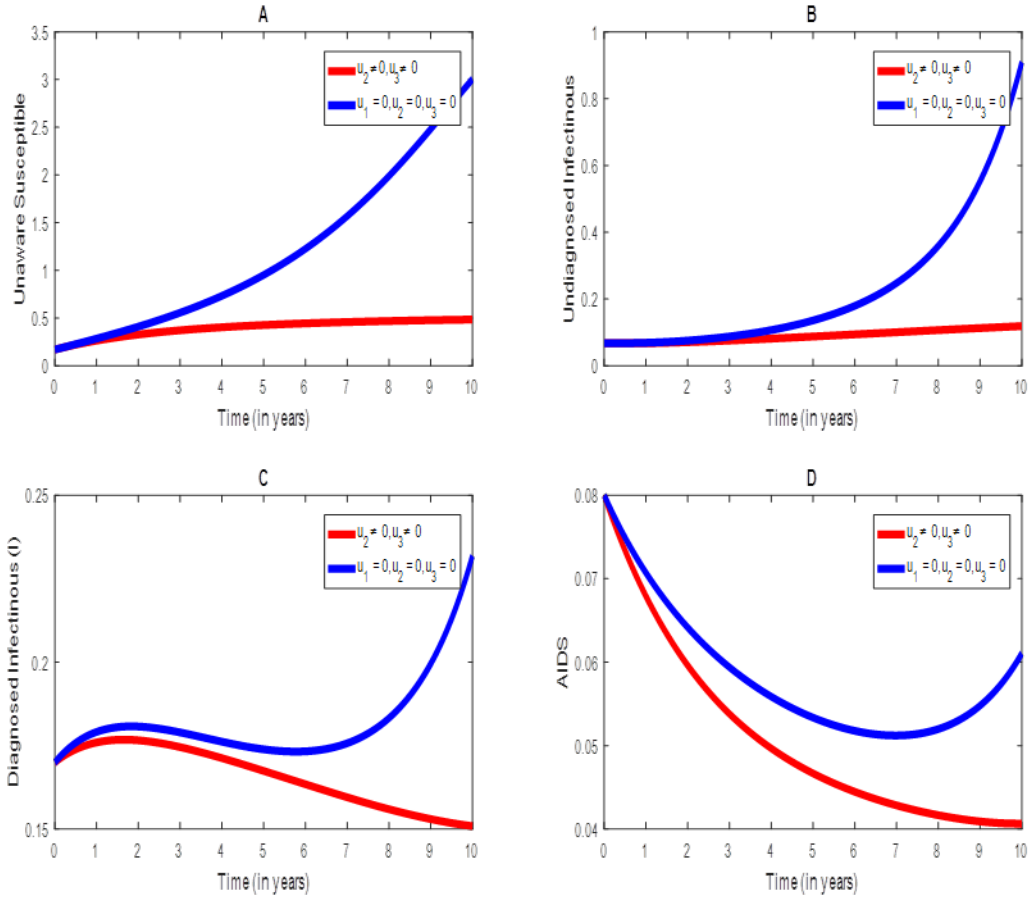

Figure 3.4: Simulations of optimal control with screening and treatment interventions.

6.556.

The comparison showed that $ICER(A) < ICER(B)$, which implies that strategy B was more costly and less effective than strategy A. Thus, we should exclude strategy B from alternative approaches, since it is strongly dominated and does not consume limited resource.

Next, we compare the cost effectiveness of strategy A and C.

We already calculated $ICER(A) = 0.5673$ and $ICER(C) = \frac{1\ 109\ 667.65\text{-}1\ 080\ 584.05}{1\ 917\ 593\text{-}1\ 904\ 762} = 2.2667$.

The comparison showed that $ICER(A) < ICER(C)$, which implies that strategy C was more costly and less effective than strategy A. Thus, we should exclude strategy C from alternative approaches.

Finally, we compared the cost effectiveness of strategy A and D.

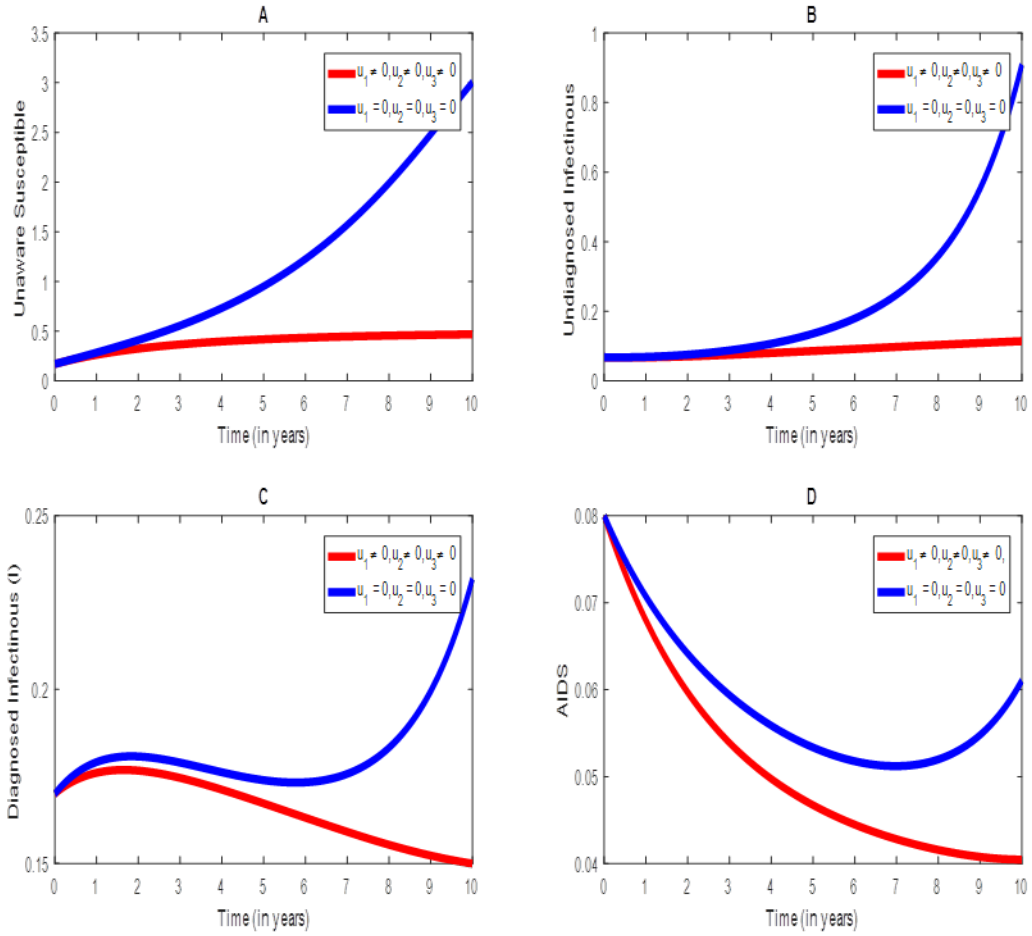

Figure 3.5: Simulations of optimal control with prevention, screening & treatment interventions.

Then

$ICER(D) = \frac{1\,109\,239.95\text{-}1\,080\,584.05}{1\,920\,801\text{-}1\,904\,762} = 1.7866$ and we already calculated $ICER(A) = 0.5673$.

Here, the strategy A was less costly and more effective than strategy D.

Therefore, the strategy A is the cheapest as compared with other alternatives.

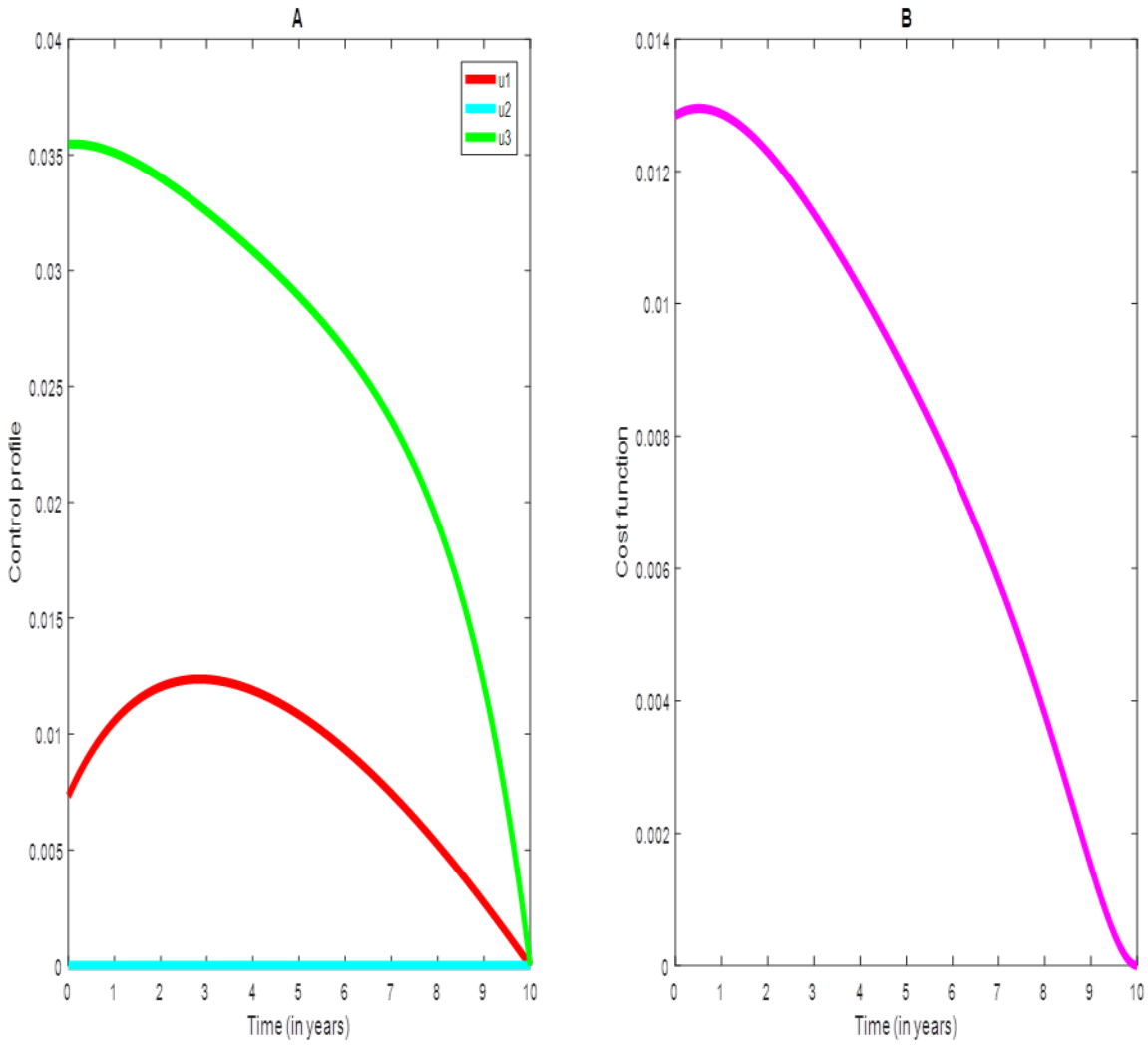

Figure 3.6: Control profiles and cost function for strategy (3.6.1).

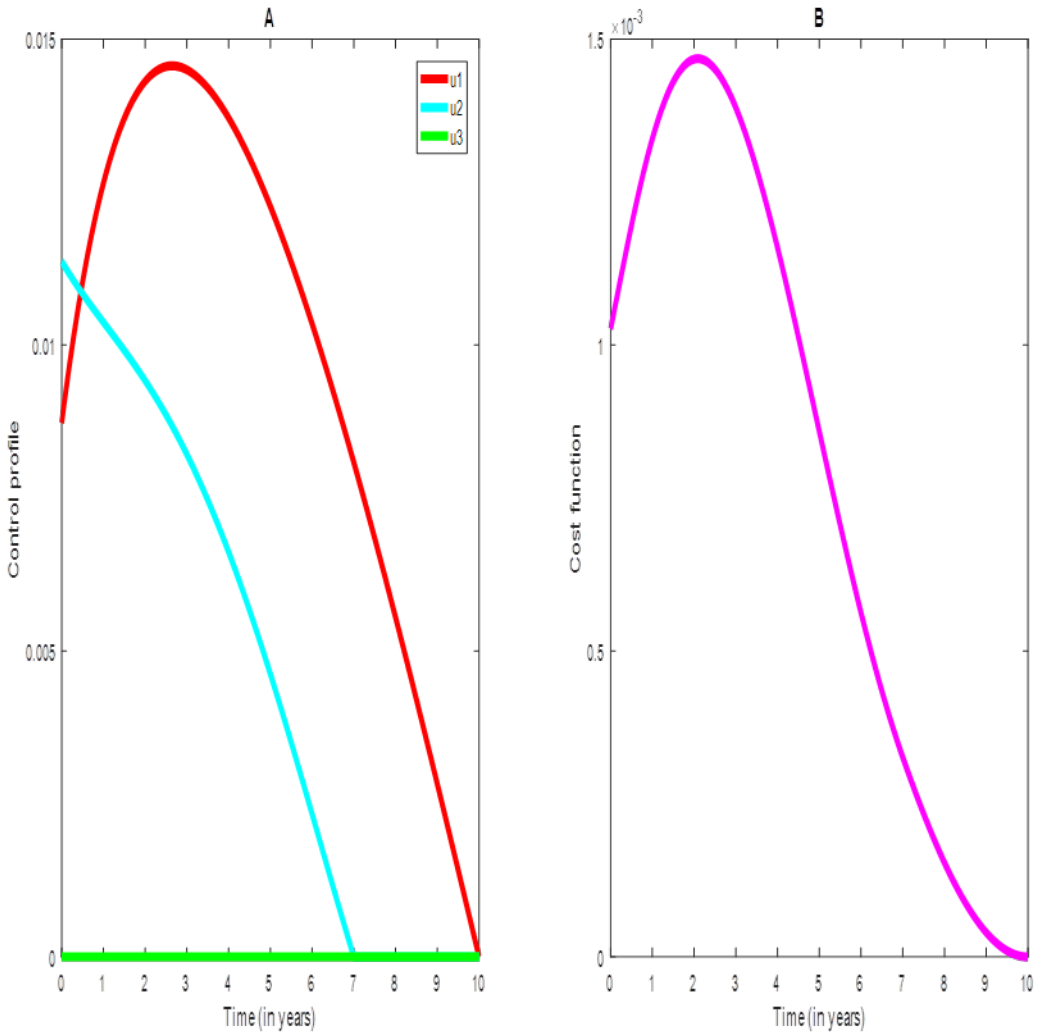

Figure 3.7: Control profiles and cost function for strategy (3.6.2).

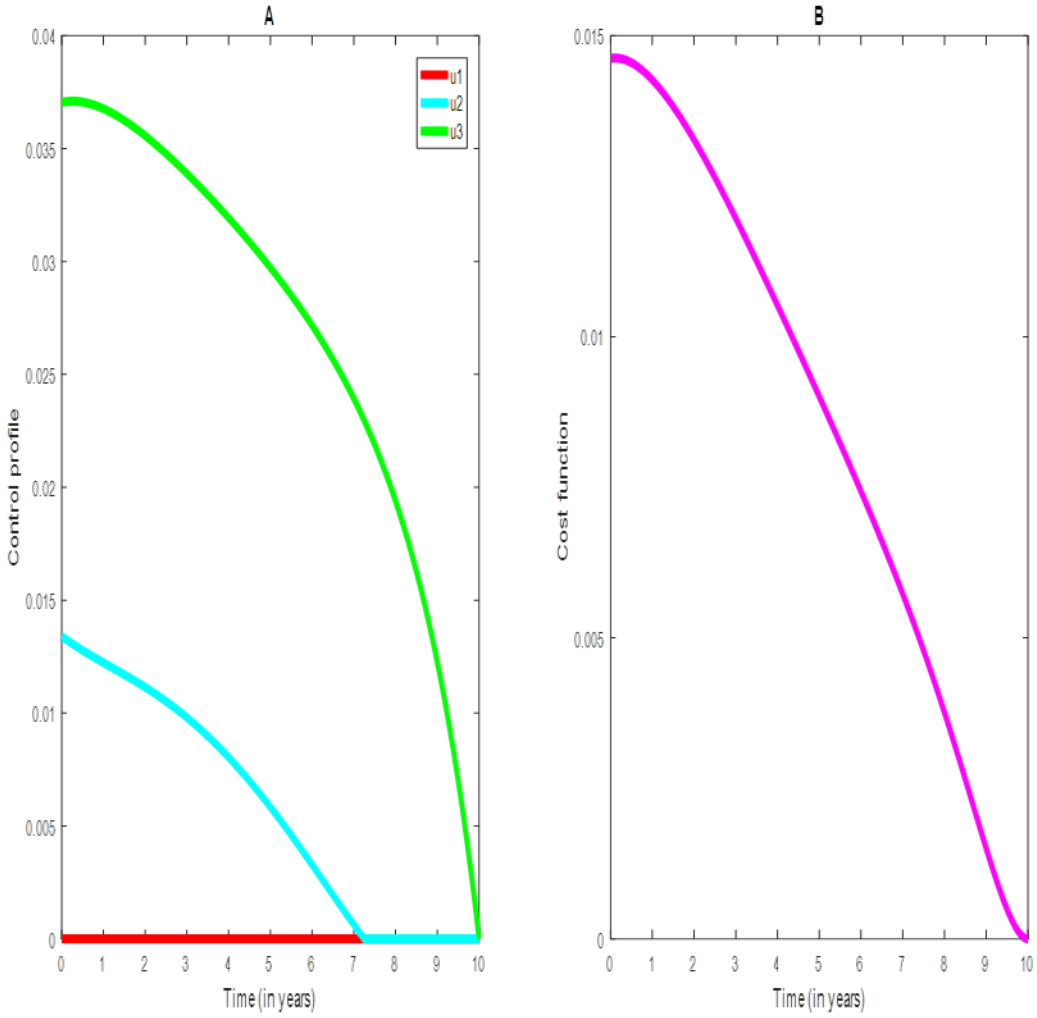

Figure 3.8: Control profiles and cost function for strategy (3.6.3).

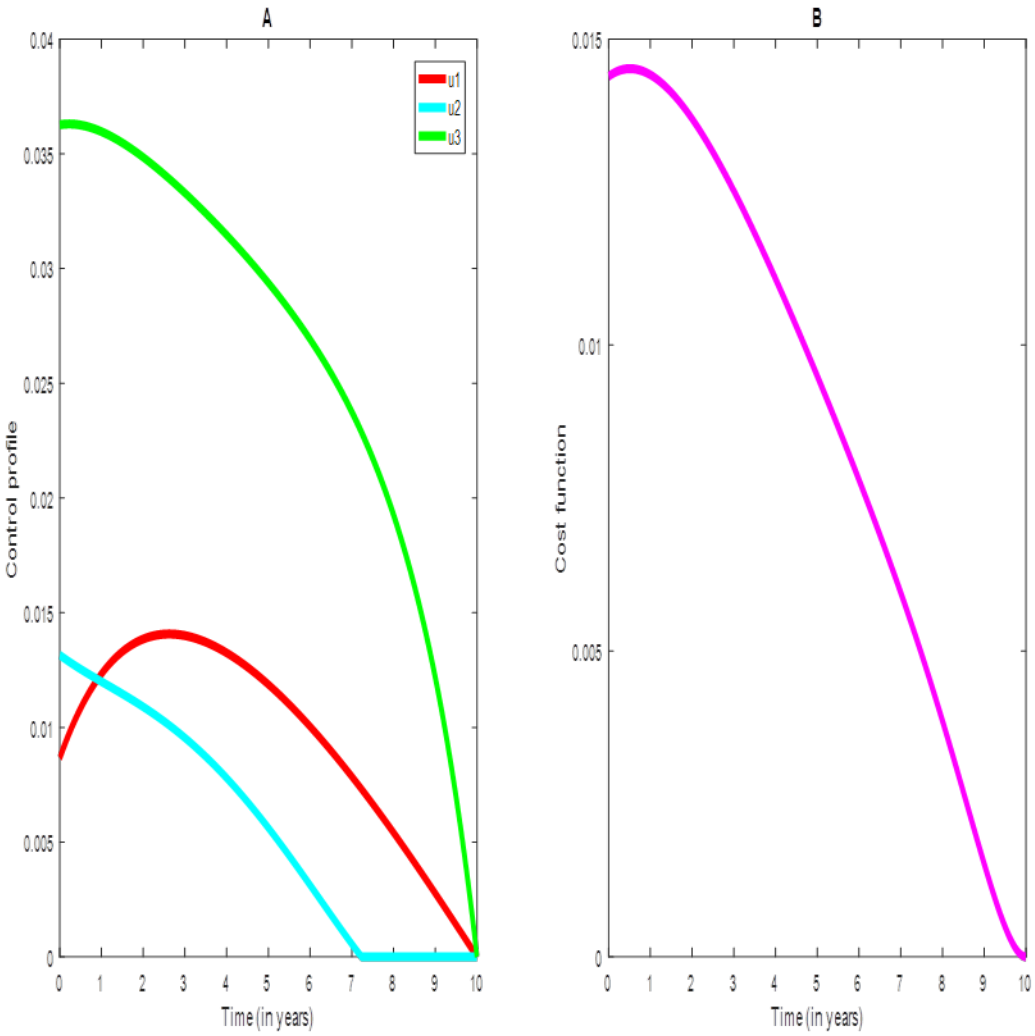

Figure 3.9: Control profiles and cost function for strategy (3.6.4).

Chapter 4

Modelling of tuberculosis disease

4.1 Introduction

Tuberculosis (TB) is one of the top deadly diseases in the world. It affects many parts of the world, but the disease burden is high in Sub-Saharan Africa [fff21]. Ethiopia is one of the regions which is severely hit by the disease [fff21]. So this epidemic in our country needs critical intervention approaches within a specific period of time through minimal cost possible. TB progression is a slow dynamic and so it needs a long duration of investigation [BT10, FKG+14]. Here, we developed and analyzed a TB mathematical model with optimal control in Ethiopia, which can guide some of the targeted interventions.

Mathematical model can play a vital role on TB disease predict and control. Several assumptions and parameters are key components to develop a model; whereas a model can be redeveloped using controlling functions. The controlling functions that have a great impact on disease elimination can be investigated through the concept of optimal control theory.

4.2 Mathematical model of tuberculosis

Model formulation

We incorporated the following assumptions to develop a TB model.

- The recruitment rate is a variable by birth only and no permanent immunity to TB.
- Individual with latent TB are not infectious and cannot transmit TB infection.
- Individuals infected with TB cannot fully recover.
- On recovery there is temporal immunity.

- Only new births individuals not vaccinated against the infection enter in to susceptible class.
- There is no highly risky latently infected individual recruited from infectious due to lack of treatment.
- At birth all individuals are equally susceptible i.e., there is no vertical transmission (all new births are susceptible).
- Only nuclei droplet of air can spread TB infection between infectious and susceptible people.
- Active TB infected individuals who do not adhere to treatment move to drug resistance TB and individuals who have resistance TB are died due to treatment failure.
- The low risk latent compartment comprises recovered individuals by treatment or naturally.
- A low risk latent individuals obtain immunity and there is no inherited immunity.
- Socio-demographic information do not affect the chance of individual been infected.

We developed the new TB model from [WCJ11] by considering the following two cohorts of the population.

1. There are people infected by drug resistance TB, where TB organisms resistant to the first line antibiotics (Anti-TB drugs) used in its treatment are widespread and occur in many countries including Ethiopia. These individuals can be grouped as (DR-TB).
2. There are also latently infected individuals infected by drug resistance TB patients.

Therefore, the total population $N(t)$ at time t, is subdivided into seven subgroups such as Susceptible (S) who are health individuals not yet exposed TB disease; Exposed (high-risk latent individuals) (E_1) infected by drug sensitive TB; Exposed (high-risk latent individuals) (E_2) infected by drug resistant TB; Low-risk latent individuals (L_1) infected by active TB(drug sensitive TB); Low-risk latent individuals(L_2) infected by drug resistant TB; Actively Infected peoples (I) who have active TB and are infectious; Drug resistant TB individuals (I_D) who are resistance to the first line of treatment. Here, high risk and low risk latently infected people are not infectious and they have not disease symptoms.
Recovered people (naturally or by treatment) are moved from infectious classes to low-risk latent classes, because treatment cannot fully remove tubercle bacilli. Besides, the populations from class E_1 and E_2 who do not progress to infectious classes are moved to classes L_1 and L_2 respectively. Thus, $N(t) = S(t) + E_1(t) + E_2(t) + L_1(t) + L_2(t) + I(t) + I_D(t)$.
The recruitment populations are entering to the susceptible class at a rate bN, where b is birth rate

and N is total population. Individuals under susceptible subgroup make sufficient contact with individuals who have active TB and drug resistant TB by a variable rate (force of infection) $\frac{\beta_1 I}{N}$ and $\frac{\beta_2 I_D}{N}$ respectively. The parameters $\beta_i\{i = 1, 2\}$ are the number of new infections by active TB and drug resistance TB per unit time respectively.
The following Table [4.1] shows that different rates with their descriptions.

Parameters	Description
π	Recruitment rate
μ	Natural death rate
θ	The per capita progress rate from the high risk latent class E_1 to infectious class I
ϕ	The per capita progress rate from the class E_2 to infectious class I_D
ϵ	Resistance rate to treatment
δ	Per capita progress rate of individuals from class E_1 to class L_1 who do not progress to class I
σ	Per capita progress rate of individuals from class E_2 to class L_2 who do not progress to class I_D
ρ	Successful treatment rate of I
γ	Successful treatment rate of I_D after resist to first line treatment
a_1	The relapse rate due to tubercle bacilli reactivation of L_1
a_2	The relapse rate due to tubercle bacilli reactivation of L_2
d_1 and d_2	Disease related death rate of I and I_D respectively.

Table 4.1: Parameters description.

The transition diagram of the model is shown below.

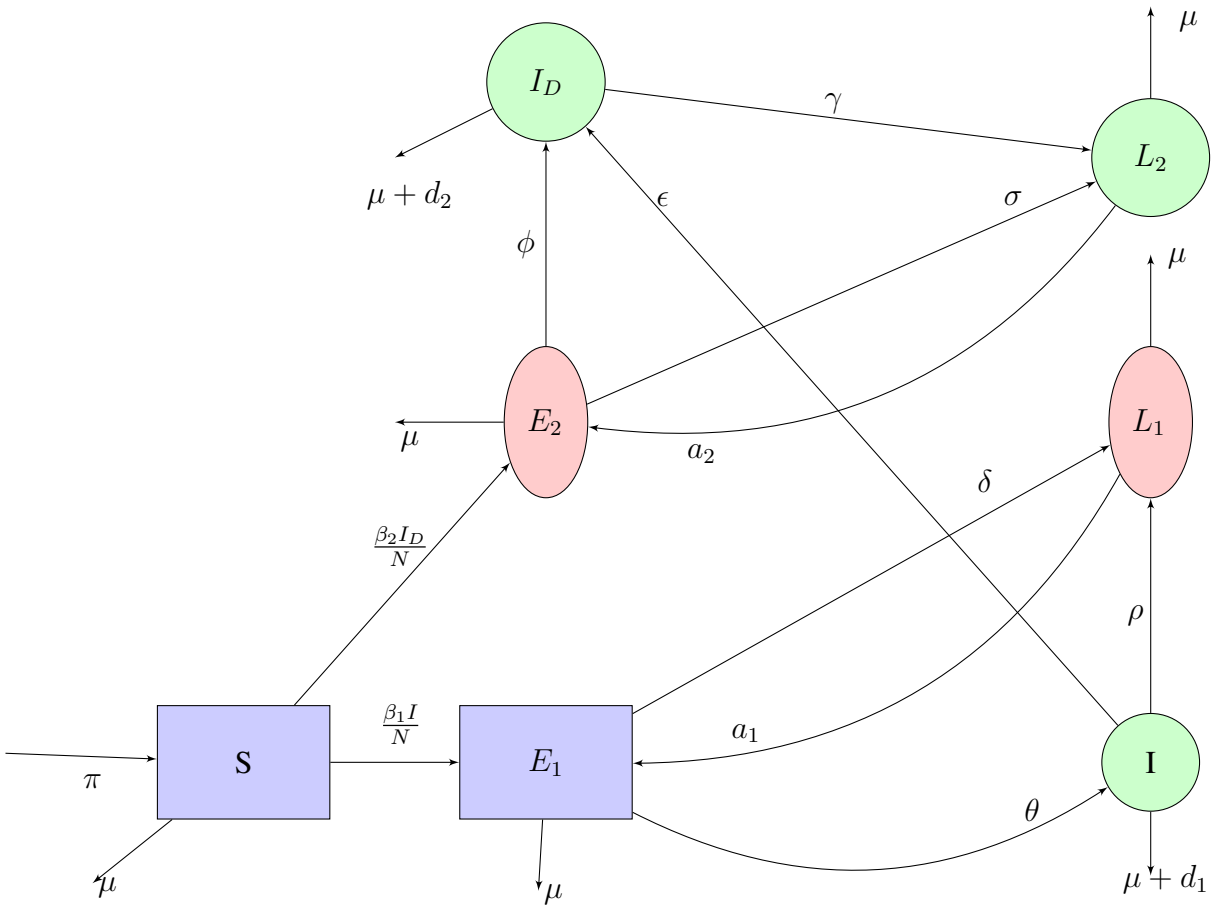

Figure 4.1: TB transmission flow diagram .

The TB transmission flow diagram can be modelled by the following system of non-linear ordinary differential equation (ODE).

$$\begin{cases} \frac{dS(t)}{dt} = \pi - (\frac{\beta_1}{N(t)} I + \frac{\beta_2}{N(t)} I_D + \mu) S, \\ \frac{dE_1(t)}{dt} = \frac{\beta_1 S}{N(t)} I + a_1 L_1 - (\theta + \delta + \mu) E_1, \\ \frac{dE_2(t)}{dt} = \frac{\beta_2 S}{N(t)} I_D + a_2 L_2 - (\phi + \sigma + \mu) E_2, \\ \frac{dI(t)}{dt} = \theta E_1 - (\epsilon + \rho + \mu + d_1) I, \\ \frac{dI_D(t)}{dt} = \phi E_2 + \epsilon I - (\gamma + \mu + d_2) I_D, \\ \frac{dL_1(t)}{dt} = \rho I + \delta E_1 - (a_1 + \mu) L_1, \\ \frac{dL_2(t)}{dt} = \gamma I_D + \sigma E_2 - (a_2 + \mu) L_2, \end{cases} \tag{4.1}$$

with inital conditions

$$S(0) > 0, E_1(0) > 0, E_2(0) > 0, I(0) > 0, I_D(0) > 0, L_1(0) > 0, \text{and } L_2(0) > 0. \tag{4.2}$$

4.3 Model analysis

4.3.1 Positivity of the solutions

Here, we discussed the condition in which the tuberculosis (TB) model (4.1) has non-negative solutions.

Theorem 14 *let* $\Omega = \{(S, E_1, E_2, I, I_D, L_1, L_2) \in \mathbb{R}^7_+ : S(0) > 0, E_1(0) \geq 0, E_2(0) \geq 0, I(0) \geq 0, I_D(0) \geq 0, L_1(0) \geq 0, L_2(0) \geq 0\}$ *then the solutions* $(S(t), E_1(t), E_2(t), I(t), I_D(t), L_1(t), L_2(t))$ *of (4.1) are non-negative for* $\forall t \geq 0$.

Proof:

Consider the system (4.1) and let us take the first equation

$$\begin{aligned}
&\frac{dS(t)}{dt} = \pi - (\frac{\beta_1}{N(t)}I + \frac{\beta_2}{N(t)}I_D + \mu)S.\\
\implies &\frac{dS(t)}{dt} \geq -(\beta_1 I + \beta_2 I_D + \mu)S.\\
\implies &\frac{dS}{S} \geq -(\beta_1 I + \beta_2 I_D + \mu)dt.\\
\implies &S(t) \geq S(0)exp^{-\mu t - \int(\beta_1 I(t) + \beta_2 I_D(t))dt} > 0 \text{ (since } S(0) > 0).
\end{aligned}$$

Let us take the second equation

$$\begin{aligned}
&\frac{dE_1(t)}{dt} = \frac{\beta_1 S}{N(t)}I + a_1 L_1 - (\theta + \delta + \mu)E_1.\\
\implies &\frac{dE_1(t)}{dt} \geq -(\theta + \delta + \mu)E_1.\\
\implies &\frac{dE_1}{E_1} \geq -(\theta + \delta + \mu)dt.\\
\implies &E_1(t) \geq E_1(0)exp^{-(\theta+\delta+\mu)t} \geq 0.
\end{aligned}$$

Again let us take the third equation

$$\begin{aligned}
&\frac{dE_2(t)}{dt} \geq -(\phi + \sigma + \mu)E_2.\\
\implies &E_2(t) \geq E_2(0)e^{-(\phi+\sigma+\mu)t} \geq 0, \forall t \geq 0.
\end{aligned}$$

The positivity solution of the rest four equations can be shown in the following way.

First $I(t) > 0, \forall t \in [0, \vartheta)$, where $0 < \vartheta \leq +\infty$. If it does not hold, then $\exists\ t_1 \in [0, \vartheta)$ such that $I(t_1) = 0, \frac{dI}{dt}(t_1) \leq 0$ and $I(t) > 0, \forall t \in [0, t_1)$. So there must have $I_D(t) > 0, \forall t \in [0, t_1)$. If it is not true, $\exists\ t_2 \in (0, t_1)$ such that $I_D(t_2) = 0, \frac{dI_D}{dt}(t_2) \leq 0$ and $I_D(t) > 0, \forall t \in (0, t_2)$. Again there must have $L_1(t) > 0, \forall t \in [0, t_2)$. If it is not true, $\exists\ t_3 \in (0, t_2)$ such that $L_1(t_3) = 0, \frac{dL_1}{dt}(t_3) \leq 0$ and $L_1(t) > 0, \forall t \in (0, t_3)$.

Our claim is $L_2(t) > 0, \forall t \in [0, t_3)$. If it is not true, then $\exists\ t_4 \in (0, t_3)$ such that $L_2(t_4) = 0, \frac{dL_2}{dt}(t_4) \leq 0$ and $L_2(t) > 0, \forall t \in (0, t_4)$.

From seventh equation of (4.1):

$\frac{dL_2}{dt}(t_4) = \gamma I_D(t_4) + \sigma E_2(t_4) - (a_2+\mu)L_2(t_4) = \gamma I_D(t_4) + \sigma E_2(t_4) > 0$, which is a contradiction to $\frac{dL_2}{dt}(t_4) \leq 0$. Thus, $L_2(t) > 0, \forall t \in [0, t_3)$.
So, sixth equation of (4.1):
$\frac{dL_1}{dt}(t_3) = \rho I(t_3) + \delta E_1(t_3) - (a_1+\mu)L_1(t_3) = \rho I(t_3) + \delta E_1(t_3) > 0$, which is a contradiction to $\frac{dL_1}{dt}(t_3) \leq 0$. Thus, $L_1(t) > 0, \forall t \in [0, t_2)$.
Again fifth equation of (4.1):
$\frac{dI_D}{dt}(t_2) = \phi E_2(t_2) + \epsilon I(t_2) - (\gamma+\mu+d_2)I_D(t_2) = \phi E_2(t_2) + \epsilon I(t_2) > 0$, which is a contradiction to $\frac{dI_D}{dt}(t_2) \leq 0$. Thus, $I_D(t) > 0, \forall t \in [0, t_1)$.
Similarly we have, $L_2(t) > 0, \forall t \in [0, t_2)$.
Now, we claim $I(t) > 0, \forall t \in [0, \vartheta)$. If it is not true, then $\exists\, t_1 \in (0, \vartheta)$ such that $I(t_1) = 0$, $\frac{dI}{dt}(t_1) \leq 0$ and $I(t) > 0, \forall t \in [0, t_1)$.
From fourth equation of (4.1):
$\frac{dI}{dt}(t_1) = \theta E_1(t_1) - (\epsilon+\rho+\mu+d_1)I(t_1) = \theta E_1(t_1) > 0$, which is a contradiction to $\frac{dI}{dt}(t_1) \leq 0$.
Thus, $I(t) > 0, \forall t \in [0, \vartheta)$.
Similarly we have, $I_D > 0, L_1(t) > 0, \forall t \in [0, \vartheta)$.
This also leads to $L_2 > 0, \forall t \in [0, \vartheta)$.
This completes the proof.

4.3.2 Invariant region

In this part, we showed the solutions of all state systems are uniformly bounded in the region, as given by the following theorem.

Theorem 15 *The model system (4.1) is biological significance on the region given by* $\Omega \in \mathbb{R}^7_+$ *such that* $\Omega = \{(S, E_1, E_2, I, I_D, L_1, L_2) \in \mathbb{R}^7_+ : N \leq \frac{\pi}{\mu}\}$.

Proof:
The rate of change of total population $\frac{dN}{dt}$ can be obtained by adding all the equations in (4.1). Hence

$$\frac{dN}{dt} = \pi - \mu N(t) - d_1 I - d_2 I_D. \tag{4.3}$$

The equation (4.3) obtained by adding (4.1) simultaneously. Hence, equation (4.3) satisfies the following relation.

$\frac{dN}{dt} \leq \pi - \mu N(t)$,
$N(t) \leq \frac{\pi}{\mu} + e^{-\mu t}(N(0) - \frac{\pi}{\mu})$.

Here, if $0 < N(0) \leq \frac{\pi}{\mu}$, then we derived $0 < N(t) \leq \frac{\pi}{\mu}$, $\forall\, t \geq 0$. This shows that Ω is positively invariant.

4.3.3 Disease Free Equilibrium (DFE), E_0

The DFE of the model (4.1) is found by setting $\frac{dS}{dt} = \frac{dE_1}{dt} = \frac{dE_2}{dt} = \frac{dI}{dt} = \frac{dI_D}{dt} = \frac{dL_1}{dt} = \frac{dL_2}{dt} = 0$.
If no disease in the community, then $E_1 = E_2 = I = I_D = L_1 = L_2 = 0$. Thus, the susceptible population is equal to total population. Then, the system (4.1) reduced to $\pi - (\mu)S^* = 0$, which gives $S^* = \frac{\pi}{\mu}$.
Therefore, the DFE (E_0) is given by $(S^*, 0, 0, 0, 0, 0, 0) = (\frac{\pi}{\mu}, 0, 0, 0, 0, 0, 0)$.

4.3.4 Control reproduction number (R_e)

In this portion, we derived the threshold value R_e that measures the average secondary infectious individuals generated by a single infected individual in a community when some interventions are in place. To calculate the number R_e, first differentiate new infected people from all other class. The infected classes are $E_1, E_2, I, I_D, L_1, L_2$. So, the system can be written as $X = F - V$ and $V = V^- - V^+$, where $X = \{S, E_1, E_2, I, I_D, L_1, L_2\}$, F is the new infection terms, V^- is the term which represent the transfer of the infectious individuals out of each class, and V^+ is the term which represent the transfer of the infectious individuals into each class by all other means.
Here, the matrix f associated with F and the matrix v associated with V can be written as:

$$f = \left[\frac{\partial f_i(E_0)}{\partial x_j} \right] \text{ and } v = \left[\frac{\partial v_i(E_0)}{\partial x_j} \right],$$

where f_i is the rate of appearance of new infection terms in state i and v_i is the rate of infection transfer terms from one state i to the other. The range of i and j are running from 1,2,3...,6 corresponding to $E_1, E_2, I, I_D, L_1, L_2$.
Now,

$$f_i = \begin{bmatrix} f_1 \\ f_2 \\ f_3 \\ f_4 \\ f_5 \\ f_6 \end{bmatrix} = \begin{bmatrix} \frac{\beta_1 SI}{N} \\ \frac{\beta_2 SI_D}{N} \\ 0 \\ 0 \\ 0 \\ 0 \end{bmatrix} \text{ and } v_i = \begin{bmatrix} v_1 \\ v_2 \\ v_3 \\ v_4 \\ v_5 \\ v_6 \end{bmatrix} = \begin{bmatrix} (\theta + \delta + \mu)E_1 - a_1 L_1 \\ (\phi + \sigma + \mu)E_2 - a_2 L_2 \\ (\epsilon + \rho + \mu + d_1)I - \theta E_1 \\ (\gamma + \mu + d_2)I_D - (\phi E_2 + \epsilon I) \\ (a_1 + \mu)L_1 - (\rho I + \varphi\delta E_1) \\ (a_2 + \mu)L_2 - (\gamma I_D + \omega\sigma E_2) \end{bmatrix}.$$

Thus, $f = \begin{bmatrix} 0 & 0 & \beta_1 & 0 & 0 & 0 \\ 0 & 0 & 0 & \beta_2 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \end{bmatrix}$ and

$$v = = \begin{bmatrix} \theta+\delta+\mu & 0 & 0 & 0 & -a_1 & 0 \\ 0 & \phi+\sigma+\mu & 0 & 0 & 0 & -a_2 \\ -\theta & 0 & \epsilon+\rho+\mu+d_1 & 0 & 0 & 0 \\ 0 & -\phi & -\epsilon & \gamma+\mu+d_2 & 0 & 0 \\ -\varphi\delta & 0 & -\rho & 0 & a_1+\mu & 0 \\ 0 & -\omega\sigma & 0 & -\gamma & 0 & a_2+\mu \end{bmatrix}.$$

The threshold value R_e is computed by simply the spectral radius of the next generation matrix [VdDW02]. In other words, it is found by taking the dominant eigenvalue (spectral radius) of fv^{-1}.

Here, the matrix $f = \begin{bmatrix} 0 & 0 & \beta_1 & 0 & 0 & 0 \\ 0 & 0 & 0 & \beta_2 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \end{bmatrix}$ is already calculated and the matrix v^{-1} is obtained after long derivation.

Hence,

$$v^{-1} = \begin{bmatrix} \frac{EC}{M} & 0 & \frac{a_1\rho}{M} & 0 & \frac{a_1C}{M} & 0 \\ \frac{Ea_2\gamma\epsilon\theta}{MN} & \frac{DF}{N} & \frac{a_2\gamma\epsilon[ECA-a_1C\delta]}{CMN} & \frac{a_2\gamma}{N} & \frac{a_2\gamma\epsilon a_1\theta}{MN} & \frac{a_2D}{N} \\ \frac{\theta E}{M} & 0 & \frac{ECA-a_1C\delta}{CM} & 0 & \frac{a_1\theta}{M} & 0 \\ \frac{E\theta\epsilon(BDF-a_2\sigma D)}{DMN} & \frac{\phi F}{N} & \epsilon\frac{[ECA-a_1C\delta][BDF-a_2\sigma D]}{CDMN} & \frac{BDF-a_2\sigma D}{DN} & \frac{a_1\epsilon\theta(BDF-a_2\sigma D)}{DMN} & \frac{a_2\phi}{N} \\ \frac{\theta\rho+C\varphi\delta}{M} & 0 & \frac{\rho A}{M} & 0 & \frac{AC}{M} & 0 \\ \frac{E\gamma\epsilon\theta B}{MN} & \frac{\phi\gamma+\sigma D}{N} & \frac{B\gamma\epsilon[ECA-a_1C\delta]}{CMN} & \frac{B\gamma}{N} & \frac{a_1\gamma\epsilon\theta B}{MN} & \frac{BD}{N} \end{bmatrix},$$

where

$$\begin{cases} A = \theta+\delta+\mu, B = \phi+\sigma+\mu, C = \epsilon+\rho+\mu+d_1, D = \gamma+\mu+d_2, \\ E = a_1+\mu, F = a_2+\mu, M = ECA - a_1(\theta\rho+C\delta), N = BDF - a_2(\phi\gamma+\sigma D). \end{cases} \tag{4.4}$$

These representations are useful for the entire chapter.
The product of f and v^{-1} gives $fv^{-1} =$

$$\begin{bmatrix} \beta_1\frac{\theta E}{M} & 0 & \frac{\beta_1(ECA-a_1C\delta)}{CM} & 0 & \frac{\beta_1 a_1\theta}{M} & 0 \\ \beta_2\frac{E\theta\epsilon(BDF-a_2\sigma D)}{DMN} & \beta_2\frac{\phi F}{N} & \beta_2\epsilon\frac{[ECA-a_1C\delta][BDF-a_2\sigma D]}{CDMN} & \beta_2\frac{BDF-a_2\sigma D}{DN} & \beta_2\epsilon\frac{a_1\theta(BDF-a_2\sigma D)}{DMN} & \beta_2\frac{a_2\phi}{N} \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \end{bmatrix}.$$

The threshold value R_e is defined as:
$R_e = max\{R_1, R_2\}$, where $R_1 = \beta_1\frac{\theta E}{M} = \beta_1\frac{\theta(a_1+\mu)}{(a_1+\mu)(\epsilon+\rho+\mu+d_1)(\theta+\delta+\mu)-a_1(\theta\rho+(\epsilon+\rho+\mu+d_1)\delta)}$
and
$R_2 = \beta_2\frac{\phi F}{N} = \beta_2\frac{\phi(a_2+\mu)}{(\phi+\sigma+\mu)(\gamma+\mu+d_2)(a_2+\mu)-a_2(\phi\gamma+\sigma(\gamma+\mu+d_2))}$.
Here R_1 and R_2 are the control reproductive numbers for DS-TB and DR-TB respectively.

4.3.5 Local stability of DFE

Theorem 16 *The DFE point is locally asymptotically stable if $R_e < 1$ and unstable if $R_e > 1$.*

Proof:

First the Jacobian matrix of (4.1) at the DFE E_0 is:

$J(\frac{\pi}{\mu}, 0, 0, 0, 0, 0, 0) =$

$$\begin{bmatrix} -\mu & 0 & 0 & -\beta_1 & -\beta_2 & 0 & 0 \\ 0 & -(\theta+\delta+b) & 0 & \beta_1 & 0 & a_1 & 0 \\ 0 & 0 & -(\phi+\sigma+\mu) & 0 & \beta_2 & 0 & a_2 \\ 0 & \theta & 0 & -(\epsilon+\rho+\mu+d_1) & 0 & 0 & 0 \\ 0 & 0 & \phi & \epsilon & -(\gamma+\mu+d_2) & 0 & 0 \\ 0 & \delta & 0 & \rho & 0 & -(a_1+\mu) & 0 \\ 0 & 0 & \sigma & 0 & \gamma & 0 & -(a_2+\mu) \end{bmatrix}.$$

$$= \begin{bmatrix} -\mu & 0 & 0 & -\beta_1 & -\beta_2 & 0 & 0 \\ 0 & -A & 0 & \beta_1 & 0 & a_1 & 0 \\ 0 & 0 & -B & 0 & \beta_2 & 0 & a_2 \\ 0 & \theta & 0 & -C & 0 & 0 & 0 \\ 0 & 0 & \phi & \epsilon & -D & 0 & 0 \\ 0 & \delta & 0 & \rho & 0 & -E & 0 \\ 0 & 0 & \sigma & 0 & \gamma & 0 & -F \end{bmatrix}.$$

Now, finding the eigenvalues of this matrix, which becomes

$$= \begin{vmatrix} -\mu-\lambda & 0 & 0 & -\beta_1 & -\beta_2 & 0 & 0 \\ 0 & -A-\lambda & 0 & \beta_1 & 0 & a_1 & 0 \\ 0 & 0 & -B-\lambda & 0 & \beta_2 & 0 & a_2 \\ 0 & \theta & 0 & -C-\lambda & 0 & 0 & 0 \\ 0 & 0 & \phi & \epsilon & -D-\lambda & 0 & 0 \\ 0 & \delta & 0 & \rho & 0 & -E-\lambda & 0 \\ 0 & 0 & \sigma & 0 & \gamma & 0 & -F-\lambda \end{vmatrix} = 0 .$$

$$\Rightarrow -\mu-\lambda \begin{vmatrix} -A-\lambda & 0 & \beta_1 & 0 & a_1 & 0 \\ 0 & -B-\lambda & 0 & \beta_2 & 0 & a_2 \\ \theta & 0 & -C-\lambda & 0 & 0 & 0 \\ 0 & \phi & \epsilon & -D-\lambda & 0 & 0 \\ \delta & 0 & \rho & 0 & -E-\lambda & 0 \\ 0 & \sigma & 0 & \gamma & 0 & -F-\lambda \end{vmatrix} = 0 .$$

$$\Rightarrow (-\mu-\lambda)(-a_2) \begin{vmatrix} -A-\lambda & 0 & \beta_1 & 0 & a_1 \\ \theta & 0 & -C-\lambda & 0 & 0 \\ 0 & \phi & \epsilon & -D-\lambda & 0 \\ \delta & 0 & \rho & 0 & -E-\lambda \\ 0 & \sigma & 0 & \gamma & 0 \end{vmatrix} +$$

$$(-\mu-\lambda)(F+\lambda) \begin{vmatrix} -A-\lambda & 0 & \beta_1 & 0 & a_1 \\ 0 & -B-\lambda & 0 & \beta_2 & 0 \\ \theta & 0 & -C-\lambda & 0 & 0 \\ 0 & \phi & \epsilon & -D-\lambda & 0 \\ \delta & 0 & \rho & 0 & -E-\lambda \end{vmatrix} = 0 .$$

$$\Rightarrow (\mu+\lambda)a_2a_1 \begin{vmatrix} \theta & 0 & -C-\lambda & 0 \\ 0 & \phi & \epsilon & -D-\lambda \\ \delta & 0 & \rho & 0 \\ 0 & \sigma & 0 & \gamma \end{vmatrix} +$$

$$(\mu+\lambda)(a_2)(E+\lambda)\begin{vmatrix} -A-\lambda & 0 & \beta_1 & 0 \\ \theta & 0 & -C-\lambda & 0 \\ 0 & \phi & \epsilon & -D-\lambda \\ 0 & \sigma & 0 & \gamma \end{vmatrix} +$$

$$(-\mu-\lambda)(F+\lambda)a_1\begin{vmatrix} 0 & -B-\lambda & 0 & \beta_2 \\ \theta & 0 & -C-\lambda & 0 \\ 0 & \phi & \epsilon & -D-\lambda \\ \delta & 0 & \rho & 0 \end{vmatrix} +$$

$$(\mu+\lambda)(F+\lambda)(E+\lambda)\begin{vmatrix} -A-\lambda & 0 & \beta_1 & 0 \\ 0 & -B-\lambda & 0 & \beta_2 \\ \theta & 0 & -C-\lambda & 0 \\ 0 & \phi & \epsilon & -D-\lambda \end{vmatrix} = 0 .$$

Finally, the above expression gives:
$(\mu+\lambda)[\lambda^3+(E+A+C)\lambda^2+(EC+EA+AC-a_1\delta-\theta\beta_1)\lambda+M-\theta\beta_1E][\lambda^3+(B+D+F)\lambda^2+(BD+BF+DF-a_2\sigma-\phi\beta_2)\lambda+N-\Phi\beta_2F]=0.$
This implies, $(\mu+\lambda)=0$ or $[\lambda^3+(E+A+C)\lambda^2+(EC+EA+AC-a_1\delta-\theta\beta_1)\lambda+M-\theta\beta_1E]=0$ or $[\lambda^3+(B+D+F)\lambda^2+(BD+BF+DF-a_2\sigma-\phi\beta_2)\lambda+N-\Phi\beta_2F]=0.$
Now, $(\mu+\lambda)=0\Rightarrow\lambda=-\mu<0$. Again,

$$[\lambda^3+(E+A+C)\lambda^2+(EC+EA+AC-a_1\delta-\theta\beta_1)\lambda+M-\theta\beta_1E]=0. \tag{4.5}$$

$$[\lambda^3+(B+D+F)\lambda^2+(BD+BF+DF-a_2\sigma-\phi\beta_2)\lambda+N-\Phi\beta_2F]=0. \tag{4.6}$$

These two equation can be written as:

$$[\lambda^3+(E+A+C)\lambda^2+(EC+EA+AC-a_1\delta-\theta\beta_1)\lambda+M(1-R_1)]=0. \tag{4.7}$$

$$[\lambda^3+(B+D+F)\lambda^2+(BD+BF+DF-a_2\sigma-\phi\beta_2)\lambda+N(1-R_2)]=0. \tag{4.8}$$

These two equations can be written in the form of $A_0\lambda^3+A_1\lambda^2+A_2\lambda+A_3=0$.
Applying the Routh–Hurwitz criterion [All08], the roots of the characteristic polynomial $P(\lambda)=A_0\lambda^3+A_1\lambda^2+A_2\lambda+A_3$ have negative real parts, if $R_1<1$ and $R_2<1$.
This implies $max\{R_1,R_2\}=R_e<1$.
Therefore, the DFE point is locally asymptotically stable if $R_e<1$ and unstable if $R_e>1$.

4.3.6 Global stability of the DFE, E_0

Theorem 17 *If $R_e < 1$, the DFE E_0 of model (4.1) is globally asymptotically stable (GAS) in its feasible region.*

Proof:
To explore the global stability of the DFE point we applied the method executed in [CCBVdD$^+$02]. First the model (4.1) can be re-written in the form:

$$\begin{cases} \frac{dX}{dt} = F(X, Z), \\ \frac{dZ}{dt} = G(X, Z), G(X, 0) = 0, \end{cases} \tag{4.9}$$

where the vectors X and Z represents the non-infected and infected compartments. Now, $X = (S)$, $Z = (E_1, E_2, I, I_D, L_1, L_2)$, and the conditions (H_1) and (H_2) are:
(H_1), $\frac{dX}{dt} = F(X, 0)$, X^* is GAS, where $F(X^*, 0) = 0$.
(H_2), $\frac{dZ}{dt} = QZ - G^*(X, Z), G^*(X, Z) \geq 0$ for $(X, Z) \in R_7^+$ where Q is a Metzler matrix (the non-diagonal entries of Q are non-negative).
The first condition $\frac{dX}{dt} = F(X, 0) = \begin{bmatrix} \pi - \mu S \\ 0 \end{bmatrix}$.

Here, this system is GAS around $X^* = (\frac{\pi}{\mu}, 0)$. This can be justified from $S(t) = \frac{\pi}{\mu} + (S(0) - \frac{\pi}{\mu})exp^{-\mu t}$, such that $\lim_{t\to\infty} S(t) = \frac{\pi}{\mu}$, which shows that the global convergence of the system in Ω.
Moreover, from the model (4.1), the matrix Q is expressed by:

$$Q = \begin{bmatrix} -(\theta + \delta + b) & 0 & \beta_1 & 0 & a_1 & 0 \\ 0 & -(\phi + \sigma + \mu) & 0 & \beta_2 & 0 & a_2 \\ \theta & 0 & -(\epsilon + \rho + \mu + d_1) & 0 & 0 & 0 \\ 0 & \phi & \epsilon & -(\gamma + \mu + d_2) & 0 & 0 \\ \delta & 0 & \rho & 0 & -(a_1 + \mu) & 0 \\ 0 & \sigma & 0 & \gamma & 0 & -(a_2 + \mu) \end{bmatrix}.$$

Again $\frac{dZ}{dt} = G(X, Z) = QZ - G^*(X, Z)$,

$$\text{where } G^*(X, Z) = \begin{bmatrix} \beta_1(1 - \frac{S}{N})I \\ \beta_2(1 - \frac{S}{N})I_D \\ 0 \\ 0 \\ 0 \\ 0 \end{bmatrix}.$$

Since $0 \leq S \leq N$, then $G^*(X, Z) \geq 0$. Thus (H_1) and (H_2) are satisfied.
Therefore, the model (4.1) is GAS when $R_e < 1$.

4.3.7 Endemic Equilibrium point (EEP)

We have three endemic equilibrium points as a special case. They are EEP for DS-TB only model, DR-TB only model, and both of the two persist in the population.
Firstly, for only DS-TB model the infected classes $E_2 = 0, I_D = 0, L_2 = 0, \epsilon = 0$. Thus, the model (4.1) will give the following result.

$$\frac{dS(t)}{dt} = \pi - (\frac{\beta_1}{N(t)}I + \mu)S = 0, \tag{4.10}$$

$$\frac{dE_1(t)}{dt} = \frac{\beta_1 S}{N(t)}I + a_1 L_1 - (\theta + \delta + \mu)E_1 = 0, \tag{4.11}$$

$$\frac{dI(t)}{dt} = \theta E_1 - (\rho + \mu + d_1)I = 0, \tag{4.12}$$

$$\frac{dL_1(t)}{dt} = \rho I + \delta E_1 - (a_1 + \mu)L_1 = 0. \tag{4.13}$$

Therefore, the solutions are $S_1 = \frac{\pi}{(\frac{\beta_1 I}{N(t)}+\mu)}$, $E_1 = \frac{(\rho+\mu+d_1)}{\theta}I$, $I = \frac{\theta(a_1+\mu)(\pi-\mu S_1)}{(\theta+\delta+\mu)(a_1+\mu)(\rho+\mu+d_1)-a_1(\theta\rho+\delta(\rho+\mu+d_1))}$, and $L_1 = [\frac{\rho\theta+\delta(\rho+\mu+d_1)}{\theta(a_1+\mu)}]I$.
Secondly, for only DR-TB model the infected classes $E_1 = 0, I = 0, L_1 = 0$. Thus, the model (4.1) will give the following result.

$$\frac{dS(t)}{dt} = \pi - (\frac{\beta_2}{N(t)}I_D + \mu)S = 0, \tag{4.14}$$

$$\frac{dE_2(t)}{dt} = \frac{\beta_2 S}{N(t)}I_D + a_2 L_2 - (\phi + \sigma + \mu)E_2 = 0, \tag{4.15}$$

$$\frac{dI_D(t)}{dt} = \phi E_2 - (\gamma + \mu + d_2)I_D = 0, \tag{4.16}$$

$$\frac{dL_2(t)}{dt} = \gamma I_D + \sigma E_2 - (a_2 + \mu)L_2 = 0. \tag{4.17}$$

Hence, we obtain $S_2 = \frac{\pi}{(\frac{\beta_2 I_D}{N(t)}+\mu)}$, $E_2 = \frac{(\gamma+\mu+d_2)}{\phi}I_D$, $I_D = \frac{\phi(a_2+\mu)(\pi-\mu S_2)}{(\phi+\sigma+\mu)(a_2+\mu)(\gamma+\mu+d_2)-a_2(\phi\gamma+\sigma(\gamma+\mu+d_2))}$, and $L_2 = [\frac{\gamma\phi+\sigma(\gamma+\mu+d_2)}{\phi(a_2+\mu)}]I_D$.

Lastly, both DS-TB and DR-TB persist in the community, we calculated the EEP as follows.

$$\frac{dS(t)}{dt} = \pi - (\frac{\beta_1}{N(t)}I + \frac{\beta_2}{N(t)}I_D + \mu)S = 0, \tag{4.18}$$

$$\frac{dE_1(t)}{dt} = \frac{\beta_1 S}{N(t)}I + a_1 L_1 - (\theta + \delta + \mu)E_1 = 0, \tag{4.19}$$

$$\frac{dE_2(t)}{dt} = \frac{\beta_2 S}{N(t)}I_D + a_2 L_2 - (\phi + \sigma + \mu)E_2 = 0, \tag{4.20}$$

$$\frac{dI(t)}{dt} = \theta E_1 - (\epsilon + \rho + \mu + d_1)I = 0, \tag{4.21}$$

$$\frac{dI_D(t)}{dt} = \phi E_2 + \epsilon I - (\gamma + \mu + d_2)I_D = 0, \tag{4.22}$$

$$\frac{dL_1(t)}{dt} = \rho I + \delta E_1 - (a_1 + \mu)L_1 = 0, \tag{4.23}$$

$$\frac{dL_2(t)}{dt} = \gamma I_D + \sigma E_2 - (a_2 + \mu)L_2 = 0. \tag{4.24}$$

If we let $\lambda_a = \frac{\beta_1}{N}I^*$ and $\lambda_b = \frac{\beta_2}{N}I_D^*$, then we obtain $S^* = \frac{\pi}{(\lambda_a+\lambda_b+\mu)}$, $E_1^* = \frac{\lambda_a S^* + a_1 L_1^*}{\theta+\delta+\mu}$, $E_2^* = \frac{\lambda_b S^* + a_2 L_2^*}{\phi+\sigma+\mu}$, $I^* = \frac{\theta E_1^*}{\epsilon+\rho+d_1+\mu}$, $I_D^* = \frac{\phi E_2^* + \epsilon I^*}{\gamma+d_2+\mu}$, $L_1^* = \frac{\rho I^* + \delta E_1^*}{a_1+\mu}$, and $L_2^* = \frac{\gamma I_D^* + \sigma E_2^*}{a_2+\mu}$. Therefore, the EE point of both diseases persist in the community say $E_* = (S^*, E_1^*, E_2^*, I^*, I_D^*, L_1^*, L_2^*)$.

Lemma 4 *A unique endemic equilibrium point E_* exist if $R_e > 1$.*

Proof.

If the disease is endemic in the community, then $\exists\, t^* > 0$ such that $\frac{dE_1(t^*)}{dt} > 0$, $\frac{dE_2(t^*)}{dt} > 0$, $\frac{dI(t^*)}{dt} > 0$, $\frac{dI_D(t^*)}{dt} > 0$, $\frac{dL_1(t^*)}{dt} > 0$ and $\frac{dL_2(t^*)}{dt} > 0$. Thus, keeping the state variables E_1, E_2, I, I_D, L_1, and L_2 at t^*, we have:

$$\frac{dE_1}{dt} = \frac{\beta_1 S}{N}I + a_1 L_1 - (\theta + \delta + \mu)E_1 > 0, \tag{4.25}$$

$$\frac{dE_2}{dt} = \frac{\beta_2 S}{N}I_D + a_2 L_2 - (\phi + \sigma + \mu)E_2 > 0, \tag{4.26}$$

$$\frac{dI}{dt} = \theta E_1 - (\epsilon + \rho + \mu + d_1)I > 0, \tag{4.27}$$

$$\frac{dI_D}{dt} = \phi E_2 + \epsilon I - (\gamma + \mu + d_2)I_D > 0, \tag{4.28}$$

$$\frac{dL_1}{dt} = \rho I + \delta E_1 - (a_1 + \mu)L_1 > 0, \tag{4.29}$$

$$\frac{dL_2}{dt} = \gamma I_D + \sigma E_2 - (a_2 + \mu)L_2 > 0. \tag{4.30}$$

Firstly, from (4.25), (4.27) and (4.29) we have

$$\begin{cases} (\theta+\delta+\mu)E_1 < \beta_1 \frac{S}{N(t)} I + a_1 L_1, \\ (\epsilon+\rho+\mu+d_1)I < \theta E_1, \\ (a_1+\mu)L_1 < \rho I + \delta E_1. \end{cases} \tag{4.31}$$

From the fact that $\frac{S}{N(t)} \leq 1$. Thus (4.31) gives:

$$\begin{cases} AE_1 < \beta_1 I + a_1 L_1, \\ CI < \theta E_1, \\ EL_1 < \rho I + \delta E_1. \end{cases} \tag{4.32}$$

Hereafter, solving (4.32) simultaneously by multiplying the first equation with θ and the second equation with A, then add vertically gives the following inequality.

$$0 < (\beta_1\theta - AC)I + a_1\theta L_1. \tag{4.33}$$

Again, multiplying the first equation with δ and the third equation with A, then add vertically gives the following inequality.

$$0 < (\beta_1\delta + \rho A)I + (a_1\delta - AE)L_1 \Rightarrow L_1 < \frac{(\beta_1\delta + \rho A)I}{AE - a_1\delta}. \tag{4.34}$$

Substituting (4.34) at (4.33) with applying rule of inequality and solve the expression gives:
$A(CEA - a_1(\theta\rho + C\delta))I < A\beta_1\theta EI$.
Now, dividing both sides with $A(CEA - a_1(\theta\rho + C\delta))I = AMI$ gives:

$$1 < \frac{\beta_1\theta E}{M} = R_1. \tag{4.35}$$

Secondly, from (4.26), (4.28) and (4.30) we have:

$$\begin{cases} (\phi+\sigma+\mu)E_2 < \beta_2 \frac{S}{N(t)} I_D + a_2 L_2, \\ (\gamma+\mu+d_2)I_D < \phi E_2 + \epsilon I, \\ (a_2+\mu)L_2 < \gamma I_D + \sigma E_2. \end{cases} \tag{4.36}$$

This implies,

$$\begin{cases} BE_2 < \beta_2 I_D + a_2 L_2, \\ DI_D < \phi E_2 + \epsilon I, \\ FL_2 < \gamma I_D + \sigma E_2. \end{cases} \tag{4.37}$$

Hereafter, solving (4.37) simultaneously likes bellow.
First multiplying the first inequality with ϕ and the second inequality with B, then add vertically gives the following inequality.

$$0 < (\beta_2\phi - BD)I_D + a_2\phi L_2 + B\epsilon I. \tag{4.38}$$

Again, multiplying the first equation with σ and the third equation with B, then add vertically gives the following inequality.

$$0 < (\beta_2\sigma + \gamma B)I_D + (a_2\sigma - BF)L_2 \Rightarrow L_2 < \frac{(\beta_2\sigma + \gamma B)I_D}{BF - a_2\sigma}. \tag{4.39}$$

Substituting (4.39) at (4.38) with applying rule of inequality and solve the expression gives:
$B(BDF - a_2(\phi\gamma + D\sigma))I_D < \beta_2\phi F I_D B + B\epsilon(BF - a_2\sigma)I$.
$\Rightarrow 1 < \frac{\beta_2\phi F}{N} + \frac{\epsilon(BF - a_2\sigma)I}{N}$.
$\Rightarrow 0 < -(1 - R_2) + \frac{\epsilon(BF - a_2\sigma)\frac{I}{I_D}}{N}$.
We have two possibilities:

1. Both $-(1 - R_2) > 0$ and $\frac{\epsilon(BF - a_2\sigma)\frac{I}{I_D}}{N} > 0$. Here $\frac{\epsilon(BF - a_2\sigma)\frac{I}{I_D}}{N}$ is always positive, since $BF - a_2\sigma > 0$ by (4.39).
   Now $-(1 - R_2) > 0 \Rightarrow R_2 > 1$.
2. $\frac{\epsilon(BF - a_2\sigma)\frac{I}{I_D}}{N} > 1 - R_2 \Rightarrow R_2 > 1 - \frac{\epsilon(BF - a_2\sigma)\frac{I}{I_D}}{N}$.

We know that $R_e = max\{R_1, R_2\}$.
Therefore, a unique endemic equilibrium exist if $R_1 > 1$ or $R_2 > 1$, which implies $R_e > 1$.

4.3.8 Global stability of the endemic equlibrum

Theorem 18 *If $R_e > 1$, the endemic equilibrium (E_*) of (4.1) is globally asymptotically stable on $\mathbb{R}^7_{+0}\backslash\varpi$, with solutions in ϖ limiting to E_0, where $\varpi = (S, 0, 0, 0, 0, 0, 0)$.*

Proof:

To prove this theorem, we used the method of Lyapunov functions.

Consider the Lyapunov function
$G = (S - S^* - S^* \ln \frac{S}{S^*}) + (E_1 - E_1^* - E_1^* \ln \frac{E_1}{E_1^*}) + (E_2 - E_2^* - E_2^* \ln \frac{E_2}{E_2^*}) + N_1(I - I^* - I^* \ln \frac{I}{I^*}) + N_2(I_D - I_D^* - I_D^* \ln \frac{I_D}{I_D^*}) + (L_1 - L_1^* - L_1^* \ln \frac{L_1}{L_1^*}) + (L_2 - L_2^* - L_2^* \ln \frac{L_2}{L_2^*})$. This type of Lyapunov function has been mentioned in [MLL03, Hou18].

Now, the derivative of G with respect to time as
$G' = (\frac{S-S^*}{S})S' + (\frac{E_1-E_1^*}{E_1})E_1' + (\frac{E_2-E_2^*}{E_2})E_2' + (\frac{I-I^*}{I})I' + (\frac{I_D-I_D^*}{I_D})I_D' + (\frac{L_1-L_1^*}{L_1})L_1' + (\frac{L_2-L_2^*}{L_2})L_2'$
$= (\frac{S-S^*}{S})[\pi - (\frac{\beta_1}{N(t)}I + \frac{\beta_2}{N(t)}I_D + \mu)S] + (\frac{E_1-E_1^*}{E_1})[\frac{\beta_1 S}{N(t)}I + a_1 L_1 - (\theta + \delta + \mu)E_1] + (\frac{E_2-E_2^*}{E_2})[\frac{\beta_2 S}{N(t)}I_D + a_2 L_2 - (\phi + \sigma + \mu)E_2] + (\frac{I-I^*}{I})[\theta E_1 - (\epsilon + \rho + \mu + d_1)I] + (\frac{I_D-I_D^*}{I_D})[\phi E_2 + \epsilon I - (\gamma + \mu + d_2)I_D] + (\frac{L_1-L_1^*}{L_1})[\rho I + \delta E_1 - (a_1 + \mu)L_1] + (\frac{L_2-L_2^*}{L_2})[\gamma I_D + \sigma E_2 - (a_2 + \mu)L_2]$
$= (1 - \frac{S^*}{S})[\pi - (\frac{\beta_1}{N(t)}I + \frac{\beta_2}{N(t)}I_D + \mu)S] + (1 - \frac{E_1^*}{E_1})[\frac{\beta_1 S}{N(t)}I + a_1 L_1 - (\theta + \delta + \mu)E_1] + (1 - \frac{E_2^*}{E_2})[\frac{\beta_2 S}{N(t)}I_D + a_2 L_2 - (\phi + \sigma + \mu)E_2] + (1 - \frac{I^*}{I})[\theta E_1 - (\epsilon + \rho + \mu + d_1)I] + (1 - \frac{I_D^*}{I_D})[\phi E_2 + \epsilon I - (\gamma + \mu + d_2)I_D] + (1 - \frac{L_1^*}{L_1})[\rho I + \varphi\delta E_1 - (a_1 + \mu)L_1] + (1 - \frac{L_2^*}{L_2})[\gamma I_D + \sigma E_2 - (a_2 + \mu)L_2]$
$= [\pi - (\frac{\beta_1}{N(t)}I + \frac{\beta_2}{N(t)}I_D + \mu)S - \pi\frac{S^*}{S} + (\frac{\beta_1}{N(t)}I + \frac{\beta_2}{N(t)}I_D + \mu)S^*] + [\frac{\beta_1 S}{N(t)}I + a_1 L_1 - (\theta + \delta + \mu)E_1 - (\frac{\beta_1 S}{N(t)}I + a_1 L_1)\frac{E_1^*}{E_1} + (\theta + \delta + \mu)E_1^*] + [\frac{\beta_2 S}{N(t)}I_D + a_2 L_2 - (\phi + \sigma + \mu)E_2 - (\frac{\beta_2 S}{N(t)}I_D + a_2 L_2)\frac{E_2^*}{E_2} + (\phi + \sigma + \mu)E_2^*] + [\theta E_1 - (\epsilon + \rho + \mu + d_1)I - \theta E_1\frac{I^*}{I} + (\epsilon + \rho + \mu + d_1)I^*] + [\phi E_2 + \epsilon I - (\gamma + \mu + d_2)I_D - (\phi E_2 + \epsilon I)\frac{I_D^*}{I_D} + (\gamma + \mu + d_2)I_D^*] + [\rho I + \delta E_1 - (a_1 + \mu)L_1 - (\rho I + \delta E_1)\frac{L_1^*}{L_1} + (a_1 + \mu)L_1^*] + [\gamma I_D + \sigma E_2 - (a_2 + \mu)L_2 - (\gamma I_D + \sigma E_2)\frac{L_2^*}{L_2} + (a_2 + \mu)L_2^*]$
$\Rightarrow G' = \frac{dG}{dt} = [\pi + (\frac{\beta_2}{N(t)}I_D + \mu)S^* + \frac{\beta_1 S}{N(t)}I + a_1 L_1 + (\theta + \delta + \mu)E_1^* + \frac{\beta_2 S}{N(t)}I_D + a_2 L_2 + (\phi + \sigma + \mu)E_2^* + \theta E_1 + (\epsilon + \rho + \mu + d_1)I^* + \phi E_2 + \epsilon I + (\gamma + \mu + d_2)I_D^* + \rho I + \delta E_1 + +(a_1 + \mu)L_1^* + \gamma I_D + \sigma E_2 + +(a_2 + \mu)L_2^*] - [(\frac{\beta_1}{N(t)}I + \frac{\beta_2}{N(t)}I_D + \mu)S + \pi\frac{S^*}{S} + (\theta + \delta + \mu)E_1 + (\frac{\beta_1 S}{N(t)}I + a_1 L_1)\frac{E_1^*}{E_1} + (\phi + \sigma + \mu)E_2 + (\frac{\beta_2 S}{N(t)}I_D + a_2 L_2)\frac{E_2^*}{E_2} + (\epsilon + \rho + \mu + d_1)I + \theta E_1\frac{I^*}{I} + (\gamma + \mu + d_2)I_D + (\phi E_2 + \epsilon I)\frac{I_D^*}{I_D} + (a_1 + \mu)L_1 + (\rho I + \delta E_1)\frac{L_1^*}{L_1} + (a_2 + \mu)L_2 + (\gamma I_D + \sigma E_2)\frac{L_2^*}{L_2}]$
Thus $G' = \frac{dG}{dt} = X - Y$, where
$X = [\pi + (\frac{\beta_2}{N(t)}I_D + \mu)S^* + \frac{\beta_1 S}{N(t)}I + a_1 L_1 + (\theta + \delta + \mu)E_1^* + \frac{\beta_2 S}{N(t)}I_D + a_2 L_2 + (\phi + \sigma + \mu)E_2^* + \theta E_1 + (\epsilon + \rho + \mu + d_1)I^* + \phi E_2 + \epsilon I + (\gamma + \mu + d_2)I_D^* + \rho I + \delta E_1 + (a_1 + \mu)L_1^* + \gamma I_D + \sigma E_2 + +(a_2 + \mu)L_2^*]$

and

$Y = [(\frac{\beta_1}{N(t)}I + \frac{\beta_2}{N(t)}I_D + \mu)S + \pi\frac{S^*}{S} + (\theta + \delta + \mu)E_1 + (\frac{\beta_1 S}{N(t)}I + a_1 L_1)\frac{E_1^*}{E_1} + (\phi + \sigma + \mu)E_2 + (\frac{\beta_2 S}{N(t)}I_D + a_2 L_2)\frac{E_2^*}{E_2} + (\epsilon + \rho + \mu + d_1)I + \theta E_1\frac{I^*}{I} + (\gamma + \mu + d_2)I_D + (\phi E_2 + \epsilon I)\frac{I_D^*}{I_D} + (a_1 + \mu)L_1 + (\rho I + \delta E_1)\frac{L_1^*}{L_1} + (a_2 + \mu)L_2 + (\gamma I_D + \sigma E_2)\frac{L_2^*}{L_2}]$
Here X and Y are positive, then $\frac{dG}{dt} = X - Y < 0$, when $X < Y$ and $\frac{dG}{dt} = 0$, when $S = S^*, E_1 = E_1^*, E_2 = E_2^*, I = I^*, I_D = I_D^*, L_1 = L_1^*$, and $L_2 = L_2^*$ in Ω
Thus, the largest compact invariant set in $\{(S^*, E_1^*, E_2^*, I^*, I_D^*, L_1^*, L_2^*) \in \Omega : \frac{dG}{dt} = 0\}$ is the singleton endemic equilibrium E_*. This implies that each solution which intersects $\mathbb{R}^7_{+0} \backslash \{E_1 = E_2 = I = I_D = L_1 = L_2 = 0\}$ limits to E_0. By LaSalles invariant principle [LaS76], it implies that E_* is globally asymptotically stable on $\mathbb{R}^7_{+0} \backslash \{E_1 = E_2 = I = I_D = L_1 = L_2 = 0\}$ if $X < Y$.

4.3.9 Determination of bifurcation at $R_e = 1$

Here, we used center manifold theory to determine the probability of forward and backward bifurcations of (4.1) by retitling the compartments like this.
Let $S = x_1, E_1 = x_2, E_2 = x_3, I = x_4, I_D = x_5, L_1 = x_6$ and $L_2 = x_7$. Thus (4.1) can be written in the form $\frac{dx}{dt} = F(x)$, where $F(x) = (f_1, f_2, f_3, f_4, f_5, f_6, f_7)^T$, $x = (x_1, x_2, x_3, x_4, x_5, x_6, x_7)^T$, and T is transpose. This expression presented likes below.

$$\begin{cases} \frac{dx_1}{dt} = \pi - (\frac{\beta_1}{N(t)}x_4 + \frac{\beta_2}{N(t)}x_5 + \mu)x_1, \\ \frac{dx_2}{dt} = \frac{\beta_1 x_1}{N(t)}x_4 + a_1 x_6 - (\theta + \delta + \mu)x_2, \\ \frac{dx_3}{dt} = \frac{\beta_2 x_1}{N(t)}x_5 + a_2 x_7 - (\phi + \sigma + \mu)x_3, \\ \frac{dx_4}{dt} = \theta x_2 - (\epsilon + \rho + \mu + d_1)x_4, \\ \frac{dx_5}{dt} = \phi x_3 + \epsilon x_4 - (\gamma + \mu + d_2)x_5, \\ \frac{dx_6}{dt} = \rho x_4 + \delta x_2 - (a_1 + \mu)x_6, \\ \frac{dx_7}{dt} = \gamma x_5 + \sigma x_3 - (a_2 + \mu)x_7. \end{cases} \tag{4.40}$$

The Jacobian matrix of this system at DFE $(E_0) = (\frac{\pi}{\mu}, 0, 0, 0, 0, 0, 0)$ is already expressed.
$J(\frac{\pi}{\mu}, 0, 0, 0, 0, 0, 0) =$

$$\begin{bmatrix} -\mu & 0 & 0 & -\beta_1 & -\beta_2 & 0 & 0 \\ 0 & -(\theta+\delta+b) & 0 & \beta_1 & 0 & a_1 & 0 \\ 0 & 0 & -(\phi+\sigma+\mu) & 0 & \beta_2 & 0 & a_2 \\ 0 & \theta & 0 & -(\epsilon+\rho+\mu+d_1) & 0 & 0 & 0 \\ 0 & 0 & \phi & \epsilon & -(\gamma+\mu+d_2) & 0 & 0 \\ 0 & \delta & 0 & \rho & 0 & -(a_1+\mu) & 0 \\ 0 & 0 & \sigma & 0 & \gamma & 0 & -(a_2+\mu) \end{bmatrix}.$$

Let $\beta_1 = \beta_1^*$ and $\beta_2 = \beta_2^*$ be two bifurcation parameter of the equation of R_1 and R_2 respectively.
Thus, $R_1 = \beta_1^* \frac{\theta E}{M} = \beta_1^* \frac{\theta(a_1+\mu)}{(a_1+\mu)(\epsilon+\rho+\mu+d_1)(\theta+\delta+\mu) - a_1(\theta\rho+(\epsilon+\rho+\mu+d_1)\delta)}$ and
$R_2 = \beta_2^* \frac{\phi F}{N} = \beta_2^* \frac{\phi(a_2+\mu)}{(\phi+\sigma+\mu)(\gamma+\mu+d_2)(a_2+\mu) - a_2(\phi\gamma+\sigma(\gamma+\mu+d_2))}$.

Hereafter, we used center manifold theory to analyse stability of the endemic equilibrium E_0 near $R_e = 1$ or bifurcation point.
Hence $1 = \beta_1^* \frac{\theta E}{M}$ and $1 = \beta_2^* \frac{\phi F}{N}$, which implies $\beta_1^* = \frac{M}{\theta E}$ and $\beta_2^* = \frac{N}{\phi F}$.
The Jacobean matrix near $\beta_1^* = \beta_1$ and $\beta_2^* = \beta_2$, has a right eigenvector $u = (u_1, u_2, u_3, u_4, u_5, u_6, u_7)^T$

and zero eigenvalue can be written like this.

$$\begin{bmatrix} -\mu & 0 & 0 & -\beta_1 & -\beta_2 & 0 & 0 \\ 0 & -A & 0 & \beta_1 & 0 & a_1 & 0 \\ 0 & 0 & -B & 0 & \beta_2 & 0 & a_2 \\ 0 & \theta & 0 & -C & 0 & 0 & 0 \\ 0 & 0 & \phi & \epsilon & -D & 0 & 0 \\ 0 & \delta & 0 & \rho & 0 & -(a_1+\mu) & 0 \\ 0 & 0 & \sigma & 0 & \gamma & 0 & -(a_2+\mu) \end{bmatrix} \begin{pmatrix} u_1 \\ u_2 \\ u_3 \\ u_4 \\ u_5 \\ u_6 \\ u_7 \end{pmatrix} = \begin{pmatrix} 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \end{pmatrix}, \tag{4.41}$$

where $A = \theta + \delta + \mu, B = \phi + \sigma + \mu, C = \epsilon + \rho + \mu + d_1, D = \gamma + \mu + d_2$.
The system of equation becomes;

$$\begin{cases} -\mu u_1 - \beta_1 u_4 - \beta_2 u_4 = 0, \\ -(\theta + \delta + b)u_2 + \beta_1 u_4 + a_1 u_6 = 0, \\ -(\phi + \sigma + \mu)u_3 + \beta_2 u_5 + a_2 u_7 = 0, \\ \theta u_2 - (\epsilon + \rho + \mu + d_1)u_4 = 0, \\ \phi u_3 + \epsilon u_4 - (\gamma + \mu + d_2)u_5 = 0, \\ \delta u_2 + \rho u_4 - (a_1 + \mu)u_6 = 0, \\ \sigma u_3 + \gamma u_5 - (a_2 + \mu)u_7 = 0. \end{cases} \tag{4.42}$$

Solving system (4.42) we obtain
$u_1 = -\frac{(\beta_1 u_4 + \beta_2 u_5)}{\mu}$, $u_2 = \frac{\beta_1 u_4 + a_1 u_6}{\theta+\delta+b}$, $u_3 = \frac{\beta_2 u_5 + a_2 u_7}{\phi+\sigma+\mu}$, $u_4 = \frac{\theta u_2}{(\epsilon+\rho+\mu+d_1)}$,
$u_5 = \frac{\phi u_3 + \epsilon u_4}{(\gamma+\mu+d_2)}$, $u_6 = \frac{\delta u_2 + \rho u_4}{(a_1+\mu)}$, and $u_7 = \frac{\sigma u_3 + \gamma u_5}{(a_2+\mu)}$.
Again, the left eigenvector associating to the zero eigenvalue given by; $v = (v_1, v_2, v_3, v_4, v_5, v_6, v_7)^T$.
Then

$$\begin{bmatrix} -\mu & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & -A & 0 & \theta & 0 & \delta & 0 \\ 0 & 0 & -B & 0 & \phi & 0 & \sigma \\ -\beta_1 & \beta_1 & 0 & -C & \epsilon & \rho & 0 \\ -\beta_2 & 0 & \beta_2 & 0 & -D & 0 & \gamma \\ 0 & a_1 & 0 & 0 & 0 & -(a_1+\mu) & 0 \\ 0 & 0 & a_2 & 0 & 0 & 0 & -(a_2+\mu) \end{bmatrix} \begin{pmatrix} v_1 \\ v_2 \\ v_3 \\ v_4 \\ v_5 \\ v_6 \\ v_7 \end{pmatrix} = \begin{pmatrix} 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \end{pmatrix}. \tag{4.43}$$

Hence, we obtain $v_1 = 0$, $v_2 = \frac{\theta v_4 + \delta v_6}{(\theta+\delta+b)}$, $v_3 = \frac{\phi v_5 + \sigma v_7}{(\phi+\sigma+\mu)}$, $v_4 = \frac{-\beta_1 v_1 + \beta_1 v_2 + \epsilon v_5 + \rho v_6}{(\epsilon+\rho+\mu+d_1)}$,
$v_5 = \frac{-\beta_2 \frac{\pi}{\mu N} v_1 + \beta_2 v_3 + \gamma v_7}{(\gamma+\mu+d_2)}$, $v_6 = \frac{a_1 v_2}{(a_1+\mu)}$, and $v_7 = \frac{a_2 v_3}{(a_2+\mu)}$.

Now, we need to calculate the bifurcation constants a and b using the formula
$a = \sum_{k,i,j=1}^{n} v_k u_i u_j \frac{\partial^2 f_k}{\partial x_i \partial x_j}(E_0)$, and $b = \sum_{k,i=1}^{n} v_k u_i \frac{\partial^2 f_k}{\partial x_i \partial \beta_1}(E_0)$ in [CCS04], where $f_1 = \frac{dx_1}{dt}$, $f_2 = \frac{dx_2}{dt}$, $f_3 = \frac{dx_3}{dt}$, $f_4 = \frac{dx_4}{dt}$, $f_5 = \frac{dx_5}{dt}$, $f_6 = \frac{dx_6}{dt}$, $f_7 = \frac{dx_7}{dt}$ (4.40).
Hence $\frac{\partial^2 f_2}{\partial x_4 \partial x_1} = \beta_1, \quad \frac{\partial^2 f_3}{\partial x_5 \partial x_1} = \beta_2$.
Then $a = v_2 u_1 u_4 \beta_1 + v_3 u_1 u_5 \beta_2$ and we have two values b_1 and b_2, due to two bifurcation parameters β_1^* and β_2^*.
Thus $b_1 = v_2 u_4$ and $b_2 = v_3 u_5$.
Hence, $a = u_1(v_2 u_4 \beta_1 + v_3 u_5 \beta_2) = -\frac{(\beta_1 u_4 + \beta_2 u_5)}{\mu}(v_2 u_4 \beta_1 + v_3 u_5 \beta_2) < 0$ and all $b_i's$, where $i = 1, 2$ are positive.
Thus, this result can be addressed the following theorem.

Theorem 19 *If $a < 0$, implies that there exists a stable positive endemic equilibrium point which is locally asymptotically stable for $R_0 > 1$ but close to 1.*

4.4 Sensitivity analysis of the parameters

The sensitivity analysis is used to govern the model robustness to parameter values. Thus, we followed [CCH06, BD94] to identify which parameters have high impact on R_0. The sensitivity of each parameter also analyzed using normalized forward sensitivity index ([CHC08]).
Thus $\Lambda_{\beta_1}^{R_1} = \frac{\partial R_1}{\partial \beta_1}\frac{\beta_1}{R_1} = +1$, $\Lambda_{\beta_2}^{R_2} = \frac{\partial R_2}{\partial \beta_2}\frac{\beta_2}{R_2} = +1$.
$\Lambda_{\delta}^{R_1} = \frac{\partial R_1}{\partial \delta}\frac{\delta}{R_1} = -\frac{\delta\mu(\epsilon+\rho+d_1+\mu)}{a_1\theta(\epsilon+d_1+\mu)+a_1\mu(\epsilon+\rho+d_1+\mu)+\mu(\epsilon+\rho+d_1+\mu)(\theta+\delta+\mu)} < 0$, which implies the parameter δ has negative(-ve) sensitivity indices.
$\Lambda_{\rho}^{R_1} = \frac{\partial R_1}{\partial \rho}\frac{\rho}{R_1} = -\frac{\rho(a_1\mu+\mu(\theta+\delta+\mu))}{a_1\theta(\epsilon+d_1+\mu)+a_1\mu(\epsilon+\rho+d_1+\mu)+\mu(\epsilon+\rho+d_1+\mu)(\theta+\delta+\mu)} < 0$, which implies the parameter ρ has negative(-ve) sensitivity indices.
$\Lambda_{\sigma}^{R_2} = \frac{\partial R_1}{\partial \sigma}\frac{\sigma}{R_1} = -\frac{\sigma\mu(\gamma+d_2+\mu)}{a_2\phi(d_2+\mu)+a_2\mu(\gamma+d_2+\mu)+\mu(\sigma+\phi+\mu)(\gamma+d_2+\mu)} < 0$, which implies the parameter σ has negative (-ve) sensitivity indices.
$\Lambda_{\gamma}^{R_2} = \frac{\partial R_1}{\partial \gamma}\frac{\gamma}{R_1} = -\frac{\gamma(a_2\mu+\mu(\phi+\sigma+\mu))}{a_2\phi(d_2+\mu)+a_2\mu(\gamma+d_2+\mu)+\mu(\sigma+\phi+\mu)(\gamma+d_2+\mu)} < 0$, which implies the parameter γ has negative(-ve) sensitivity indices.
The other indices are $\Lambda_{\theta}^{R_1}$, $\Lambda_{a_1}^{R_1}$, $\Lambda_{\mu}^{R_1}$, $\Lambda_{\epsilon}^{R_1}$, $\Lambda_{d_1}^{R_1}$, $\Lambda_{\phi}^{R_2}$, $\Lambda_{a_2}^{R_2}$, $\Lambda_{\mu}^{R_2}$, $\Lambda_{\sigma}^{R_2}$, $\Lambda_{\gamma}^{R_2}$, and $\Lambda_{d_2}^{R_2}$. Applying similar technique, We found the sensitivity indices of the rest of parameters involved in (R_1) and (R_2) and presented in Table (4.2) below.

4.4.1 Interpretation of sensitivity indices

Table (4.2) shows the sensitivity indices of the parameters involved in R_1 and R_2 for the tuberculosis model (4.1). We used the values of the parameters in Table (4.3) to find out the sensitivity induces of the parameters.

Parameters	Sensitivity indices	Parameters	Sensitivity indices
β_1	+1	β_2	+1
θ	+ve	ϕ	+ve
a_1	+ve	σ	-ve
ϵ	-ve	γ	-ve
ρ	-ve	d_2	-ve
d_1	-ve	a_2	+ve
δ	-ve	μ	-ve

Table 4.2: Indices of sensitivity.

The result shows that when the parameters $\beta_1, \beta_2, a_1, a_2, \theta$ and ϕ are increased, keeping others constant. They increase the values of R_1 or R_2.
This shows us the control reproduction number (R_1) is most sensitive to the parameters β_1, a_1 and θ, where as R_2 is most sensitive to the parameters β_2, a_2 and ϕ. They raise the disease burden as they have positive indices.
However, the parameters $\epsilon, \gamma, \rho, \delta, \sigma, d_1, d_2$, and μ have negative indices. They reduce the values of R_1 or R_2 when keeping others constant. This shows us treatment rates (γ, ρ) and progression rates (σ, δ) have an inversely proportional relationship with the control reproduction numbers. This implies that if incrementing those parameters reduces the threshold number ($R_0 = max\{R_1, R_2\}$) and, consequently, the TB burden would be reduced.

4.5 Model with optimal control

Here, we apply optimal control theory on the model (4.1) which helps to identify the best intervention strategy to eradicate/minimize the disease in the specified time.
From our sensitivity analysis, we found that R_1 and R_2 are most sensitive to the contact rate β_1 and β_2 respectively. This shows the effectiveness of preventive measures in controlling disease transmission. Moreover, the progression and treatment rates have negative induces implies that incrementing them can reduce the disease burden. Therefore, based on the analysis we suggested that the time based preventive, case finding, and case holding controlling strategies would be an effective option. This motivates us to incorporate the following three controls defined as:

1. u_1 and u_2: Prevention effort for drug sensitive TB (DS-TB) and drug resistance TB (DR-TB) disease respectively.

2. u_3 and u_4: Case finding control for DS-TB and DR-TB respectively.

3. u_5 and u_6: Case holding control for DS-TB and DR-TB respectively.

Here, the case finding controls, $u_3(t)$ and $u_4(t)$ are refers to the effort required to screening of high-risk exposed individuals and the treatment of latent TB, whereas the case holding controls, $u_5(t)$ and $u_6(t)$ are refers to the efforts required to complete the treatment of infectious people. Thus, the TB model (4.1) can be reformulated as follows.

$$\begin{cases} \frac{dS(t)}{dt} = \pi - ((1-u_1(t))\frac{\beta_1}{N(t)}I + (1-u_2(t))\frac{\beta_2}{N(t)}I_D)S - \mu S, \\ \frac{dE_1(t)}{dt} = (1-u_1(t))\frac{\beta_1 S}{N(t)}I + a_1 L_1 - (\theta + \delta(1+u_3(t)) + \mu)E_1, \\ \frac{dE_2(t)}{dt} = (1-u_2(t))\frac{\beta_2 S}{N(t)}I_D + a_2 L_2 - (\phi + \sigma(1+u_4(t)) + \mu)E_2, \\ \frac{dI(t)}{dt} = \theta E_1 - (\epsilon(1-u_5(t)) + \rho + u_5(t) + \mu + d_1)I, \\ \frac{dI_D(t)}{dt} = \phi E_2 + \epsilon(1-u_5)I - (\gamma(1+u_6(t)) + \mu + d_2)I_D, \\ \frac{dL_1(t)}{dt} = (\rho + u_5(t))I + \delta(1+u_3(t))E_1 - (a_1+\mu)L_1, \\ \frac{dL_2(t)}{dt} = \gamma(1+u_6(t))I_D + \sigma(1+u_4(t))E_2 - (a_2+\mu)L_2, \end{cases} \tag{4.44}$$

where $N(t) = S(t) + E_1(t) + E_2(t) + I(t) + I_D(t) + L_1(t) + L_2(t)$.
We set optimal controls in the set U is defined as : $U = \{u_i(t) : 0 \leq u_i(t) \leq 1, 0 \leq t \leq T\}$, where $i = 1, 2, ..., 6$. Here $u_1 = 0$ is no response and $u_1 = 1$ is the full response which means susceptible populations applied preventive measures. This explanation is the same for other controlling efforts. Let the objective function be defined as [PRL$^+$15, BLVDL14]:

$$J(t) = \int_0^{t_f} [b_1 E_1(t) + b_2 E_2(t) + b_3 I(t) + b_4 I_D(t) + \frac{1}{2}\sum_{i=1}^{6} w_i u_i^2(t)]dt, \tag{4.45}$$

where b_1, b_2, b_3, and b_4 are the cost associated with a number of E_1, E_2, I, and I_D compartments respectively. In addition, the constants $w_i, i = 1, 2, ..., 6$ are the costs of implementing the control efforts from u_1 up to u_6 respectively [Mar15].
Thus, we try to find the optimal controls $u_1^*, u_2^*, u_3^*, u_4^*, u_5^*$ and u_6^* satisfying:
$J(u_1^*, u_2^*, u_3^*, u_4^*, u_5^*, u_6^*) = \min\{J(u_1, u_2, u_3, u_4, u_5, u_6) | (u_1, u_2, u_3, u_4, u_5, u_6) \in U\}$, where U is Lebesgue measurable set expressed above.

Theorem 20 *(Existence of optimal solution). There exists an optimal control $u_1^*(t)$, $u_2^*(t)$, $u_3^*(t)$, $u_4^*(t)$, $u_5^*(t)$, $u_6^*(t)$ and corresponding solutions (S, E_1, E_2, I, I_D, L_1, L_2) such that the function $J(u_i(t)), i = 1, 2, ...6$ over U. For given these optimal solutions, there exist adjoint variables,*

$\lambda_1(t), ..., \lambda_7(t)$, *satisfying.*

$$\begin{cases} \frac{d\lambda_1}{dt} = \lambda_1[((1-u_1)\frac{\beta_1 I}{N} + (1-u_2)\frac{\beta_2 I_D}{N} + \mu)] - \lambda_2(1-u_1)\frac{\beta_1 I}{N} - \lambda_3(1-u_2)\frac{\beta_2 I_D}{N}, \\ \frac{d\lambda_2}{dt} = -b_1 + \lambda_2[\theta + \delta(1+u_3) + \mu)] - \lambda_4\theta - \lambda_6\delta(1+u_3), \\ \frac{d\lambda_3}{dt} = -b_2 + \lambda_3[\phi + \sigma(1+u_4) + \mu)] - \lambda_5\phi - \lambda_7\sigma(1+u_4), \\ \frac{d\lambda_4}{dt} = -b_3 + \lambda_1\beta_1(1-u_1)\frac{S}{N} - \lambda_2\beta_1(1-u_1)\frac{S}{N} + \lambda_4(\epsilon(1-u_5) + \rho + u_5 + \mu + d_1) \\ \qquad -\lambda_5\epsilon(1-u_5) - \lambda_6(\rho + u_5), \\ \frac{d\lambda_5}{dt} = -b_4 + \lambda_1\beta_2(1-u_2)\frac{S}{N} - \lambda_3\beta_2(1-u_2)\frac{S}{N} + \lambda_5(\gamma(1+u_6) + \mu + d_2) - \lambda_7\gamma(1+u_6), \\ \frac{d\lambda_6}{dt} = -\lambda_2 a_1 + \lambda_6(a_1 + \mu), \\ \frac{d\lambda_7}{dt} = -\lambda_3 a_2 + \lambda_7(a_2 + \mu), \end{cases} \tag{4.46}$$

with the transversality conditions $\lambda_i(t_f) = 0, i = 1, 2, 3, ..., 7$. *Moreover, we get the control set* $(u_1^*(t), u_2^*(t), u_3^*(t), u_4^*(t), u_5^*(t), u_6^*(t))$ *characterized by* $u_1^*(t) = max\{0, min(1, u_1^*)\}$, $u_2^*(t) = max\{0, min(1, u_2^*)\}$, $u_3^*(t) = max\{0, min(1, u_3^*)\}$, $u_4^*(t) = max\{0, min(1, u_4^*)\}$, $u_5^*(t) = max\{0, min(1, u_5^*)\}$, $u_6^*(t) = max\{0, min(1, u_6^*)\}$,

where $u_1^* = \frac{\frac{\beta_1 SI}{N}(\lambda_2 - \lambda_1)}{w_1}$, $u_2^* = \frac{\frac{\beta_2 SI_D}{N}(\lambda_3 - \lambda_1)}{w2}$, $u_3^* = \frac{\delta E_1(\lambda_2 - \lambda_6)}{w_3}$,
$u_4^* = \frac{\sigma E_2(\lambda_3 - \lambda_7)}{w_4}$, $u_5^* = I\frac{(\lambda_4 - \epsilon\lambda_4 + \epsilon\lambda_5 - \lambda_6)}{w_5}$ *and* $u_6^* = \frac{\gamma I_D(\lambda_5 - \lambda_7)}{w_6}$.

Proof:
Consider the following conditions are verified thanks to Fleming and Rishel's theorem.

1. The set of all solutions of (4.44) and the associated control functions in U is non-empty.

2. The state system is linear equations of the control functions with coefficients are depending on time and the state variables.

3. The integrand L in (4.45) given by $L(x, u, t) = b_1E_1 + b_2E_2 + b_3I + b_4I_D + \frac{1}{2}(w_1u_1^2 + w_2u_2^2 + w_3u_3^2 + w_4u_4^2 + w_5u_5^2 + w_6u_6^2)$ is convex on U and it also fulfills $L(x, u, t) \geq \delta_1 \mid (u_1, u_2, u_3, u_4, u_5, u_6) \mid^{\beta} -\delta_2$, where $\delta_1 > 0$ and $\beta > 1$.

Firstly, to proof 1, we remarked to [CL55, GCF$^+$08]. In fact, if the solutions of (4.44) are bounded and Lipschitz, then there is a unique solution associated to any control U.
Thus, the sum $N(t)$ also bounded below by a positive non-zero number N_0 and above by $\frac{\pi}{\mu}$. Each compartment which is a subset of $N(t)$ is bounded. In that case, the state systems are bounded and continuous. Therefore, this shows that in the state system there is the boundedness of the partial derivatives with respect to the state variables [Cod12].
This concludes the proof that 1 holds.

Secondly, 2 is confirmed by observing the state equations which are linear functions of the controls u_i, for $i = 1, 2, ..., 6$.

Lastly, to verify condition 3, we referred to [BP12, Ped06] any constant, linear and quadratic functions are convex. Hence, $L(x, u, t)$ is convex on U. Afterwards, to prove the boundedness on L, as shown below.

$w_5 u_5^2 \leq w_5$, since $u_5 \in [0, 1]$.

$\Rightarrow \frac{1}{2} w_5 u_5^2 \leq \frac{w_5}{2} \Rightarrow \frac{1}{2} w_5 u_5^2 - \frac{w_5}{2} \leq 0.$

Then $L(x, u, t) = b_1 E_1 + b_2 E_2 + b_3 I + b_3 I_D + \frac{1}{2} \sum_{i=1}^{5} w_i u_i^2 \geq \frac{1}{2} \sum_{i=1}^{6} w_i u_i^2 - \frac{w_5}{2}$,

$\Rightarrow L(x, u, t) \geq \min(\frac{w_1}{2}, \frac{w_2}{2}, \frac{w_3}{2}, \frac{w_4}{2}, \frac{w_5}{2}, \frac{w_6}{2})(u_1^2 + u_2^2 + u_3^2 + u_4^2 + u_5^2 + u_6^2) - \frac{w_5}{2}$,

$\Rightarrow L(x, u, t) \geq \min(\frac{w_1}{2}, \frac{w_2}{2}, \frac{w_3}{2}, \frac{w_4}{2}, \frac{w_5}{2}, \frac{w_6}{2}) \mid\mid (u_1, u_2, u_3, u_4, u_5, u_6) \mid\mid^2 - \frac{w_5}{2}$.

Therefore, the function $L(x, u, t) \geq \delta_1 \mid\mid (u_1, u_2, u_3, u_4, u_5, u_6) \mid\mid^{\beta} - \delta_2$, where $\delta_1 = \min(\frac{w_1}{2}, \frac{w_2}{2}, \frac{w_3}{2}, \frac{w_4}{2}, \frac{w_5}{2}, \frac{w_6}{2})$, $\delta_2 = \frac{w_5}{2}$ and $\beta = 2$.

By using PMP [PM86], we found a Hamiltonian (H) stated as:

$H(S, E_1, E_2, I, I_D, L_1, L_2, u, t) = L(x, u, t) + \lambda_1 \frac{dS}{dt} + \lambda_2 \frac{dE_1}{dt} + \lambda_3 \frac{dE_2}{dt} + \lambda_4 \frac{dI}{dt} + \lambda_5 \frac{dI_D}{dt} + \lambda_6 \frac{dL_1}{dt} + \lambda_7 \frac{dL_2}{dt}$,

where $\lambda_i, i = 1, 2, ..., 7$ are the adjoint functions. The existence of optimal control pairs, we refereed to [FR82].

To prove the ordinary derivative of the adjoint variables with respect to time and controlling variables, we used the following principle.

The Hamiltonian function H is expressed by:

$H = L(x, u, t) + \lambda_1 \frac{dS}{dt} + \lambda_2 \frac{dE_1}{dt} + \lambda_3 \frac{dE_2}{dt} + \lambda_4 \frac{dI}{dt} + \lambda_5 \frac{dI_D}{dt} + \lambda_6 \frac{dL1}{dt} + \lambda_7 \frac{dL2}{dt}$.

$= b_1 E_1 + b_2 E_2 + b_3 I + b_4 I_D + \frac{1}{2}(w_1 u_1^2 + w_2 u_2^2 + w_3 u_3^2 + w_4 u_4^2 + w_5 u_5^2 + w_6 u_6^2) + \lambda_1[\pi - ((1 - u_1(t))\frac{\beta_1}{N(t)} I + (1 - u_2(t))\frac{\beta_2}{N(t)} I_D)S - \mu S] + \lambda_2[(1 - u_1(t))\frac{\beta_1 S}{N(t)} I + a_1 L_1 - (\theta + \delta(1 + u_3(t)) + \mu)E_1] + \lambda_3[(1 - u_2(t))\frac{\beta_2 S}{N(t)} I_D + a_2 L_2 - (\phi + \sigma(1 + u_4(t)) + \mu)E_2] + \lambda_4[\theta E_1 - (\epsilon(1 - u_5(t)) + \rho + u_5(t) + \mu + d_1)I] + \lambda_5[\phi E_2 + \epsilon(1 - u_5(t))I - (\gamma(1 + u_6(t)) + \mu + d_2)I_D] + \lambda_6[(\rho + u_5(t))I + \delta(1 + u_3(t))E_1 - (a_1 + \mu)L_1] + \lambda_7[\gamma(1 + u_6(t))I_D + \sigma(1 + u_4(t))E_2 - (a_2 + \mu)L_2]$.

Next, the second condition of the PMP sates that $\exists$ adjoint variables $\lambda_i, i = 1, 2, ..., 7$ which satisfy equations like below.

$\frac{d\lambda_1}{dt} = -\frac{dH}{dS}$, $\frac{d\lambda_2}{dt} = -\frac{dH}{dE_1}$, $\frac{d\lambda_3}{dt} = -\frac{dH}{dE_2}$,

$\frac{d\lambda_4}{dt} = -\frac{dH}{dI}$, $\frac{d\lambda_5}{dt} = -\frac{dH}{dI_D}$, $\frac{d\lambda_6}{dt} = -\frac{dH}{dL_1}$, $\frac{d\lambda_7}{dt} = -\frac{dH}{dL_2}$

.

So, we have

$$\begin{cases} \frac{d\lambda_1}{dt} = \lambda_1[((1-u_1)\frac{\beta_1 I}{N} + (1-u_2)\frac{\beta_2 I_D}{N} + \mu)] - \lambda_2(1-u_1)\frac{\beta_1 I}{N} - \lambda_3(1-u_2)\frac{\beta_2 I_D}{N}, \\ \frac{d\lambda_2}{dt} = -b_1 + \lambda_2[\theta + \delta(1+u_3) + \mu)] - \lambda_4\theta - \lambda_6\delta(1+u_3), \\ \frac{d\lambda_3}{dt} = -b_2 + \lambda_3[\phi + \sigma(1+u_4) + \mu)] - \lambda_5\phi - \lambda_7\sigma(1+u_4), \\ \frac{d\lambda_4}{dt} = -b_3 + \lambda_1\beta_1(1-u_1)\frac{S}{N} - \lambda_2\beta_1(1-u_1)\frac{S}{N} + \lambda_4(\epsilon(1-u_5) + \rho + u_5 + \mu + d_1) - \lambda_5\epsilon(1-u_5) - \lambda_6(\rho + u_5), \\ \frac{d\lambda_5}{dt} = -b_4 + \lambda_1\beta_2(1-u_2)\frac{S}{N} - \lambda_3\beta_2(1-u_2)\frac{S}{N} + \lambda_5(\gamma(1+u_6) + \mu + d_2) - \lambda_7\gamma(1+u_6), \\ \frac{d\lambda_6}{dt} = -\lambda_2 a_1 + \lambda_6(a_1 + \mu), \\ \frac{d\lambda_7}{dt} = -\lambda_3 a_2 + \lambda_7(a_2 + \mu), \end{cases}$$

with the transversality conditions $\lambda_i(t_f) = 0, i = 1, 2, 3, ..., 7$.

Now, from optimality conditions, $\frac{dH}{du_1}\,|_{u_1=u_1^*} = 0$, $\frac{dH}{du_2}\,|_{u_2=u_2^*} = 0$, $\frac{dH}{du_3}\,|_{u_3=u_3^*} = 0$, $\frac{dH}{du_4}\,|_{u_4=u_4^*} = 0$, $\frac{dH}{du_5}\,|_{u_5=u_5^*} = 0$, $\frac{dH}{du_6}\,|_{u_6=u_6^*} = 0$.

So, $u_1^* = \frac{\frac{\beta_1 SI}{N}(\lambda_2-\lambda_1)}{w_1}$, $u_2^* = \frac{\frac{\beta_2 SI_D}{N}(\lambda_3-\lambda_1)}{w_2}$, $u_3^* = \frac{\delta E_1(\lambda_2-\lambda_6)}{w_3}$,

$u_4^* = \frac{\sigma E_2(\lambda_3-\lambda_7)}{w_4}$, $u_5^* = I\frac{(\lambda_4-\epsilon\lambda_4+\epsilon\lambda_5-\lambda_6)}{w_5}$, and $u_6^* = \frac{\gamma I_D(\lambda_5-\lambda_7)}{w_6}$.

Now, these result can be written in U like below:

$$u_1(t) = \begin{cases} 0, & \text{if} \quad u_1^* \le 0 \\ u_1^*, & \text{if} \quad 0 < u_1^* < 1 \\ 1, & \text{if} \quad u_1^* \ge 1 \end{cases}, \qquad u_2(t) = \begin{cases} 0, & \text{if} \quad u_2^* \le 0 \\ u_2^*, & \text{if} \quad 0 < u_2^* < 1 \\ 1, & \text{if} \quad u_2^* \ge 1 \end{cases},$$

$$u_3(t) = \begin{cases} 0, & \text{if} \quad u_3^* \le 0 \\ u_3^*, & \text{if} \quad 0 < u_3^* < 1 \\ 1, & \text{if} \quad u_3^* \ge 1 \end{cases}, \qquad u_4(t) = \begin{cases} 0, & \text{if} \quad u_4^* \le 0 \\ u_4^*, & \text{if} \quad 0 < u_4^* < 1 \\ 1, & \text{if} \quad u_2^* \ge 1 \end{cases},$$

$$u_5(t) = \begin{cases} 0, & \text{if} \quad u_5^* \le 0 \\ u_5^*, & \text{if} \quad 0 < u_5^* < 1 \\ 1, & \text{if} \quad u_5^* \ge 1 \end{cases}, \qquad u_6(t) = \begin{cases} 0, & \text{if} \quad u_6^* \le 0 \\ u_6^*, & \text{if} \quad 0 < u_6^* < 1 \\ 1, & \text{if} \quad u_6^* \ge 1. \end{cases}$$

Which is equivalent to:

$u_i^*(t) = \max\{0, \min(1, u_i^*)\}$, where $i = 1, 2, ..., 6$.

4.6 Numerical simulations

In this section, we presented the numerical results of the model incorporating with controlling strategies to validate the analytical findings studied so far. The strategies are used to mainly mini-

mize the disease and the cost burden.
The estimated initial size of population are $E_1 = 1.19 \times 10^7$, $E_2 = 1.4 \times 10^6$, $I = 3.73 \times 10^5$, $I_D = 9.7 \times 10^4$, $L_1 = 2.18 \times 10^7$, and $L_2 = 114.52 \times 10^4$ collected from [KMW19, SSA$^+$21, DY14, cgt21b, SFMA17]. Here, the number of TB and DR-TB patients in Ethiopia are greater than the data mentioned, because the remaining are co-infected with other infectious diseases not necessarily to this model simulation. The rest is the number of susceptible class is calculated by $S = N - (E_1 + E_2 + I + I_D + L_1 + L_2) = 456.848 \times 10^5$, where N=$82.4 \times 10^6$ from [cgt21b]. The fixed final time of this study is $t_f = 10$ years and the inclusive estimation scheme of the value of the parameters is like bellow.

- The per capita natural death rate is the inverse of life expectancy in Ethiopia. Hence $\frac{1}{61} \approx 0.016$.
- The total population N is bounded above by $\frac{\pi}{\mu}$. Thus π is calculated by the product of μ and the average population size of Ethiopia 110 000 000 gives 1.76×10^6.
- According to the data found from Federal ministry of health report [vvv22] around 78.3% and 67.5% are successfully treated from first line and second line anti-TB drugs. Thus, we calculated $\rho = \frac{1}{78.3} = 0.78$ and $\gamma = \frac{1}{67.5} = 0.675$.
- The remaining parameters are estimated based on the data collected from Ethiopian tuberculosis prevention and control (2018-2020/21), WHO report, and latest literature [vvv22, cgt21b, KMW19].

Thus, the overall data is summarized in Table (4.3).

Parameters	Values	References	Parameters	Values	References
π	1.76×10^6	Calculated	β_2	0.014	Estimated
β_1	0.00151	[cgt21b]	ϕ	0.001	Assumed
μ	0.016	Calculated	σ	0.2	Calculated
θ	0.023	[KMW19]	γ	0.675	Estimated
a_1	0.0013	[KMW19]	a_2	0.01	[SS19]
ϵ	0.01	Estimated	d_2	0.675	Calculated
ρ	0.78	Calculated	δ	0.153	Calculated
d_1	0.17	[cgt21b]			

Table 4.3: Symbols and values of parameters.

The values of coefficient parameters associated for targeted infected people ($b_1 = 1, b_2 = 1.64, b_3 = 1$, and $b_4 = 1.8$) are taken from [WCJ11, HAHA18, NM21]. Moreover, we can assume that the values of weight constants ($w_i = 10^4$, for $i = 1, 2, ..., 6$) are the same order [WCJ11] and the remaining

are just for numerical purpose. However, the accurate data on TB and DR-TB attributes for these targeted parameters are scarce.

We used MATLAB software and we discussed the graphical scenarios of the state system with and without optimal approach. The targeted infected individuals and the control profiles of each strategy are plotted. We applied four intervention strategies which are combination of controlling efforts described before. This study is a greatest and necessary imputes for minimized DS-TB and DR-TB burden rather than Solomon et al. investigated the risk factors of MDR TB in our country Ethiopia [ATG18]. It also showed the occurrence and controlling system of DR-TB rather than only TB infection were discussed at [WCJ11].

Thus, in this investigation four intervention strategies are considered. They designed two combinations and all strategies at a time. Owing to these approaches both DS-TB and DR- TB were highly minimized in our country Ethiopia. However, the single intervention is not an effective [AGM21, SS19, TMM17]. Therefore, applying coupling two or more strategies at a time, we constructed the graphical solutions of infected host populations, control profiles, and cost function in the next portion.

4.6.1 Control with prevention effort and case finding for both diseases

We considered prevention together with case finding as an alternative optimal intervention approach (i.e.,$u_i \neq 0$, for $i = 1, 2, 3, 4$, whereas $u_5 = 0$, and $u_6 = 0$). The graphs (A-D) of Figure (4.2) displays that the effect of these optimal strategies on high risk latent and infectious individuals. Before this clarification our country Ethiopia is one of the highest TB/MDR-TB burden in WHO lists from 17 countries in the globe. However, through continuously TB elimination plan proposed by the government there is a significant improvement has been made over the past 5 years [cgt21b]. That is to say individuals without optimal control strategies also decreased as shown in all plots. Thus, the numerical simulation at Figure (4.2) shows that the number of E_1 and E_2 are decreased as compared from without control. These control strategies have no effect on the numbers of I and I_D individuals around for the first one and half year, but they have a great effect after a while. The corresponding control profiles have been given in Figure (4.6) (A). The control $u_1 + u_3$ is maximum and constant for around 8.8 years, whereas the control $u_2 + u_4$ is maximum and constant for around 7 years. However, they declined left and slow down to 0 at the final time; which means finally these strategies will be expected to be stopped. The cost function is also shown in the Figure (4.6) (B) which displayed more economic cost for around seven years. Hereafter, it decreases continuously and slowing to 0 at the final period. This shows that the cost burden is minimized due to the number of infectious individuals decreased leads to increase productive people.

4.6.2 Control with prevention effort and case holding for both diseases

We considered prevention together with case holding as an alternative optimal intervention approach (i.e.,$u_i \neq 0$, for $i = 1, 2, 5, 6$, whereas $u_3 = 0$, and $u_4 = 0$). The plots (A-D) of Figure (4.3) explain that the effect of these optimal strategies on highly risk latent and infectious individuals. These strategies have less effect on individuals with in classes E_1 and E_2, but more effect on drug sensitive TB individuals. If no controls used, the drug resistance TB infectious individuals increased for the first of two years and then decreased dramatically. However, the population in the class I_D declined extremely for the entire period of time. The corresponding control profiles and the cost function have been given in Figure (4.7) (A and B) respectively. The control $u_2 + u_6$ is maximum for around the first one year and seven months and then it decreases left. Finally, it falls to 0 at the final time. Whereas the control $u_1 + u_5$ is maximum and constant almost for the entire period of time before drop to 0. The cost function displays that more economic cost for the first around one year and eight months. Hereafter, it decreases continuously and slowdown to 0 at the final period.

4.6.3 Control with case finding and case holding for both diseases

We considered case finding together with case holding as an alternative optimal intervention (i.e.,$u_i \neq 0$, for $i = 3, 4, 5, 6$, whereas $u_1 = 0$, and $u_2 = 0$). The plots (A-D) of Figure (4.4) clarify the outcome of these optimal strategies on high risk latent and infectious persons. These schemes can help to decrease the number of E_1, E_2 and I intensely rather than without optimal control. The numbers of drug resistance people increased at the beginning of the year and then after decreased further in case of without control. Whereas controls are used optimally, these infectious communities are decreased extremely for the entire period. The control profiles for this strategy have been given in Figure (4.8) (A). The coupled strategy $u_3 + u_5$ would require maximum for almost 9 years before decreasing to zero. However, the optimal control $u_4 + u_6$ would require maximum almost the first two years. It decreases left for nearby 7.5 years before drop to zero. The cost function is also shown in the Figure (4.8) (B). Because of more effort needed at the beginning would require more economic cost almost for 2 years. This function reduced left nearly 7.5 years and dropped to zero at the final time. As a result, this strategy helps to minimize the targeted individuals as well as the economic costs.

Strategies	Description	Total infected averted	Total cost (USD)
B	Preventive and Case holding	4.5×10^5	12.348×10^6
C	Case finding and Case holding	1.969×10^6	14.617×10^6
A	Preventive and Case finding	1.989×10^6	16.652×10^6
D	Preventive, Case finding, and case holding	2.006×10^6	19.574×10^6

Table 4.4: Total infected averted (increasing order) and total cost.

4.6.4 Control with prevention, case finding, and case holding for both diseases

We considered optimal control of prevention, case finding, and case holding strategies at a time for both diseases. The plots (A-D) of Figure (4.5) clarify the outcome of these optimal strategies on E_1, E_2, I, and I_D compartments. The interpretation of this graphical scenario is similar to the third strategy. The significant difference is as shown on the control profiles and the cost function are given in Figure (4.9) (A) and (B) respectively.

All efforts of DS-TB would require maximum for almost 8.4 years before radically decrease to zero. However, the optimal control of all efforts of DR-TB at a time would require maximum almost the first 1.8 years. Hereafter, they decreased nearby 7.8 years before dropped to zero.

Figure (4.9) (B) shows the graphical result of cost function. Because of more effort needed at the beginning would require more economic cost around the first 1.8 years. This function reduced left nearby 6.2 years and intensely decreased later. Finally, it is dropped to zero.

Therefore, this strategy also helps to minimize or eliminate the high risk latent and infectious individuals in the community.

4.7 Cost-effectiveness analysis

Here, we presented the cost-effectiveness rank of one implemented strategy over the other. We achieved this by (Baba and Makinde, 2014); they had declared that

Incremental Cost-Effectiveness Ratio (ICER)= $\frac{\text{Difference in costs between strategies}}{\text{Difference in health effects between strategies}}$.

We applied this technique by ranked increasing order of effectiveness with respect to infected averted. The total number of infected averted which is the difference between the total infected without and with control. Besides to this, the total cost is also mentioned in Table (4.4).

We compare the strategy of B and C by computing the ICER:

$$ICER(B) = \frac{12.348\times10^6}{4.5\times10^5} = 27.44 \qquad \text{and} \qquad \text{ICER (C)} = \frac{14.617\times10^6 - 12.348\times10^6}{1.969\times10^6 - 4.5\times10^5} = 1.4937.$$

The comparison displayed that $ICER(C) < ICER(B)$, which shows that strategy B is strongly dominated and does not consume limited resource.

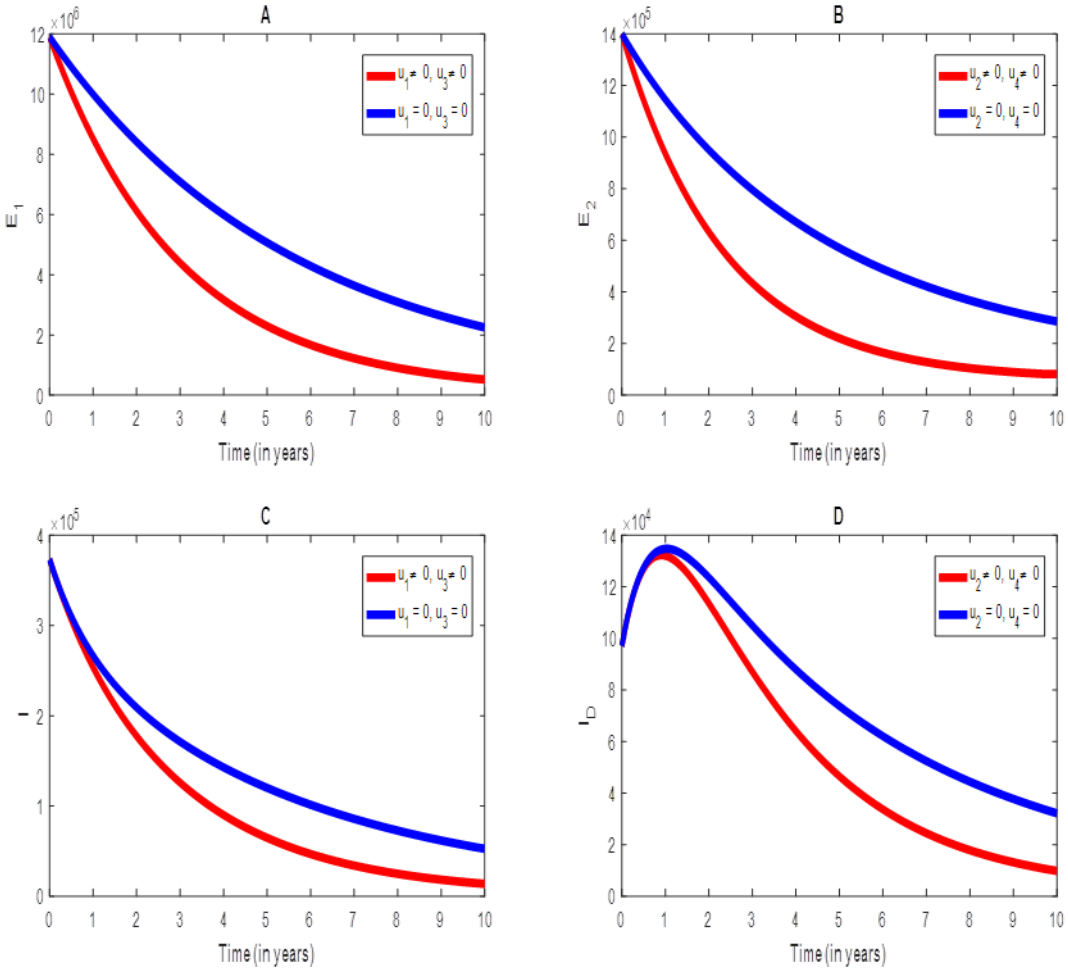

Figure 4.2: Optimal combined effect of prevention and case finding simulation results.

Hence, the strategy B is more costly and remove from the set of choices.

Next, we compare strategy C and A.

$$ICER(C) = \frac{14.617\times10^6}{1.969\times10^6} = 7.4236 \quad \text{and} \quad ICER(A) = \frac{16.652\times10^6 - 14.617\times10^6}{1.989\times10^6 - 1.969\times10^6} = 101.75.$$

The comparison showed that strategy A is more costly and less effectiveness than strategy C. Hence, we should remove strategy A from the set of choices.

Finally, we compare strategy C and D.

Already, we calculated $ICER(C) = 7.4236$ and

$$ICER(D) = \frac{19.574\times10^6 - 16.652\times10^6}{2.006\times10^6 - 1.989\times10^6} = 171.8824.$$

This implies that, the strategy D is more costly and it should remove from the set of choices.

Therefore, the strategy C is the most cost-effective approach as compared with other alternatives.

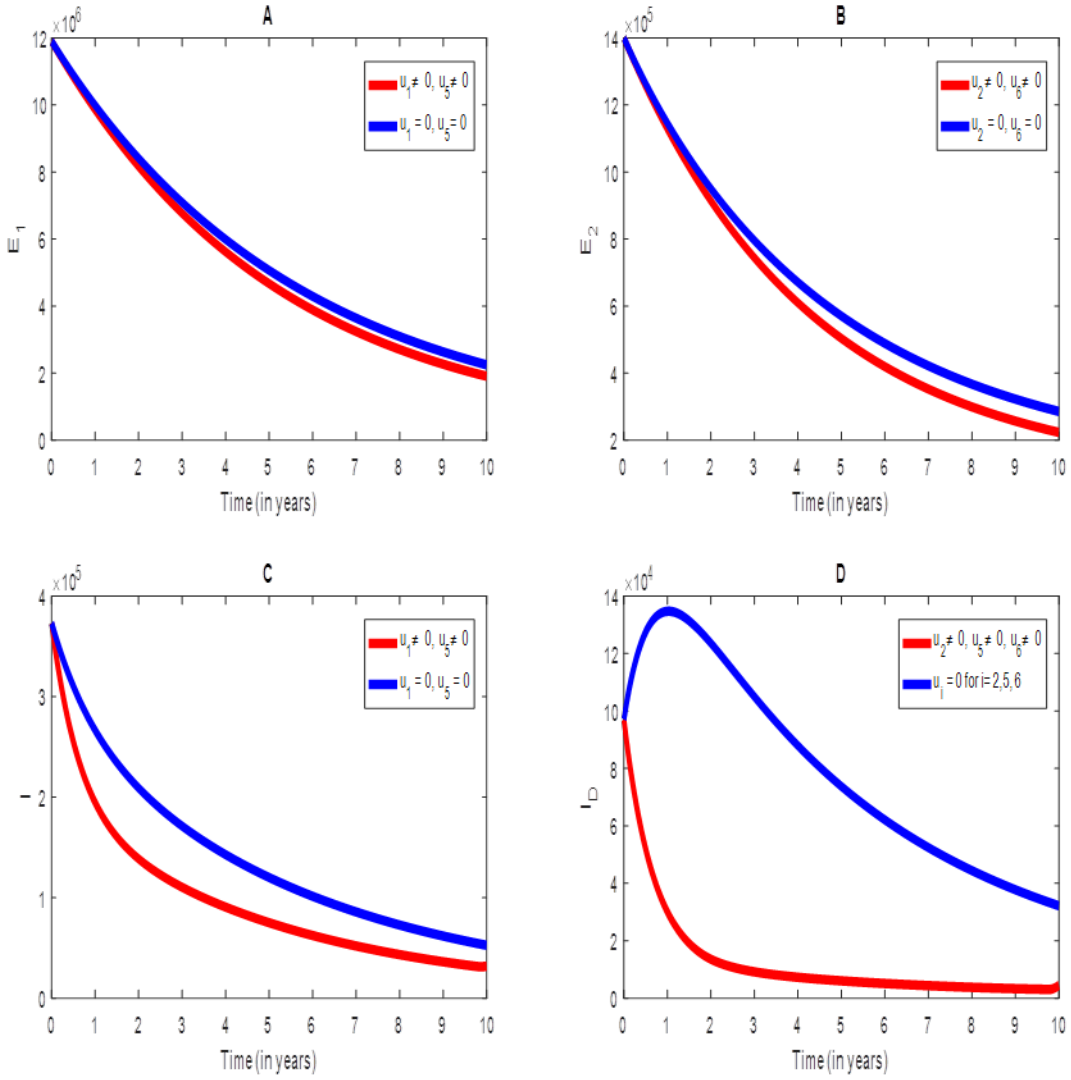

Figure 4.3: Optimal combined effect of prevention and case holding simulation results.

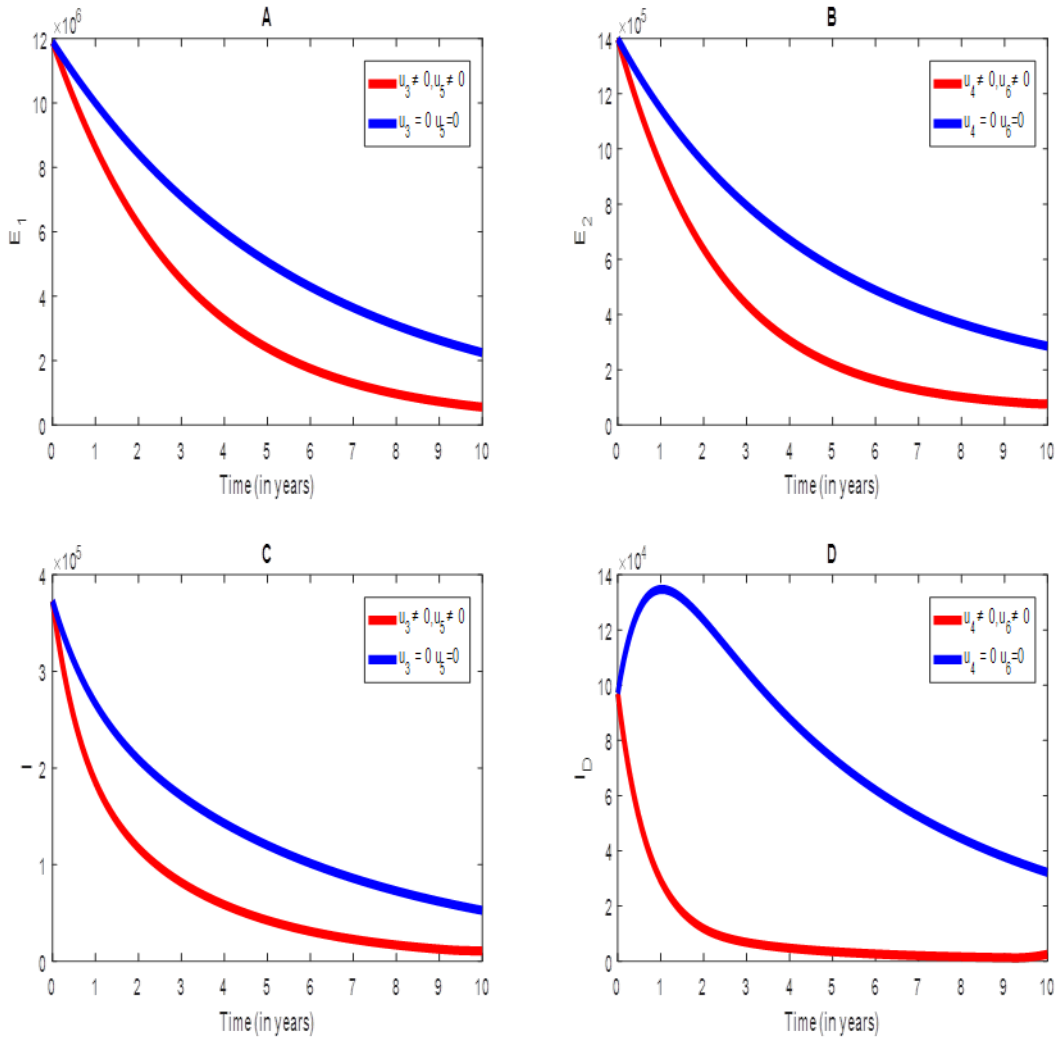

Figure 4.4: Optimal combined effect of case finding and case holding simulation results.

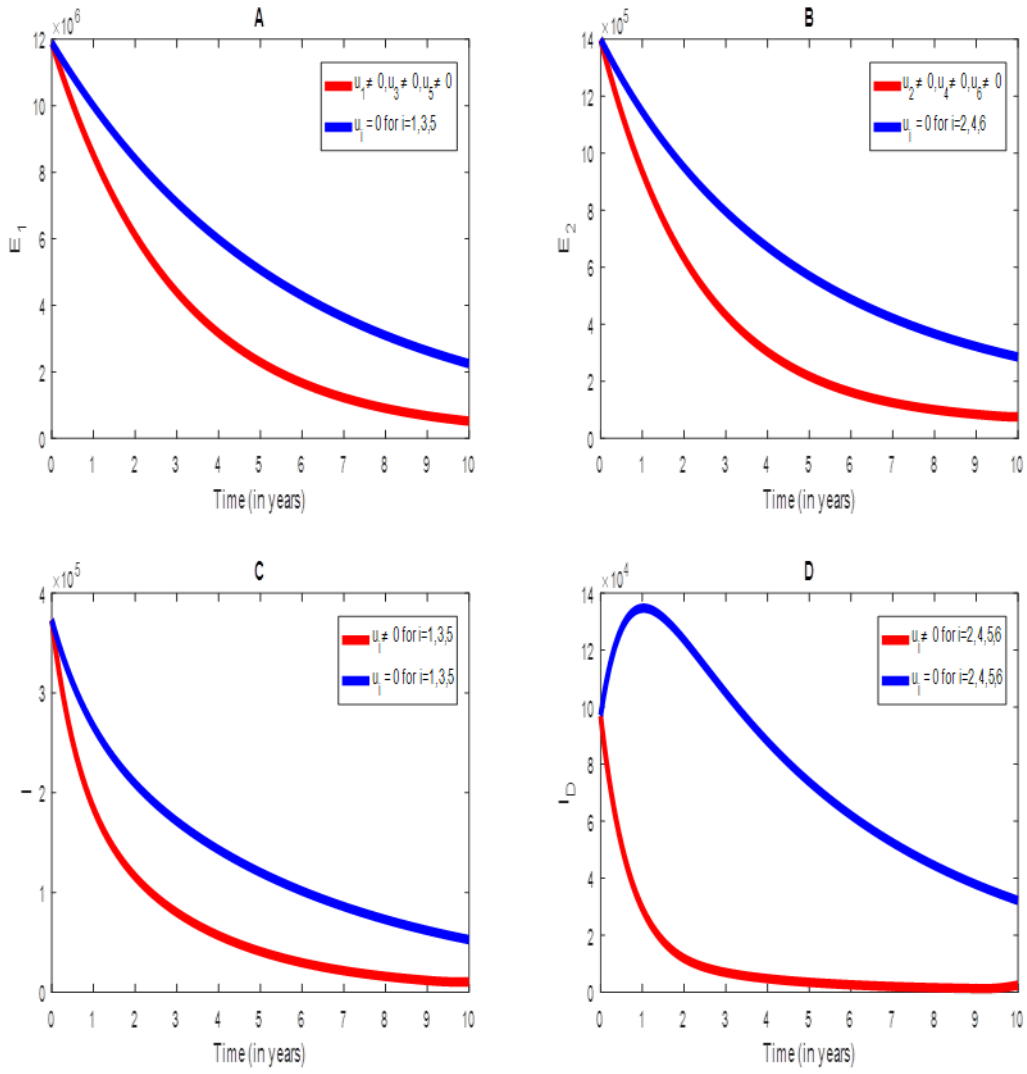

Figure 4.5: Optimal combined effect of preventive, case finding, and case holding simulation results.

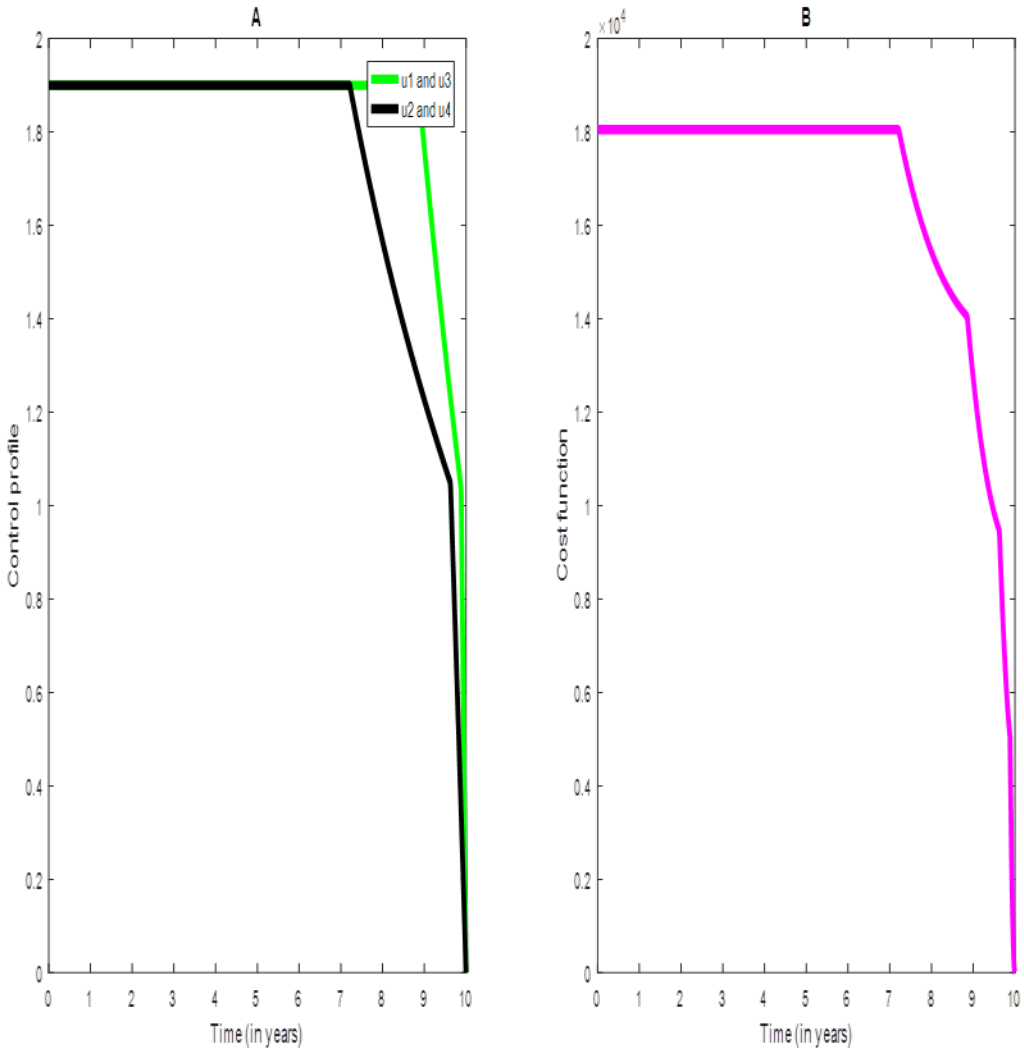

Figure 4.6: Control profiles and cost function for strategy (4.6.1).

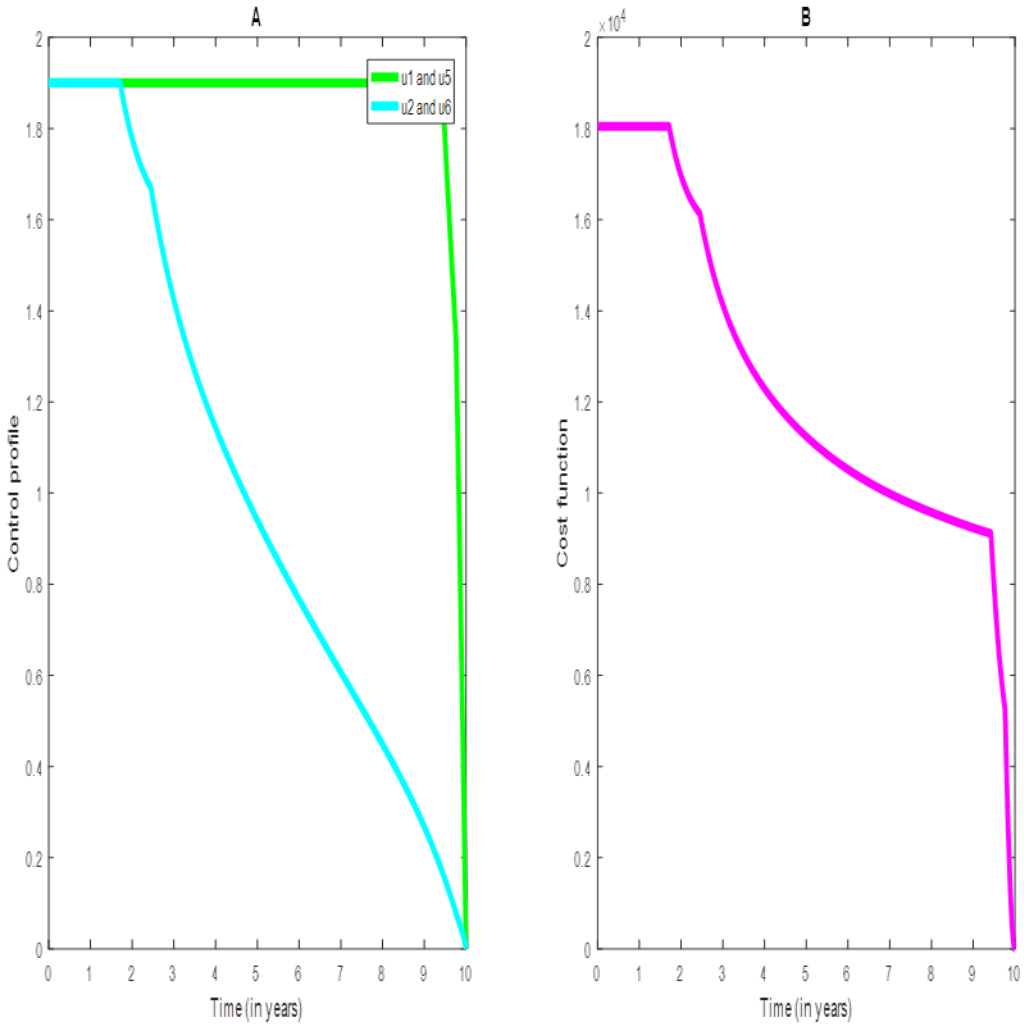

Figure 4.7: Control profiles and cost function for strategy (4.6.2).

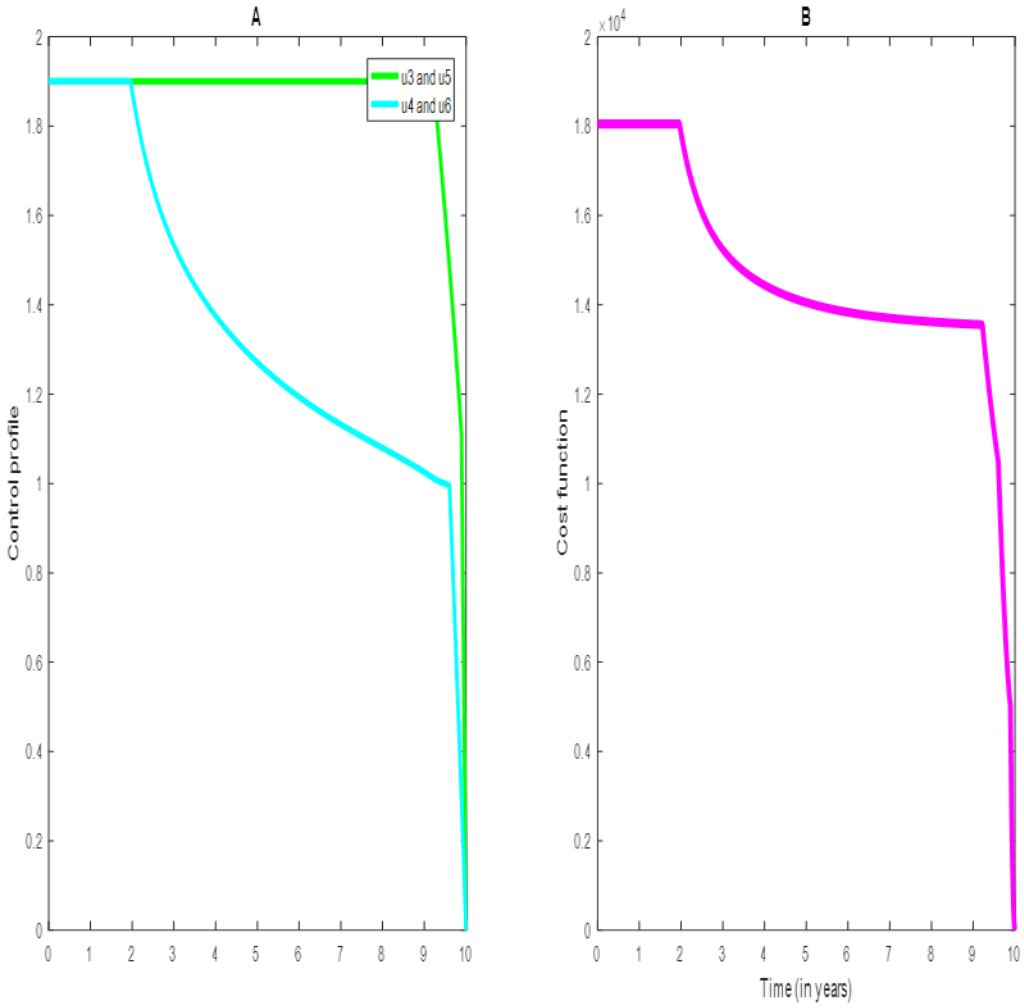

Figure 4.8: Control profiles and cost function for strategy (4.6.3).

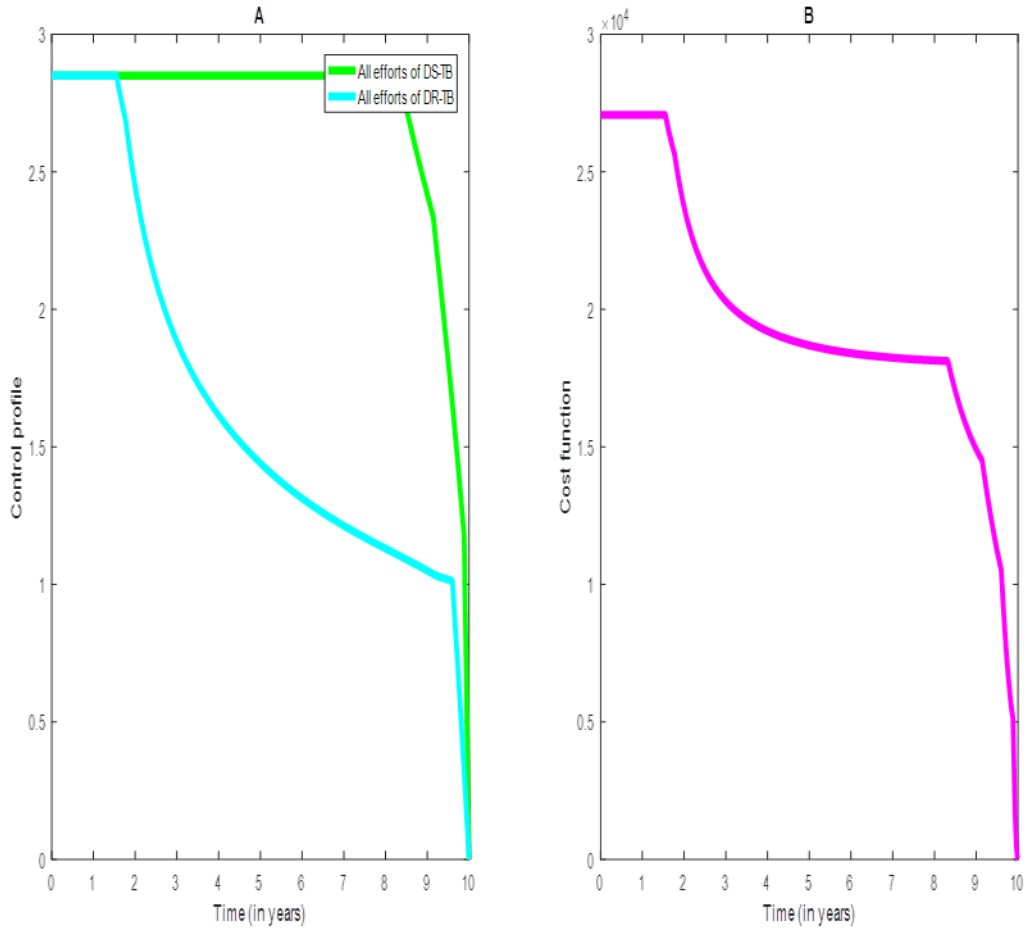

Figure 4.9: Control profiles and cost function for strategy (4.6.4).

Chapter 5

A co-infection model of HIV and TB diseases

5.1 Introduction

HIV/TB co-infection is an infection caused by both HIV and TB. TB disease is contemplated as AIDS-defining situation in HIV-infected people. The situation is a severe infection that can be life-threatening in patients. Similarly HIV can accelerate the rate of TB infection, which can rouse the latent TB progress to TB disease. This disease affects many parts of the world and becomes a global burden including Ethiopia. This dual infection disease needs more exploration and the research communities have to put forward effective control measures from different perspectives. The best investigation here is we can discover the transmission dynamics and prospect preventive and control strategies of the disease from a mathematical modelling view point.
Mathematical models are very crucial to study such types of problems. Lots of components are necessary to develop a model about this dual epidemic and the concept of optimal control theory is a backbone to analyzing the suggesting control efforts optimally. The ICER calculation in this study can give the best cost-effective strategy against the burden of TB and HIV/AIDS dual epidemics.

5.2 Mathematical model of TB-HIV/AIDS co-infection diseases

Model assumptions

- The susceptible people enter into the population (N) at a constant rate π.
- Individual with latent TB are not infectious and cannot transmit TB infection.

- Individuals infected with TB cannot fully recover, but to latent TB.
- On recovery there is temporal immunity.
- People in each compartment have equal natural death rate μ.
- Individuals co-infected with AIDS and Active TB are very ill. They have not transmitted HIV virus due to sexual intercourse.
- HIV infected Individuals under ART treatment are aware of transmitting the disease.
- At birth all individuals are equally susceptible.
- Only nuclei droplets of air can spread TB infection between infectious and susceptible people.
- The model does not incorporate vertical transmission of HIV-AIDS and immigrant individuals.
- Co-infected individuals started TB treatment before the launch of HIV treatment.
- The human population is variable.
- People leave the susceptible class only as a way of infection and leave the infected class by recovering from the infection.
- Individuals with AIDS do not completely withdraw from sexual activities due to the disease [MW09].
- The mode of HIV/AIDS transmission is via heterosexual contacts.
- Susceptible individuals cannot get HIV and TB infection concurrently at the same time.
- Low risk latent TB compartment comprises recovered individuals by treatment or naturally.

We developed the new TB-HIV co-infection model by coupling HIV/AIDS (susceptible, HIV infection with and without AIDS symptoms, and treated individuals from HIV infection) with TB model [WCJ11].
Hence, this model divided the human population into the following mutually-exclusive epidemiological compartments. Namely susceptible individuals (S), exposed (or a high-risk latent TB) (E) that is infected but not infectious individuals, infectious TB (I), and low-risk latent TB (L), HIV-infected individuals with no clinical symptoms of AIDS (H), HIV-infected people under treatment for HIV infection (T), HIV-infected individuals with AIDS clinical symptoms (A), exposed (or a

high-risk latent TB) co-infected with HIV (H_E), low risk latent TB individuals co-infected with HIV (H_L), HIV-infected individuals (pre-AIDS) co-infected with active TB disease (H_I), HIV-infected individuals with AIDS symptoms and co-infected with active TB (A_I), low risk latent TB individuals infected by HIV-infection with AIDS symptoms (A_L).

Thus, the total population at time t, denoted by N(t), is given by:

$N(t) = S(t)+E(t)+I(t)+L(t)+H(t)+A(t)+T(t)+H_E(t)+H_L(t)+H_I(t)+A_I(t)+A_L(t)$.

The susceptible population is increased by the recruitment of individuals at a rate π. These individuals acquire TB and HIV infection at a variable rate:

$\lambda_T(t) = \frac{\beta_1[I(t)+H_I(t)+A_I(t)]}{N(t)}$ and $\lambda_H(t) = \frac{\beta_2[H(t)+H_E(t)+H_L(t)+H_I(t)+\eta(A(t)+A_L(t))]}{N(t)}$ respectively.

The modification parameter η represents the relative infectiousness of people with AIDS symptoms compared to HIV infected people without AIDS symptoms. HIV-infected People (pre-AIDS) are less infectious than people with AIDS symptoms because they have lower viral load and positive relationship among infectiousness and viral load [WLG$^+$08]. The remaining model parameters are described in Table (5.1).

Parameters	Description
π	Recruitment rate
μ	Per capita natural mortality rate
β_1	TB transmission rate
β_2	HIV transmission rate
k	Per capita progression rate from class E to I
α	Treatment rate of E
σ	The relapse rate due to tubercle bacilli reactivation
$1-p$	Successful treatment rate of I
γ	TB treatment rate
$\omega_i, i = 1, 2, 5, 6$	Rate of recruitment to receive HIV treatment for H, A, H_L, and A_L respectively
ω_4, ω_7	Rate of recruitment to receive both HIV and TB treatment for H_I and A_I respectively
ω_3	Rate of recruitment to receive HIV treatment and treatment of high risk latent TB
$\omega, \theta, \epsilon_1, \epsilon_2$	Modification parameters
δ	Progression rate from H to A
ϵ	Per capita progression rate of TB from class H_E to H_I
ϕ	Fraction of individuals from H_I class that receive treatments for TB only
σ_1	HIV progression rate from H_E to A_I
δ_1	TB progression rate from H_E to A_I
θ_1	The relapse rate due to tubercle bacilli reactivation
θ_2	The recruitment rate of individuals from H_E to H_L due to treatment of latent TB
$(1-\psi)$	Successful TB treatment rate of H_I
ψ_1	Progression rate from H_I to A_I
φ	Rate of failure to properly adhere to HIV treatment rules
θ_3	Progression rate from H_L to A_L
τ	Complete treatment rate of TB from A_I to A_L
$d_i\{i = 1, 2, 3\}$	Per capita TB, HIV, and TB-HIV co-infection induced death rate

Table 5.1: Descriptions of the parameters.

The transition diagram of the model is like below.

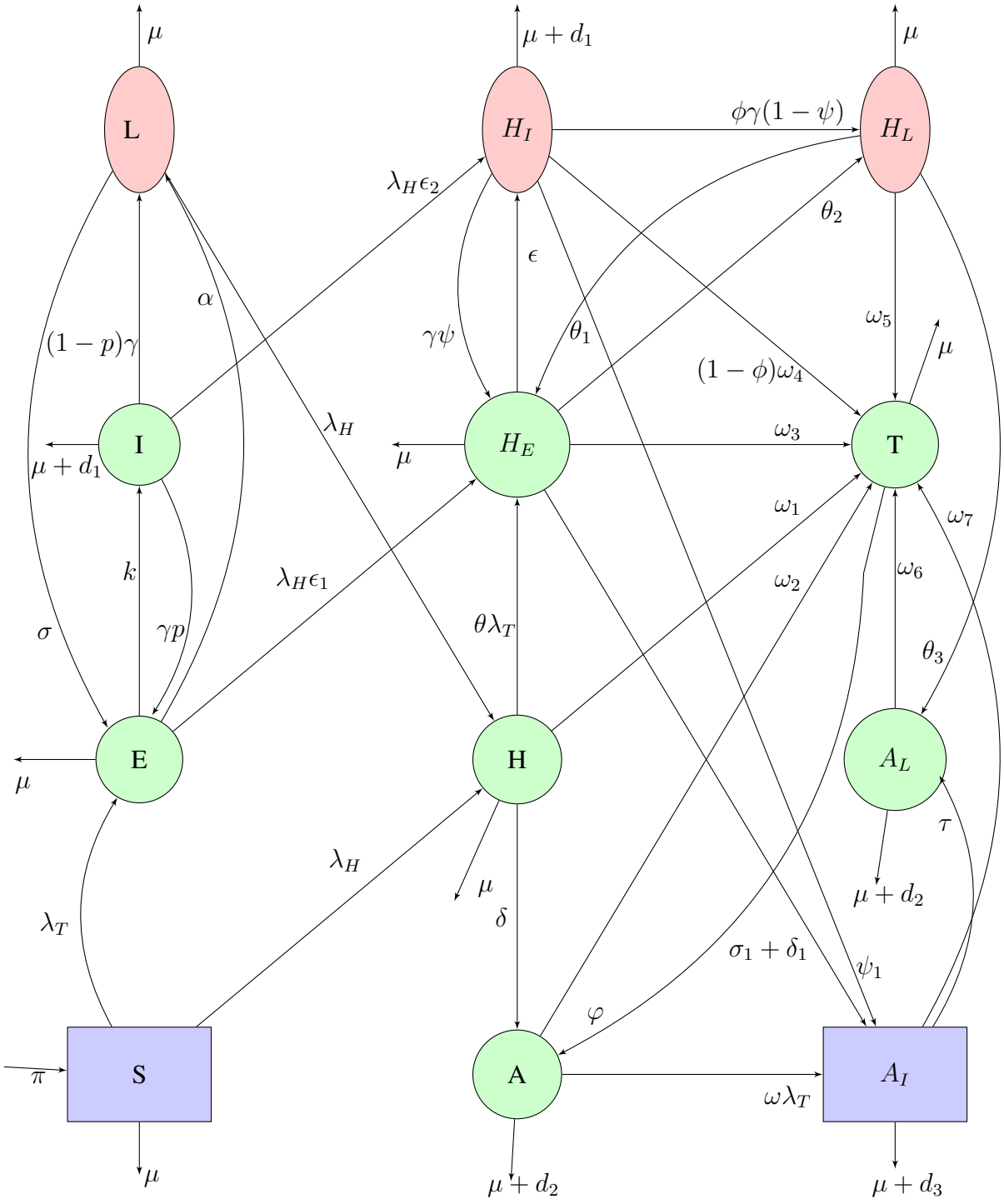

Figure 5.1: Flow diagram of the TB-HIV/AIDS transmission .

Depending on the above points mentioned, the TB-HIV transmission dynamics described by the following deterministic system of non-linear ODE.

$$\begin{cases} \frac{dS}{dt} = \pi - (\lambda_H + \lambda_T + \mu)S, \\ \frac{dE}{dt} = \lambda_T S + \gamma p I + \sigma L - (k + \alpha + \epsilon_1 \lambda_H + \mu)E, \\ \frac{dI}{dt} = kE - (\gamma + \epsilon_2 \lambda_H + d_1 + \mu)I, \\ \frac{dL}{dt} = (1-p)\gamma I + \alpha E - (\sigma + \lambda_H + \mu)L, \\ \frac{dH}{dt} = \lambda_H(S + L) - (\theta \lambda_T + \delta + \omega_1 + \mu)H, \\ \frac{dA}{dt} = \delta H + \varphi T - (\omega_2 + \omega \lambda_T + \mu + d_2)A, \\ \frac{dH_E}{dt} = \epsilon_1 \lambda_H E + \theta \lambda_T H + \psi \gamma H_I + \theta_1 H_L - (\epsilon + \omega_3 + \theta_2 + \sigma_1 + \delta_1 + \mu)H_E, \\ \frac{dH_I}{dt} = \epsilon_2 \lambda_H I + \epsilon H_E - (\psi\gamma + (1-\psi)\phi\gamma + (1-\phi)\omega_4 + \psi_1 + \mu + d_1)H_I, \\ \frac{dH_L}{dt} = (1-\psi)\phi\gamma H_I + \theta_2 H_E - (\theta_1 + \theta_3 + \omega_5 + \mu)H_L, \\ \frac{dT}{dt} = \omega_1 H + \omega_2 A + \omega_3 H_E + \omega_4(1-\phi)H_I + \omega_5 H_L + \omega_6 A_L + \omega_7 A_I - (\varphi + \mu)T, \\ \frac{dA_L}{dt} = \tau A_I + \theta_3 H_L - (\omega_6 + \mu + d_2)A_L, \\ \frac{dA_I}{dt} = (\sigma_1 + \delta_1)H_E + \psi_1 H_I + \omega \lambda_T A - (\omega_7 + \mu + d_3 + \tau)A_I, \end{cases} \tag{5.1}$$

with inital conditions

$$S(0) > 0, E(0) > 0, I(0) > 0, L(0) > 0, H(0) > 0, A(0) > 0, H_E(0) > 0, \tag{5.2}$$

$$H_I(0) > 0, H_L(0) > 0, T(0) > 0, A_L(0) > 0, A_I(0) > 0. \tag{5.3}$$

5.3 Model analysis

5.3.1 Positivity invariance and boundedness of solutions

The system of equation (5.1) expresses that human population in different compartments. Every state variable and parameters of the model are positive. Thus, the solution of each state variable with positive initial value is positive, due to M. Bodnar [Bod00] displayed that the solutions of any physical or biological model that have non-negative initial values are non-negative $\forall\ t > 0$. Moreover, the condition in which the positivity of the solution set is justifying easily similar to the method in chapter 3 and 4.

Let Ω be the biological feasible region such that $\Omega = \{(S, E, I, L, H, A,\ H_E, H_I, H_L, T,\ A_L,\ A_I) \in \mathbb{R}^{12}_+ : N \leq \frac{\pi}{\mu}\}$. The solution of every state variable in the set remains in the set. Then Ω is positive invariance.

We showed this clue by adding (5.1) simultaneously the rate of change of $N(t)$ is given by:

$$\frac{dN}{dt} = \pi - \mu N(t) - d_1 I - d_1 H_I - d_2 A - d_2 A_L - d_3 A_I. \tag{5.4}$$

Hence, the equation (5.1) which is a first order ODE is specified as follows [Jan95].

$\frac{dN}{dt} \leq \pi - \mu N(t)$,
$N(t) \leq \frac{\pi}{\mu} + e^{-\mu t}(N(0) - \frac{\pi}{\mu})$.

Here, $0 < N(0) \leq \frac{\pi}{\mu}$, then, we derived $0 < N(t) \leq \frac{\pi}{\mu}$, $\forall\ t \geq 0$. This shows that the solutions of all state variables in co-infection model (5.1) are bounded $\forall\ t > 0$.
This acknowledged the result bellow.

Lemma 5 *The region Ω is positively invariant for the model (5.1) with positive initial conditions in $\in \mathbb{R}^{12}_{+}$.*

Hereafter, we analyzed each sub model before explored the full co-infection model.

5.3.2 HIV-only model

The model that contemplates purely HIV/AIDS (found by setting $E = L = I = H_E = H_I = H_L = A_L = A_I = 0$) is arranged by:

$$\begin{cases} \frac{dS}{dt} = \pi - (\lambda_H + \mu)S, \\ \frac{dH}{dt} = \lambda_H S - (\delta + \omega_1 + \mu)H, \\ \frac{dA}{dt} = \delta H + \varphi T - (\omega_2 + \mu + d_2)A, \\ \frac{dT}{dt} = \omega_1 H + \omega_2 A - (\varphi + \mu)T, \end{cases} \tag{5.5}$$

where $\lambda_H(t) = \frac{\beta_2[H(t)+\eta A(t)]}{N(t)}$ and $N(t) = S(t) + H(t) + A(t) + T(t)$. Let Ω_A be the set such that $\Omega_A = \{(S, E, H, A, T \in \mathbb{R}^4_+ : N \leq \frac{\pi}{\mu}\}$, then similar to lemma (5) we can show that Ω_A is positively invariant and attracting.

5.3.3 Local stability of disease free equlibrum

In the absence of HIV infection, we obtained the DFE of HIV only sub-model (5.5) by equating the right-hand side of this system to be zero and is given by $E_0 = (\frac{\pi}{\mu}, 0, 0, 0)$.

Theorem 21 *The DFE point of system (5.5) is locally asymptotically stable (LAS) if $R_H < 1$ and unstable if $R_H > 1$.*

Proof:

Firstly, find the basic reproduction number R_H which is the spectral radius of the matrix FV^{-1}, where F is the matrix of new infection terms given by:

$$F = \begin{bmatrix} \frac{\beta_2\pi}{N\mu} & \frac{\beta_2\eta\pi}{N\mu} & 0 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{bmatrix} = \begin{bmatrix} \beta_2 & \beta_2\eta & 0 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{bmatrix} \text{ and}$$

V is the matrix of remaining transfer terms given by:

$$V = \begin{bmatrix} \delta+\omega_1+\mu & 0 & 0 \\ -\delta & \omega_2+d_2+\mu & -\varphi \\ -\omega_1 & -\omega_2 & (\varphi+\mu) \end{bmatrix} \text{ at DFE point [VdDW02].}$$

Now, the inverse of V is calculated, which is:

$$V^{-1} = \begin{bmatrix} \frac{1}{A} & 0 & 0 \\ \frac{\delta}{AB} - \frac{\varphi(\delta\omega_2+\omega_1 B)}{AB(\varphi\omega_2-CB)} & \frac{1}{B} - \frac{\omega_2\varphi}{B(\varphi\omega_2-CB)} & \frac{-\varphi}{\varphi\omega_2-CB} \\ \frac{\delta\omega_2+\omega_1 B}{A(\varphi\omega_2-CB)} & \frac{-\omega_2}{\varphi\omega_2-CB} & \frac{-B}{\varphi\omega_2-CB} \end{bmatrix},$$

where

$$A = \delta+\omega_1+\mu, B = \omega_2+d_2+\mu, C = \varphi+\mu. \tag{5.6}$$

The dominant eigenvalue of FV^{-1} is the basic reproduction number R_H which is simplified to:

$$R_H = \frac{\beta_2}{(\delta+\omega_1+\mu)}[1 + \frac{\eta(\delta\varphi+\delta\mu+\omega_1\varphi)}{\varphi d_2+\varphi\mu+\omega_2\mu+d_2\mu+\mu^2}].$$

Now, the jacobian matrix of the system (5.5) at DFE point is given by:

$$J(\tfrac{\pi}{\mu},0,0,0) = \begin{bmatrix} -\mu & -\beta_2 & -\beta_2\eta & 0 \\ 0 & \beta_2-(\delta+\omega_1+\mu) & \beta_2\eta & 0 \\ 0 & \delta & -(\omega_2+d_2+\mu) & \varphi \\ 0 & \omega_1 & \omega_2 & -(\varphi+\rho) \end{bmatrix}.$$

Secondly, we calculate the eigenvalues of this matrix as follows.

$$\begin{vmatrix} -\mu-\lambda & -\beta_2 & -\beta_2\eta & 0 \\ 0 & [\beta_2-(\delta+\omega_1+\mu)]-\lambda & \beta_2\eta & 0 \\ 0 & \delta & -(\omega_2+d_2+\mu)-\lambda & \varphi \\ 0 & \omega_1 & \omega_2 & -(\varphi+\rho)-\lambda \end{vmatrix} = 0.$$

$$\Longrightarrow \begin{vmatrix} -\mu-\lambda & -\beta_2 & -\beta_2\eta & 0 \\ 0 & [\beta_2-A]-\lambda & \beta_2\eta & 0 \\ 0 & \delta & -B-\lambda & \varphi \\ 0 & \omega_1 & \omega_2 & -C-\lambda \end{vmatrix} = 0.$$

$$\Longrightarrow -\mu-\lambda \begin{vmatrix} [\beta_2-A]-\lambda & \beta_2\eta & 0 \\ \delta & -B-\lambda & \varphi \\ \omega_1 & \omega_2 & -C-\lambda \end{vmatrix} = 0.$$

Finally, we obtain a third order polynomial equation like below.

$(-\mu-\lambda)[\lambda^3+\lambda^2(A+B+C-\beta_2)+\lambda(BA+BC+AC-B\beta_2-\delta\beta_2-\omega_2\varphi-C\beta_2)+ABC-CB\beta_2-\delta\beta_2+\varphi\omega_2\beta_2-\omega_2\varphi A-\omega_1\varphi\eta\beta_2=0]$.

$\Longrightarrow -\mu-\lambda=0 \Longrightarrow \lambda_1=-\mu<0$ or

$$\lambda^3+\lambda^2(A+B+C-\beta_2)+\lambda(BA+BC+AC-B\beta_2-\delta\beta_2-\omega_2\varphi-C\beta_2)+$$
$$ABC-CB\beta_2-\delta\beta_2+\varphi\omega_2\beta_2-\omega_2\varphi A-\omega_1\varphi\eta\beta_2=0. \tag{5.7}$$

The equation (5.7) has the form:

$A_0\lambda^3+A_1\lambda^2+A_2\lambda+A_3=0$, where

$A_0=1, \quad A_1=A+B+C-\beta_2, \quad A_2=BA+BC+AC-B\beta_2-\delta\beta_2-\omega_2\varphi-C\beta_2$ and

$A_3=ABC-CB\beta_2-\delta\beta_2+\varphi\omega_2\beta_2-\omega_2\varphi A-\omega_1\varphi\eta\beta_2$.

$$= A(\varphi\omega_2-BC)[1-\tfrac{\beta_2(\varphi\omega_2-CB-\eta\delta C-\eta\omega_1\varphi)}{A(\varphi\omega_2-CB)}].$$

$= (d_2\varphi+\mu^2+\mu\varphi+\mu d_2+\omega_2\varphi)[1-R_H]>0$, if $R_H<1$.

Applying the Routh–Hurwitz criterion [All08], it can be shown that the eigenvalues of the 3×3 Jacobin matrix (the roots of the characteristic polynomial $P(\lambda)=\lambda^3+A_1\lambda^2+A_2\lambda+A_3$) have negative real parts, if $R_H<1$.

Hence, DFEP E_0 is locally asymptotically stable if $R_H<1$ and unstable if $R_H>1$.

5.3.4 Global stability of the DFE, E_0

The global stability of the DFE can be explored by using the method in [CCBVdD$^+$02]. The model (5.5) can be expressed likes bellow :

$$\begin{cases} \frac{dX_s}{dt}=Q(X_s-X_{DFE,s})+Q_1X_i, \\ \frac{dX_i}{dt}=Q_2X_i, \end{cases} \tag{5.8}$$

where X_s and X_i are vectors which designates the non-transferring and transferring compartments. If Q has real negative eigenvalues and Q_2 is a Metzler matrix, then the DFE is globally asymptotically stable (GAS).

Thus, $X_s = (S, T)^T$, $X_i = (I, A)^T$, and

$X_s - X_{DFE,s} = \begin{bmatrix} S \\ T \end{bmatrix} - \begin{bmatrix} \frac{\pi}{\mu} \\ 0 \end{bmatrix} = \begin{bmatrix} S - \frac{\pi}{\mu} \\ T \end{bmatrix}$.

Now, the following matrices are constructed from X_s and X_i vectors.

$Q = \begin{bmatrix} -\mu & 0 \\ 0 & -(\varphi + \mu) \end{bmatrix}$,

$Q_1 = \begin{bmatrix} -\beta_2 \frac{S}{N(t)} & -\beta_2 \eta \\ \omega_1 & \omega_2 \end{bmatrix}$, and $Q_2 = \begin{bmatrix} -(\delta + \omega_1 + \mu) & 0 \\ \delta & -(\omega_2 + d_2 + \mu) \end{bmatrix}$.

As a result, the eigenvalues of Q are negative and real infers that the system $\frac{dX_s}{dt} = Q(X_s - X_{DFE,s}) + Q_1 X_i$ is GAS at DFE.

5.3.5 Endemic equilibrium

The endemic equilibrium (EE) point can be obtained by make it zero for the right side of the equations (5.5), where the disease is persist in the population.

Thus,

$$\frac{dS}{dt} = \pi - (\lambda_H + \mu)S = 0, \tag{5.9}$$

$$\frac{dH}{dt} = \lambda_H S - (\delta + \omega_1 + \mu)H = 0, \tag{5.10}$$

$$\frac{dA}{dt} = \delta H + \varphi T - (\omega_2 + \mu + d_2)A = 0, \tag{5.11}$$

$$\frac{dT}{dt} = \omega_1 H + \omega_2 A - (\varphi + \mu)T = 0. \tag{5.12}$$

Therefore, the solutions are

$S^* = \frac{\pi}{\lambda_H^* + \mu}$, $H^* = \frac{\lambda_H^* S^*}{\delta + \omega_1 + \mu}$, $A^* = \frac{\delta H^* + \varphi T^*}{\omega_2 + \mu + d_2}$, and $T^* = \frac{\omega_1 H^* + \omega_2 A^*}{\varphi + \mu}$, where $\lambda_H^*(t) = \frac{\beta_2 [H^*(t) + \eta A^*(t)]}{N^*(t)}$ and $N^*(t) = S^*(t) + H^*(t) + A^*(t) + T^*(t)$.

Therefore, the EE point say $E_1 = (S^*, H^*, A^*, T^*)$.

Lemma 6 *A unique endemic equilibrium point E_1 exist if $R_H > 1$.*

Proof.

If the disease is endemic in the community, then $\exists\ t^* > 0$ such that $\frac{dH(t^*)}{dt} > 0, \frac{dT(t^*)}{dt} > 0$ and $\frac{dA(t^*)}{dt} > 0$. Thus, keeping the state variables H, T and A at t^*, the system (5.5) becomes:

$$\begin{cases} \frac{dH}{dt} &= \lambda_H S - (\delta + \omega_1 + \mu)H > 0, \\ \frac{dA}{dt} &= \delta H + \varphi T - (\omega_2 + \mu + d_2)A > 0, \\ \frac{dT}{dt} &= \omega_1 H + \omega_2 A - (\varphi + \mu)T > 0. \end{cases} \tag{5.13}$$

This becomes,

$$\begin{cases} (\delta + \omega_1 + \mu)H < \lambda_H S = (\frac{\beta_2[H(t)+\eta A(t)]}{N(t)})S, \\ (\omega_2 + \mu + d_2)A < \delta H + \varphi T, \\ (\varphi + \mu)T < \omega_1 H + \omega_2 A. \end{cases} \tag{5.14}$$

From the fact that $\frac{S}{N(t)} \leq 1$. Thus (5.14) gives:

$$\begin{cases} (\delta + \omega_1 + \mu)H < \beta_2[H(t) + \eta A(t)], \\ (\omega_2 + \mu + d_2)A < \delta H + \varphi T, \\ (\varphi + \mu)T < \omega_1 H + \omega_2 A. \end{cases} \tag{5.15}$$

Next, multiplying the second and the third equation of (5.15) with $(\varphi + \mu)$ and φ respectively, then add vertically gives:

$$A < \frac{\delta(\varphi + \mu) + \omega_1 \varphi}{(\varphi + \mu)(\omega_2 + \mu + d_2) - \omega_2 \varphi} H. \tag{5.16}$$

Substitute (5.16) to the first equation of (5.15), we obtained the following inequality.

$(\delta + \omega_1 + \mu)H(t) < \beta_2[H(t) + \eta(\frac{\delta(\varphi+\mu)+\omega_1\varphi}{(\varphi+\mu)(\omega_2+\mu+d_2)-\omega_2\varphi})H(t)].$

$\Longrightarrow AH(t) < \beta_2[H(t) + \eta(\frac{\delta C+\omega_1\varphi}{CB-\omega_2\varphi})]H(t).$

$\Longrightarrow 1 < \frac{\beta_2}{A}[1 + \eta(\frac{\delta C+\omega_1\varphi}{CB-\omega_2\varphi})].$

$\Longrightarrow 1 < \frac{\beta_2}{A}[1 + \eta(\frac{\delta C+\omega_1\varphi}{CB-\omega_2\varphi})] = R_H$.

$\Longrightarrow \qquad R_H > 1$.

This completes the proof.

5.3.6 Global stability of the EE point

Theorem 22 *The endemic equilibrium (E_1) of model (5.5) is globally asymptotically stable (GAS) on $\mathbb{R}^4_{+0}$ if $R_H > 1$.*

Proof: We applied the procedure of Lyapunov functions.

Set the Lyapunov function

$G = (S - S^* - S^* \ln \frac{S}{S^*}) + (H - H^* - H^* \ln \frac{H}{H^*}) + (A - A^* - A^* \ln \frac{A}{A^*}) + (T - T^* - T^* \ln \frac{T}{T^*})$.

Such form of Lyapunov function has been stated in [MLL03, Hou18].

Now, $\frac{dG}{dt} = G' = (\frac{S-S^*}{S})S' + (\frac{H-H^*}{H})H' + (\frac{A-A^*}{A})A' + (\frac{T-T^*}{T})T'$

$= (\frac{S-S^*}{S})[\pi - (\lambda_H + \mu)S] + (\frac{H-H^*}{H})[\lambda_H S - (\delta + \omega_1 + \mu)H] + (\frac{A-A^*}{A})[\delta H + \varphi T - (\omega_2 + \mu + d_2)A] + (\frac{T-T^*}{T})[\omega_1 H + \omega_2 A - (\varphi + \mu)T]$

$= (1 - \frac{S^*}{S})[\pi - (\lambda_H + \mu)S] + (1 - \frac{H^*}{H})[\lambda_H S - (\delta + \omega_1 + \mu)H] + (1 - \frac{A^*}{A})[\delta H + \varphi T - (\omega_2 + \mu + d_2)A] + (1 - \frac{T^*}{T})[\omega_1 H + \omega_2 A - (\varphi + \mu)T]$

$= [\pi - (\lambda_H + \mu)S] - \frac{S^*}{S}[\pi - (\lambda_H + \mu)S] + [\lambda_H S - (\delta + \omega_1 + \mu)H] - \frac{H^*}{H}[\lambda_H S - (\delta + \omega_1 + \mu)H] + [\delta H + \varphi T - (\omega_2 + \mu + d_2)A] - \frac{A^*}{A}[\delta H + \varphi T - (\omega_2 + \mu + d_2)A] + [\omega_1 H + \omega_2 A - (\varphi + \mu)T] - \frac{T^*}{T}[\omega_1 H + \omega_2 A - (\varphi + \mu)T]$

$= [\pi + S^*(\lambda_H + \mu) + \lambda_H S + H^*(\delta + \omega_1 + \mu) + \delta H + \varphi T + A^*(\omega_2 + \mu + d_2) + \omega_1 H + \omega_2 A + T^*(\varphi + \mu)] - [(\lambda_H + \mu)S + \frac{S^*}{S}\pi + (\delta + \omega_1 + \mu)H + \frac{H^*}{H}\lambda_H S + (\omega_2 + \mu + d_2)A + \frac{A^*}{A}(\delta H + \varphi T) + (\varphi + \mu)T + \frac{T^*}{T}(\omega_1 H + \omega_2 A)]$

Thus $G' = \frac{dG}{dt} = X - Y$, where

$X = [\pi + S^*(\lambda_H + \mu) + \lambda_H S + H^*(\delta + \omega_1 + \mu) + \delta H + \varphi T + A^*(\omega_2 + \mu + d_2) + \omega_1 H + \omega_2 A + T^*(\varphi + \mu)]$

and

$Y = [(\lambda_H + \mu)S + \frac{S^*}{S}\pi + (\delta + \omega_1 + \mu)H + \frac{H^*}{H}\lambda_H S + (\omega_2 + \mu + d_2)A + \frac{A^*}{A}(\delta H + \varphi T) + (\varphi + \mu)T + \frac{T^*}{T}(\omega_1 H + \omega_2 A)]$

Here X and y are positive, then $\frac{dG}{dt} = X - Y < 0$, when $X < Y$ and $\frac{dG}{dt} = 0$, when $S = S^*, H = H^*, A = A^*$, and $T = T^*$ in Ω

Hence, the largest compact invariant set in $\{(S^*, H^*, A^*, T^*) \in \Omega : \frac{dG}{dt} = 0\}$ is the singleton EEP E_1. By LaSalles invariant principle [LaS76], it implies that E_1 is globally asymptotically stable on $\mathbb{R}^4_{+0}$ if $X < Y$.

5.3.7 TB-only model

The sub-model of (5.1) with no HIV/AIDS disease, that is, $H_I, H_E, H, A, H_L, T, A_L, A_I = 0$, is expressed by:

$$\begin{cases} \frac{dS}{dt} = \pi - (\lambda_T + \mu)S, \\ \frac{dE}{dt} = \lambda_T S + \gamma p I + \sigma L - (k + \alpha + \mu)E, \\ \frac{dI}{dt} = kE - (\gamma + d_1 + \mu)I, \\ \frac{dL}{dt} = (1-p)\gamma I + \alpha E - (\sigma + \mu)L, \end{cases} \tag{5.17}$$

where $\lambda_T = \frac{\beta_1 I(t)}{N(t)}$ and $N(t) = S(t) + E(t) + I(t) + L(t)$.
The model (5.17) was formulated and analysed in [WCJ11]. The basic reproduction number of this model is calculated by the usual approach.

$$R_T = \beta_1 [\frac{k(\sigma+\mu)}{(k+\alpha+\mu)(\gamma+d_1+\mu)(\sigma+\mu) - kp\gamma\mu - \alpha\sigma(\gamma+d_1+\mu) - k\sigma\gamma}].$$

Moreover, the existence, uniqueness, and stability of equlibra point are proven in [KMW19].

5.3.8 Analysis of the full model

We now study the full model (2.1), with the DFEP expressed by:
$\varepsilon_0 = (S^0, E^0, I^0, L^0, H^0, A^0, H_E^0, H_I^0, H_L^0, T^0, A_L^0, A_I^0) = (\frac{\pi}{\mu}, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0)$.
The associated matrices F and V are expressed as follows.

$$F = \begin{bmatrix} F_1 & F_2 \end{bmatrix}$$

with $F_1 = \begin{bmatrix} 0 & 0 & 0 & 0 & 0 & 0 \\ \lambda_T & 0 & \frac{\beta_1 S}{N} & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ \lambda_H & 0 & 0 & \lambda_H & \frac{\beta_2(S+L)}{N} & \frac{\beta_2\eta(S+L)}{N} \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & \epsilon_1\lambda_H & 0 & 0 & \theta\lambda_T & 0 \\ 0 & 0 & \epsilon_2\lambda_H & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & \frac{\beta_1 A}{N} & 0 & 0 & \omega\lambda_T \end{bmatrix}$,

$$F_2 = \begin{bmatrix} 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & \frac{\beta_1 S}{N} & 0 & 0 & 0 & \frac{\beta_1 S}{N} \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ \frac{\beta_2(S+L)}{N} & \frac{\beta_2(S+L)}{N} & \frac{\beta_2(S+L)}{N} & 0 & \eta\frac{\beta_2(S+L)}{N} & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & \frac{\beta_1 A}{N} & 0 & 0 & 0 & \frac{\beta_1 A}{N} \end{bmatrix} \text{ and } V = \begin{bmatrix} V_1 & V_2 \end{bmatrix} \text{ with}$$

$$V_1 = \begin{bmatrix} \lambda_T + \lambda_T + \mu & 0 & \frac{\beta_1 S}{N} & 0 & \frac{\beta_2 S}{N} & \eta\frac{\beta_2 S}{N} \\ 0 & (k + \alpha + \epsilon_1\lambda_H + \mu) & -\gamma p & -\sigma & 0 & 0 \\ 0 & -k & (\gamma\epsilon_2\lambda_H + d_1 + \mu) & 0 & \frac{\epsilon_2\beta_2 I}{N} & \eta\frac{\epsilon_2\beta_2 I}{N} \\ 0 & -\alpha & -(1-p)\gamma & \sigma + \mu + \lambda_H & \frac{\beta_2 L}{N} & \frac{\beta_2 L}{N} \\ 0 & 0 & \theta\frac{\beta_1 H}{N} & 0 & \theta\lambda_T + \delta + \omega_1 + \mu & 0 \\ 0 & 0 & \frac{\omega\beta_1 A}{N} & 0 & -\delta & U \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & -\omega_1 & -\omega_2 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \end{bmatrix},$$

$$V_2 = \begin{bmatrix} \frac{\beta_2 S}{N} & \frac{\beta_2 S}{N} & \frac{\beta_2 S}{N} & 0 & \eta\frac{\beta_2 S}{N} & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ \epsilon_2\frac{\beta_2 I}{N} & \epsilon_2\frac{\beta_2 I}{N} & \epsilon_2\frac{\beta_2 I}{N} & 0 & \eta\epsilon_2\frac{\beta_2 I}{N} & 0 \\ \frac{\beta_2 L}{N} & \frac{\beta_2 L}{N} & \frac{\beta_2 L}{N} & 0 & \eta\frac{\beta_2 L}{N} & 0 \\ 0 & \theta\frac{\beta_1 H}{N} & 0 & 0 & 0 & \theta\frac{\beta_1 H}{N} \\ 0 & \frac{\omega\beta_1 A}{N} & 0 & -\varphi & 0 & \frac{\omega\beta_1 A}{N} \\ M & -\psi\gamma & -\theta_1 & 0 & 0 & 0 \\ -\epsilon & P & 0 & 0 & 0 & 0 \\ -\theta_2 & {}(1-\psi)\gamma\phi & -(\theta_1+\theta_3+\omega_5+\mu) & 0 & 0 & 0 \\ -\omega_3 & -\omega_4(1-\phi) & -\omega_5 & (\varphi+\mu) & -\omega_6 & -\omega_7 \\ 0 & 0 & -\theta_3 & 0 & (\omega_6+d_2+\mu) & -\tau \\ -(\sigma_1+\delta_1) & -\psi_1 & 0 & 0 & 0 & (\omega_7+\tau+d_3+\mu) \end{bmatrix},$$

where $M = \epsilon + \omega_3 + \theta_2 + \sigma_1 + \delta_1 + \mu$ and $P = \gamma(\psi + \phi - \psi\phi) + \omega_4(1-\phi) + \psi_1 + \mu + d_1$.

The spectral radius of the matrix FV^{-1} at ε_0 are:

$R_1 = \frac{\beta_2}{A}[1 + \frac{\eta(\delta C + \omega_1\varphi)}{CB - \varphi\omega_2}] = R_H$ and

$R_2 = \frac{\beta_1 k(\sigma+\mu)}{(k+\alpha+\mu)(\gamma+d_1+\mu)(\sigma+\mu) - kp\gamma\mu - \alpha\sigma(\gamma+d_1+\mu) - k\sigma\gamma} = R_T.$

Hence, the control reproduction number of (5.1) is expressed by:

$R_0 = max\{R_H, R_T\}$ justified in [VdDW02].

5.3.9 Local stability of DFE point

Theorem 23 *The DFE of the full HIV-TB model (5.1) is LAS if $R_0 < 1$, and unstable if $R_0 > 1$.*

Proof.

The Jacobian matrix of the model at the DFE point is;

$J(\frac{\pi}{\mu}, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0) = \begin{bmatrix} J_1 & J_2 \end{bmatrix}$, with

$$J_1(\varepsilon_0) = \begin{bmatrix} -\mu & 0 & -\beta_1 & 0 & -\beta_2 & -\beta_2\eta \\ 0 & -(k+\alpha+\mu) & \gamma p + \beta_1 & \sigma & 0 & 0 \\ 0 & k & -(\gamma+d_1+\mu) & 0 & 0 & 0 \\ 0 & \alpha & (1-p)\gamma & -(\sigma+\mu) & 0 & 0 \\ 0 & 0 & 0 & 0 & \beta_2 - (\delta+\omega_1+\mu) & \beta_2\eta \\ 0 & 0 & 0 & 0 & \delta & -(d_2+\omega_2+\mu) \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & \omega_1 & \omega_2 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \end{bmatrix},$$

$J_2(\varepsilon_0) =$

$$\begin{bmatrix} -\beta_2 & -(\beta_2+\beta_1) & -\beta_2 & 0 & -\beta_2\eta & -\beta_1 \\ 0 & \beta_1 & 0 & 0 & 0 & \beta_1 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ \beta_2 & \beta_2 & \beta_2 & 0 & \eta\beta_2 & 0 \\ 0 & 0 & 0 & \varphi & 0 & 0 \\ -M & \psi\gamma & \theta_1 & 0 & 0 & 0 \\ \epsilon & -P & 0 & 0 & 0 & 0 \\ \theta_2 & (1-\psi)\phi\gamma & -(\theta_1+\theta_3+\omega_5+\mu) & 0 & 0 & 0 \\ \omega_3 & \omega_4(1-\phi) & \omega_5 & -(\varphi+\mu) & \omega_6 & \omega_7 \\ 0 & 0 & \theta_3 & 0 & -(\omega_6+d_2+\mu) & \tau \\ (\sigma_1+\delta_1) & \psi_1 & 0 & 0 & 0 & -(\omega_7+d_3+\tau+\mu) \end{bmatrix}.$$

Afterwards, we get the eigenvalues of J in this way.

$$= \begin{vmatrix} -\mu-\lambda & 0 & -\beta_1 & 0 & -\beta_2 & -\beta_2\eta \\ 0 & -(k+\alpha+\mu)-\lambda & \gamma p+\beta_1 & \sigma & 0 & 0 \\ 0 & k & -(\gamma+d_1+\mu)-\lambda & 0 & 0 & 0 \\ 0 & \alpha & (1-p)\gamma & -(\sigma+\mu)-\lambda & 0 & 0 \\ 0 & 0 & 0 & 0 & \beta_2-A-\lambda & \beta_2\eta \\ 0 & 0 & 0 & 0 & \delta & -B-\lambda \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & \omega_1 & \omega_2 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \end{vmatrix},$$

$$\begin{vmatrix} -\beta_2 & -(\beta_2+\beta_1) & -\beta_2 & 0 & -\beta_2\eta & -\beta_1 \\ 0 & \beta_1 & 0 & 0 & 0 & \beta_1 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ \beta_2 & \beta_2 & \beta_2 & 0 & \eta\beta_2 & 0 \\ 0 & 0 & 0 & \varphi & 0 & 0 \\ -M-\lambda & \psi\gamma & \theta_1 & 0 & 0 & 0 \\ \epsilon & -P-\lambda & 0 & 0 & 0 & 0 \\ \theta_2 & (1-\psi)\phi\gamma & -(\theta_1+\theta_3+\omega_5+\mu)-\lambda & 0 & 0 & 0 \\ \omega_3 & \omega_4(1-\phi) & \omega_5 & -C-\lambda & \omega_6 & \omega_7 \\ 0 & 0 & \theta_3 & 0 & -(\omega_6+d_2+\mu)-\lambda & \tau \\ (\sigma_1+\delta_1) & \psi_1 & 0 & 0 & 0 & -(\omega_7+d_3+\tau+\mu)-\lambda \end{vmatrix} =$$

0.

After huge calculations, we get the following result.

$(\mu+\lambda)(J+\lambda)(H+\lambda)[\epsilon\psi\gamma(G+\lambda)+\epsilon\theta_1(1-\psi)\phi\gamma+(P+\lambda)(\theta_1\theta_2-(M+\lambda)(G+\lambda))][(\beta_2-A-\lambda)((B+\lambda)(C+\lambda)-\varphi\omega_2)+\beta_2\eta(\delta(C+\lambda)+\varphi\omega_1)][k((\gamma p+\beta_1)(\sigma+\mu+\lambda)+\sigma(1-p)\gamma)-(F+\lambda)((E+\lambda)(\sigma+\mu+\lambda)-\alpha\sigma)]=0$, where

$A=\delta+\omega_1+\mu, B=\omega_2+d_2+\mu, C=\varphi+\mu, E=k+\alpha+\mu, F=\gamma+d_1+\mu, G=\theta_1+\theta_3+\omega_5+\mu, H=\omega_6+d_2+\mu, J=\omega_7+d_3+\tau+\mu.$

The above equation becomes:

$(\mu+\lambda)(J+\lambda)(H+\lambda)=0\Longrightarrow\lambda=-\mu<0$ or $\lambda=-J<0$ or $\lambda=-H<0$ or

$$\epsilon\psi\gamma(G+\lambda)+\epsilon\theta_1(1-\psi)\phi\gamma+(P+\lambda)(\theta_1\theta_2-(M+\lambda)(G+\lambda))=0. \tag{5.18}$$

$$(\beta_2-A-\lambda)((B+\lambda)(C+\lambda)-\varphi\omega_2)+\beta_2\eta(\delta(C+\lambda)+\varphi\omega_1)=0. \tag{5.19}$$

$$k((\gamma p+\beta_1)(\sigma+\mu+\lambda)+\sigma(1-p)\gamma)-(F+\lambda)((E+\lambda)(\sigma+\mu+\lambda)-\alpha\sigma)=0. \tag{5.20}$$

The system (5.18) is simplified to:

$\lambda^3+\lambda^2(P+M+G)+\lambda(PM+PG+MG-\theta_1\theta_2-\epsilon\psi\gamma)+PMG+\epsilon\theta_1\psi\phi\gamma-(P\theta_1\theta_2+\epsilon\theta_1\phi\gamma+G\epsilon\psi\gamma)=0.$

The roots λ_1, λ_2 and λ_3 are negative, because all coefficients are positive after simplification.

Again, the two equations (5.19) and (5.20) can be simplified as:

$$\frac{1}{A(BC-\varphi\omega_2)}[\lambda^3+\lambda^2(A+B+C-\beta_2)+\lambda((BC-\varphi\omega_2)+(B+C)A-\beta_2(B+C+\eta\delta))]+(1-R_H)=0.$$

$$\frac{1}{(k+\alpha+\mu)(\gamma+d_1+\mu)(\sigma+\mu)-kp\gamma\mu-\alpha\sigma(\gamma+d_1+\mu)-k\sigma\gamma}[\lambda^3+\lambda^2(\alpha+\sigma+k+\gamma+d_1+3\mu)+$$

$\lambda((\alpha + k + \gamma + d_1 + 2\mu)(\sigma + \mu) - kp\gamma - \alpha\sigma\beta_1)] + (1 - R_T) = 0.$

We applied Routh-Hurwitz criteria [All08], the roots of the above two polynomial expressions will have negative real part iff the two constant terms $(1 - R_H) > 0$ and $(1 - R_T) > 0$.

Thus, $R_H < 1$ and $R_T < 1$ gives $R_0 < 1$, this completed the proof.

5.3.10 Global stability of DFE point

Theorem 24 *The fixed point $U_0 = (X^*, 0)$ is GAS, if $R_0 < 1$ (LAS) and the two conditions (H_1) and (H_2) are satisfied.*

We explored the theorem using the technique in [CCBVdD$^+$02]. The model (5.1) can be expressed likes below :

$\frac{dX}{dt} = F(X, Z)$,

$\frac{dZ}{dt} = G(X, Z), G(X, 0) = 0$,

where X and Z are vectors which designates the uninfected and infected compartments. So $X = (S)$, $Z = (E, L, T, I, H, A, H_E, H_I, H_L, A_L, A_I)$ and the conditions (H_1) and (H_2) are:

(H_1), $\frac{dX}{dt} = F(X, 0)$, X^* is GAS

(H_2), $\frac{dZ}{dt} = QZ - G^*(X, Z), G^*(X, Z) \geq 0$ for $(X, Z) \in R^+_{12}$ where Q is a Metzler matrix (the non diagonal entries of Q are non-negative).

Thus, $Q = \begin{bmatrix} Q_a & Q_b \end{bmatrix}$ with

$$Q_a = \begin{bmatrix} -(k+\alpha+\mu) & \gamma p + \beta_1 & \sigma & 0 & 0 \\ k & -(\gamma + d_1 + \mu) & 0 & 0 & 0 \\ \alpha & (1-p)\gamma & -(\sigma+\mu) & 0 & 0 \\ 0 & 0 & 0 & \beta_2 - (\delta + \omega_1 + \mu) & \beta_2\eta \\ 0 & 0 & 0 & \delta & -(d_2 + \omega_2 + \mu) \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & \omega_1 & \omega_2 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \end{bmatrix},$$

and

$$Q_b = \begin{bmatrix} 0 & \beta_1 & 0 & 0 & 0 & \beta_1 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ \beta_2 & \beta_2 & \beta_2 & 0 & \eta\beta_2 & 0 \\ 0 & 0 & 0 & \varphi & 0 & 0 \\ -M & \psi\gamma & \theta_1 & 0 & 0 & 0 \\ \epsilon & -P & 0 & 0 & 0 & 0 \\ \theta_2 & (1-\psi)\phi\gamma & -(\theta_1+\theta_3+\omega_5+\mu) & 0 & 0 & 0 \\ \omega_3 & \omega_4(1-\phi) & \omega_5 & -(\varphi+\mu) & \omega_6 & \omega_7 \\ 0 & 0 & \theta_3 & 0 & -(\omega_6+d_2+\mu) & \tau \\ (\sigma_1+\delta_1) & \psi_1 & 0 & 0 & 0 & -(\omega_7+d_3+\tau+\mu) \end{bmatrix}.$$

The non diagonal entries of Q, are non-negative.

$G(X,Z) = QZ - G^*(X,Z)$,

where $G^*(X,Z) = \begin{bmatrix} \beta_1(1-\frac{S}{N})[I+H_I+A_I] \\ 0 \\ 0 \\ \beta_2(1-\frac{S}{N})[H+H_E+H_L+H_I+\eta A_I+\eta A_L] \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \end{bmatrix}$.

Since $0 \leq S \leq N$, then $G^*(X,Z) \geq 0$ and the model (5.1) is GAS.

5.3.11 EEP of HIV-TB model

The EEP of (5.1) occurs when TB and HIV/AIDS co-infection persist in the community. This can be calculated by as follows.

$$
\begin{cases}
\frac{dS}{dt} &= \pi - (\lambda_H + \lambda_T + \mu)S = 0, \\
\frac{dE}{dt} &= \lambda_T S + \gamma p I + \sigma L - (k + \alpha + \epsilon_1\lambda_H + \mu)E = 0, \\
\frac{dI}{dt} &= kE - (\gamma + \epsilon_2\lambda_H + d_1 + \mu)I = 0, \\
\frac{dL}{dt} &= (1-p)\gamma I + \alpha E - (\sigma + \lambda_H + \mu)L = 0, \\
\frac{dH}{dt} &= \lambda_H(S + L) - (\theta\lambda_T + \delta + \omega_1 + \mu)H = 0, \\
\frac{dA}{dt} &= \delta H + \varphi T - (\omega_2 + \omega\lambda_T + \mu + d_2)A = 0, \\
\frac{dH_E}{dt} &= \epsilon_1\lambda_H E + \theta\lambda_T H + \psi\gamma H_I + \theta_1 H_L - (\epsilon + \omega_3 + \theta_2 + \sigma_1 + \delta_1 + \mu)H_E = 0, \\
\frac{dH_I}{dt} &= \epsilon_2\lambda_H I + \epsilon H_E - (\psi\gamma + (1-\psi)\phi\gamma + (1-\phi)\omega_4 + \psi_1 + \mu + d_1)H_I = 0, \\
\frac{dH_L}{dt} &= (1-\psi)\phi\gamma H_I + \theta_2 H_E - (\theta_1 + \theta_3 + \omega_5 + \mu)H_L = 0, \\
\frac{dT}{dt} &= \omega_1 H + \omega_2 A + \omega_3 H_E + \omega_4(1-\phi)H_I + \omega_5 H_L + \omega_6 A_L + \omega_7 A_I - (\varphi + \mu)T = 0, \\
\frac{dA_L}{dt} &= \tau A_I + \theta_3 H_L - (\omega_6 + \mu + d_2)A_L = 0, \\
\frac{dA_I}{dt} &= (\sigma_1 + \delta_1)H_E + \psi_1 H_I + \omega\lambda_T A - (\omega_7 + \mu + d_3 + \tau)A_I = 0.
\end{cases}
\tag{5.21}
$$

If we let $\lambda_{T*} = \frac{\beta_1[I_* + H_{I*} + A_{I*}]}{N}$ and $\lambda_{H*} = \frac{\beta_2[H_* + H_{E*} + H_{L*} + H_{I*} + \eta(A_* + A_{L*})]}{N}$, then we get:
$S_* = \frac{\pi}{(\lambda_{T*} + \lambda_{H*} + \mu)}$, $E_* = \frac{\lambda_{T*}S_* + \gamma p I_* + \sigma L_*}{k + \alpha + \epsilon_1\lambda_{H*} + \mu}$, $I_* = k\frac{E_*}{\gamma + \epsilon_2\lambda_{H*} + d_1 + \mu}$, $L_* = \frac{(1-p)\gamma I_* + \alpha E_*}{\sigma + \lambda_{H*} + \mu}$,
$H_* = \frac{\lambda_{H*}(S_* + L_*)}{\theta\lambda_{T*} + \delta + \omega_1 + \mu}$, $A_* = \frac{\delta H_* + \varphi T_*}{\omega_2 + \omega\lambda_{T*} + \mu + d_2}$,, $H_{E*} = \frac{\epsilon_1\lambda_{H*}E_* + \theta\lambda_{T*}H + \psi\gamma H_{I*} + \theta_1 H_{L*}}{\epsilon + \omega_3 + \theta_2 + \sigma_1 + \delta_1 + \mu}$,
$H_{I*} = \frac{\epsilon_2\lambda_{H*}I_* + \epsilon H_{E*}}{\psi\gamma + (1-\psi)\phi\gamma + (1-\phi)\omega_4 + \psi_1 + \mu + d_1}$, $H_{L*} = \frac{(1-\psi)\phi\gamma H_{I*} + \theta_2 H_{E*}}{\theta_1 + \theta_3 + \omega_5 + \mu}$,
$T_* = \frac{\omega_1 H_* + \omega_2 A_* + \omega_3 H_{E*} + \omega_4(1-\phi)H_{I*} + \omega_5 H_{L*} + \omega_6 A_{L*} + \omega_7 A_{I*}}{\varphi + \mu}$, $A_{L*} = \frac{\tau A_{I*} + \theta_3 H_{L*}}{\omega_6 + \mu + d_2}$,
$A_{I*} = \frac{(\sigma_1 + \delta_1)H_{E*} + \psi_1 H_{I*} + \omega\lambda_{T*}A_*}{\omega_7 + \mu + d_3 + \tau}$.
Thus, the EEP of HIV-TB co-epidemics model is symbolized by:
$E_* = (S_*, E_*, I_*, L_*, H_*, H_{E*}, H_{L*}, H_{I*}, T_*, A_*, A_{L*}, A_{I*})$.

Lemma 7 *A unique endemic equilibrium point E_* exist if $R_0 > 1$.*

Proof:

If the disease is endemic in the community, then $\exists\, t^* > 0$ such that $\frac{dE(t^*)}{dt} > 0$, $\frac{dI(t^*)}{dt} > 0$, $\frac{dL(t^*)}{dt} > 0$, $\frac{dH(t^*)}{dt} > 0$, $\frac{dA(t^*)}{dt} > 0$, $\frac{dH_E(t^*)}{dt} > 0$, $\frac{dH_I(t^*)}{dt} > 0$, $\frac{dH_L(t^*)}{dt} > 0$, $\frac{dT(t^*)}{dt} > 0$, $\frac{dA_L(t^*)}{dt} > 0$ and $\frac{dA_I(t^*)}{dt} > 0$. Thus, keeping the state variables $E, I, L, H, A, H_E, H_I, H_L, T, A_L$ and A_I at t^*, the system (5.1) becomes:

$$\begin{cases} \frac{dE}{dt} &= \lambda_T S + \gamma p I + \sigma L - (k + \alpha + \epsilon_1 \lambda_H + \mu)E > 0, \\ \frac{dI}{dt} &= kE - (\gamma + \epsilon_2 \lambda_H + d_1 + \mu)I > 0, \\ \frac{dL}{dt} &= (1-p)\gamma I + \alpha E - (\sigma + \lambda_H + \mu)L > 0, \\ \frac{dH}{dt} &= \lambda_H (S + L) - (\theta \lambda_T + \delta + \omega_1 + \mu)H > 0, \\ \frac{dA}{dt} &= \delta H + \varphi T - (\omega_2 + \omega \lambda_T + \mu + d_2)A > 0, \\ \frac{dH_E}{dt} &= \epsilon_1 \lambda_H E + \theta \lambda_T H + \psi \gamma H_I + \theta_1 H_L - (\epsilon + \omega_3 + \theta_2 + \sigma_1 + \delta_1 + \mu)H_E > 0, \\ \frac{dH_I}{dt} &= \epsilon_2 \lambda_H I + \epsilon H_E - (\psi\gamma + (1-\psi)\phi\gamma + (1-\phi)\omega_4 + \psi_1 + \mu + d_1)H_I > 0, \\ \frac{dH_L}{dt} &= (1-\psi)\phi\gamma H_I + \theta_2 H_E - (\theta_1 + \theta_3 + \omega_5 + \mu)H_L > 0, \\ \frac{dT}{dt} &= \omega_1 H + \omega_2 A + \omega_3 H_E + \omega_4 (1-\phi)H_I + \omega_5 H_L + \omega_6 A_L + \omega_7 A_I - (\varphi + \mu)T > 0, \\ \frac{dA_L}{dt} &= \tau A_I + \theta_3 H_L - (\omega_6 + \mu + d_2)A_L > 0, \\ \frac{dA_I}{dt} &= (\sigma_1 + \delta_1)H_E + \psi_1 H_I + \omega \lambda_T A - (\omega_7 + \mu + d_3 + \tau)A_I > 0. \end{cases} \tag{5.22}$$

Now, from the first three equations of (5.22), we have

$$\begin{cases} (k + \alpha + \epsilon_1 \lambda_H + \mu)E < \lambda_T S + \gamma p I + \sigma L, \\ (\gamma + \epsilon_2 \lambda_H + d_1 + \mu)I < kE, \\ (\sigma + \lambda_H + \mu)L < (1-p)\gamma I + \alpha E. \end{cases} \tag{5.23}$$

From the fact that $\frac{S}{N} \leq 1$. Thus (5.23) can gives:

$$\begin{cases} (k + \alpha + \mu)E < \beta_1 I + \gamma p I + \sigma L, \\ (\gamma + d_1 + \mu)I < kE, \\ (\sigma + \mu)L < (1-p)\gamma I + \alpha E. \end{cases} \tag{5.24}$$

Next, adding the first and the third equation of (5.24) simultaneously to eliminate the term L, we get the following results.

$$\begin{cases} ((k + \alpha + \mu)(\sigma + \mu) - \alpha\sigma)E < ((\beta_1 + \gamma p)(\sigma + \mu) + \sigma(1-p)\gamma)I, \\ (\gamma + d_1 + \mu)I < kE. \end{cases} \tag{5.25}$$

Thus, the system (5.25), gives the following result.
$(k + \alpha + \mu)(\gamma + d_1 + \mu)(\sigma + \mu) - \alpha\sigma(\gamma + d_1 + \mu) - k\sigma\gamma + k\sigma p\gamma - kp\gamma\mu - k\alpha\gamma p < k\beta_1(\sigma + \mu)$.

$\Rightarrow (k+\alpha+\mu)(\gamma+d_1+\mu)(\sigma+\mu)-\alpha\sigma(\gamma+d_1+\mu)-k\sigma\gamma-kp\gamma\mu-k\alpha\gamma p < k\beta_1(\sigma+\mu).$
$\Rightarrow 1 < \frac{k\beta_1(\sigma+\mu)}{(k+\alpha+\mu)(\gamma+d_1+\mu)(\sigma+\mu)-\alpha\sigma(\gamma+d_1+\mu)-k\sigma\gamma-kp\gamma\mu-k\alpha\gamma p} = R_T.$
$\Rightarrow R_T > 1.$
This indicated that a unique EEP exists if $R_0 = max\{R_H, R_T\} > 1$.

5.3.12 Bifurcation analysis

Now, we used centre manifold theory to analysis the nature of bifurcation at the point $R_0 = 1$.
To apply this technique, the next shifts of variables are made.
Let $S = x_1, E = x_2, I = x_3, L = x_4, H = x_5, A = x_6, H_E = x_7, H_I = x_8, H_L = x_9, T = x_{10}, A_L = x_{11}$, and $A_I = x_{12}$.
Thus, the system (5.1) becomes:

$$\begin{cases} \frac{dx_1}{dt} = \pi - (\lambda_H + \lambda_T + \mu)x_1, \\ \frac{dx_2}{dt} = \lambda_T x_1 + \gamma p x_3 + \sigma x_4 - (k + \alpha + \epsilon_1\lambda_H + \mu)x_2, \\ \frac{dx_3}{dt} = kx_2 - (\gamma + \epsilon_2\lambda_H + d_1 + \mu)x_3, \\ \frac{dx_4}{dt} = (1-p)\gamma x_3 + \alpha x_2 - (\sigma + \lambda_H + \mu)x_4, \\ \frac{dx_5}{dt} = \lambda_H(x_1 + x_4) - (\theta\lambda_T + \delta + \omega_1 + \mu)x_5, \\ \frac{dx_6}{dt} = \delta x_3 + \varphi x_{10} - (\omega_2 + \omega\lambda_T + \mu + d_2)x_6, \\ \frac{dx_7}{dt} = \epsilon_1\lambda_H x_2 + \theta\lambda_T x_5 + \psi\gamma x_8 + \theta_1 x_9 - (\epsilon + \omega_3 + \theta_2 + \sigma_1 + \delta_1 + \mu)x_7, \\ \frac{dx_8}{dt} = \epsilon_2\lambda_H x_3 + \epsilon x_7 - (\psi\gamma + (1-\psi)\phi\gamma + (1-\phi)\omega_4 + \psi_1 + \mu + d_1)x_8, \\ \frac{dx_9}{dt} = (1-\psi)\phi\gamma x_8 + \theta_2 x_7 - (\theta_1 + \theta_3 + \omega_5 + \mu)x_9, \\ \frac{dx_{10}}{dt} = \omega_1 x_5 + \omega_2 x_6 + \omega_3 x_7 + \omega_4(1-\phi)x_8 + \omega_5 x_9 + \omega_6 x_{11} + \omega_7 x_{12} - (\varphi + \mu)x_{10}, \\ \frac{dx_{11}}{dt} = \tau x_{12} + \theta_3 x_9 - (\omega_6 + \mu + d_2)x_{11}, \\ \frac{dx_{12}}{dt} = (\sigma_1 + \delta_1)x_7 + \psi_1 x_8 + \omega\lambda_T x_6 - (\omega_7 + \mu + d_3 + \tau)x_{12}, \end{cases} \tag{5.26}$$

where $\lambda_T = \frac{\beta_1[x_3+x_8+x_{12}]}{N}$ and $\lambda_H = \frac{\beta_2[x_5+x_7+x_8+x_9+\eta(x_6+x_{11})]}{N}$.
The Jacobian matrix J of (5.26) at DFEP is already articulated.
$J(\frac{\pi}{\mu}, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0) = \begin{bmatrix} J_1 & J_2 \end{bmatrix}$, with

$$J_1(\varepsilon_0) = \begin{bmatrix} -\mu & 0 & -\beta_1 & 0 & -\beta_2 & -\beta_2\eta \\ 0 & -(k+\alpha+\mu) & \gamma p+\beta_1 & \sigma & 0 & 0 \\ 0 & k & -(\gamma+d_1+\mu) & 0 & 0 & 0 \\ 0 & \alpha & (1-p)\gamma & -(\sigma+\mu) & 0 & 0 \\ 0 & 0 & 0 & 0 & \beta_2-(\delta+\omega_1+\mu) & \beta_2\eta \\ 0 & 0 & 0 & 0 & \delta & -(d_2+\omega_2+\mu) \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & \omega_1 & \omega_2 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \end{bmatrix},$$

$$J_2(\varepsilon_0) = \begin{bmatrix} -\beta_2 & -(\beta_2+\beta_1) & -\beta_2 & 0 & -\beta_2\eta & -\beta_1 \\ 0 & \beta_1 & 0 & 0 & 0 & \beta_1 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ \beta_2 & \beta_2 & \beta_2 & 0 & \eta\beta_2 & 0 \\ 0 & 0 & 0 & \varphi & 0 & 0 \\ -M & \psi\gamma & \theta_1 & 0 & 0 & 0 \\ \epsilon & -P & 0 & 0 & 0 & 0 \\ \theta_2 & (1-\psi)\phi\gamma & -(\theta_1+\theta_3+\omega_5+\mu) & 0 & 0 & 0 \\ \omega_3 & \omega_4(1-\phi) & \omega_5 & -(\varphi+\mu) & \omega_6 & \omega_7 \\ 0 & 0 & \theta_3 & 0 & -(\omega_6+d_2+\mu) & \tau \\ (\sigma_1+\delta_1) & \psi_1 & 0 & 0 & 0 & -(\omega_7+d_3+\tau+\mu) \end{bmatrix}.$$

Hereafter, we calculate the right eigenvectors of $J(\varepsilon_0)$ symbolized by:
$u = (u_1, u_2, u_3, u_4, u_5, u_6, u_7, u_8, u_9, u_{10}, u_{11}, u_{12})^T$ corresponding to zero eigenvalue as follows.

$$\begin{bmatrix} J_1(\varepsilon_0) & J_2(\varepsilon_0) \end{bmatrix} \begin{pmatrix} u_1 \\ u_2 \\ u_3 \\ u_4 \\ u_5 \\ u_6 \\ u_7 \\ u_8 \\ u_9 \\ u_{10} \\ u_{11} \\ u_{12} \end{pmatrix} = \begin{pmatrix} 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \end{pmatrix}. \tag{5.27}$$

Equation (5.27) becomes;

$$\begin{cases} -\mu u_1 - \beta_1 u_3 - \beta_2 u_5 - \beta_2 \eta u_6 - \beta_2 u_7, \\ -(\beta_2 + \beta_1)u_8 - \beta_2 u_9 - \beta_2 \eta u_{11} - \beta_1 u_{12} = 0, \\ -(k + \alpha + \mu)u_2 + (\gamma p + \beta_1)u_3 + \sigma u_4 + \beta_1 u_8 + \beta_1 u_{12} = 0, \\ k u_2 - (\gamma + d_1 + \mu)u_3 = 0, \\ \alpha u_2 + (1-p)\gamma u_3 - (\sigma + \mu)u_4 = 0, \\ (\beta_2 - (\delta + \omega_1 + \mu))u_5 + \beta_2 \eta u_6 + \beta_2 u_7 + \\ \beta_2 u_8 + \beta_2 u_9 + \eta \beta_2 u_{11} = 0, \\ \delta u_5 - (d_2 + \omega_2 + \mu)u_6 + \varphi u_{10} = 0, \\ -M u_7 + \psi \gamma u_8 + \theta_1 u_9 = 0, \\ \epsilon u_7 - P u_8 = 0, \\ \theta_2 u_7 + (1-\psi)\phi\gamma u_8 - (\theta_1 + \theta_3 + \omega_5 + \mu)u_9 = 0, \\ \omega_1 u_5 + \omega_2 u_6 + \omega_3 u_7 + \omega_4(1-\phi)u_8 + \omega_5 u_9 - (\varphi + \mu)u_{10} + \omega_6 u_{11} + \omega_7 u_{12} = 0, \\ \theta_3 u_9 - (\omega_6 + d_2 + \mu)u_{11} + \tau u_{12} = 0, \\ (\sigma_1 + \delta_1)u_7 + \psi_1 u_8 - (\omega_7 + d_3 + \tau + \mu)u_{12} = 0. \end{cases} \tag{5.28}$$

Solving system (5.28) we get
$u_1 = -\left(\frac{\beta_1 u_3 + \beta_2 u_5 + \beta_2 \eta u_6 + \beta_2 u_7 + (\beta_2 + \beta_1)u_8 + \beta_2 u_9 + \beta_2 \eta u_{11} + \beta_1 u_{12}}{\mu}\right)$.

$u_2 = \frac{(\gamma p+\beta_1)u_3+\sigma u_4+\beta_1 u_8+\beta_1 u_{12}}{(k+\alpha+\mu)}$.
$u_3 = \frac{ku_2}{(\gamma+d_1+\mu)}$.
$u_4 = \frac{\alpha u_2+(1-p)\gamma u_3}{(\sigma+\mu)}$.
$u_5 = \frac{\beta_2\eta u_6+\beta_2 u_7+\beta_2 u_8+\beta_2 u_9+\eta\beta_2 u_{11}}{(\delta+\omega_1+\mu)-\beta_2}$.
$u_6 = \frac{\delta u_5+\varphi u_{10}}{(d_2+\omega_2+\mu)}$.
$u_7 = \frac{\psi\gamma u_8+\theta_1 u_9}{M}$.
$u_8 = \frac{\epsilon u_7}{P}$.
$u_9 = \frac{\theta_2 u_7+(1-\psi)\phi\gamma u_8}{(\theta_1+\theta_3+\omega_5+\mu)}$.
$u_{10} = \frac{\omega_1 u_5+\omega_2 u_6+\omega_3 u_7+\omega_4(1-\phi)u_8+\omega_5 u_9+\omega_6 u_{11}+\omega_7 u_{12}}{(\varphi+\mu)}$.
$u_{11} = \frac{\theta_3 u_9+\tau u_{12}}{(\omega_6+d_2+\mu)}$.
$u_{12} = \frac{(\sigma_1+\delta_1)u_7+\psi_1 u_8}{(\omega_7+d_3+\tau+\mu)}$.

Again, the left eigenvectors of $J(\varepsilon_0)$ symbolized by $v = (v_1, v_2, v_3, v_4, v_5, v_6, v_7, v_8, v_9, v_{10}, v_{11}, v_{12})^T$ is calculated likes below.

$Y(\frac{\pi}{\mu}, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0) = \begin{bmatrix} Y_1 & Y_2 \end{bmatrix}$, with

$$Y_1(\varepsilon_0) = \begin{bmatrix} -\mu & 0 & 0 & 0 & 0 & 0 \\ 0 & -(k+\alpha+\mu) & k & \alpha & 0 & 0 \\ -\beta_1 & \gamma p+\beta_1 & -(\gamma+d_1+\mu) & (1-p)\gamma & 0 & 0 \\ 0 & \sigma & 0 & -(\sigma+\mu) & 0 & 0 \\ -\beta_2 & 0 & 0 & 0 & \beta_2-(\delta+\omega_1+\mu) & \delta \\ -\beta_2\eta & 0 & 0 & 0 & \beta_2\eta & -(d_2+\omega_2+\mu) \\ -\beta_2 & 0 & 0 & 0 & \beta_2 & 0 \\ -(\beta_2+\beta_1) & \beta_1 & 0 & 0 & \beta_2 & 0 \\ -\beta_2 & 0 & 0 & 0 & \beta_2 & 0 \\ 0 & 0 & 0 & 0 & 0 & \varphi \\ -\beta_2\eta & 0 & 0 & 0 & \eta\beta_2 & 0 \\ -\beta_1 & \beta_1 & 0 & 0 & 0 & 0 \end{bmatrix},$$

$$Y_2(\varepsilon_0) = \begin{bmatrix} 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & \omega_1 & 0 & 0 \\ 0 & 0 & 0 & \omega_2 & 0 & 0 \\ -M & \epsilon & \theta_2 & \omega_3 & 0 & (\sigma_1+\delta_1) \\ \psi\gamma & -P & (1-\psi)\phi\gamma & \omega_4(1-\phi) & 0 & \psi_1 \\ \theta_1 & 0 & -(\theta_1+\theta_3+\omega_5+\mu) & \omega_5 & \theta_3 & 0 \\ 0 & 0 & 0 & -(\varphi+\mu) & 0 & 0 \\ 0 & 0 & 0 & \omega_6 & -(\omega_6+d_2+\mu) & 0 \\ 0 & 0 & 0 & \omega_7 & \tau & -(\omega_7+d_3+\tau+\mu) \end{bmatrix}.$$

Thus

$$\begin{bmatrix} Y_1(\varepsilon_0) & Y_2(\varepsilon_0) \end{bmatrix} \begin{pmatrix} v_1 \\ v_2 \\ v_3 \\ v_4 \\ v_5 \\ v_6 \\ v_7 \\ v_8 \\ v_9 \\ v_{10} \\ v_{11} \\ v_{12} \end{pmatrix} = \begin{pmatrix} 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \end{pmatrix}. \tag{5.29}$$

Equation (5.29) becomes;

$-\mu v_1 = 0 \Rightarrow v_1 = 0,\ \ v_2 = \frac{kv_3+\alpha v_4}{(k+\alpha+\mu)},\ \ v_3 = \frac{\gamma p+\beta_1 v_2+(1-p)\gamma v_4}{(\gamma+d_1+\mu)},\ \ v_4 = \frac{\sigma v_2}{\sigma+\mu},$

$v_5 = \frac{\delta v_6+\omega_1 v_{10}}{(\delta+\omega_1+\mu)-\beta_2},\ \ v_6 = \frac{\beta_2\eta v_5+\omega_2 v_{10}}{d_2+\omega_2+\mu},\ v_7 = \frac{\beta_2 v_5+\epsilon v_8+\theta_2 v_9+\omega_3 v_{10}+(\sigma_1+\delta_1)v_{12}}{M},$

$v_8 = \frac{\beta_1 v_2+\beta_2 v_5+\psi\gamma v_7+(1-\psi)\phi\gamma v_9+\omega_4(1-\phi)v_{10}+\psi_1 v_{12}}{P},\ \ v_9 = \frac{\beta_2 v_5+\theta_1 v_7+\omega_5 v_{10}+\theta_3 v_{11}}{\theta_1+\theta_3+\omega_5+\mu},$

$v_{10} = \frac{\varphi v_6}{\varphi+\mu},\ \ v_{11} = \frac{\eta\beta_2 v_5+\omega_6 v_{10}}{\omega_6+d_2+\mu},\ \ v_{12} = \frac{\beta_1 v_2+\omega_7 v_{10}+\tau v_{11}}{\omega_7+d_3+\tau+\mu}.$

Now, we need to calculate the bifurcation constants a and b using the formula:
$a = \sum_{k,i,j=1}^{n} v_k u_i u_j \frac{\partial^2 f_k}{\partial x_i \partial x_j}(\varepsilon_0)$, and $b = \sum_{k,i=1}^{n} v_k u_i \frac{\partial^2 f_k}{\partial x_i \partial \beta_r}(\varepsilon_0)$, for $r = 1$ or 2 in [CCS04], where n is the number of compartments, and $f_i = \frac{dx_i}{dt}$ for $i = 1, 2, 3, ..., 12$ (5.26).
Hence, $\frac{\partial^2 f_2}{\partial x_3 \partial x_1} = \frac{\partial^2 f_2}{\partial x_8 \partial x_1} = \frac{\partial^2 f_2}{\partial x_{12} \partial x_1} = \frac{\beta_1}{N}$, $\frac{\partial^2 f_2}{\partial x_5 \partial x_2} = \frac{\partial^2 f_2}{\partial x_7 \partial x_2} = \frac{\partial^2 f_2}{\partial x_8 \partial x_2} = \frac{\partial^2 f_2}{\partial x_9 \partial x_2} =$

$-\epsilon_1 \frac{\beta_2}{N}$, $\frac{\partial^2 f_2}{\partial x_6 \partial x_2} = \frac{\partial^2 f_2}{\partial x_{11} \partial x_2} = -\epsilon_1 \eta \frac{\beta_2}{N}$,

$\frac{\partial^2 f_3}{\partial x_5 \partial x_3} = \frac{\partial^2 f_3}{\partial x_7 \partial x_3} = \frac{\partial^2 f_3}{\partial x_8 \partial x_3} = \frac{\partial^2 f_3}{\partial x_9 \partial x_3} = -\epsilon_2 \frac{\beta_2}{N}$, $\frac{\partial^2 f_3}{\partial x_6 \partial x_3} = \frac{\partial^2 f_3}{\partial x_{11} \partial x_3} = -\epsilon_2 \eta \frac{\beta_2}{N}$,

$\frac{\partial^2 f_4}{\partial x_5 \partial x_4} = \frac{\partial^2 f_4}{\partial x_7 \partial x_4} = \frac{\partial^2 f_4}{\partial x_8 \partial x_4} = \frac{\partial^2 f_4}{\partial x_9 \partial x_4} = -\frac{\beta_2}{N}$, $\frac{\partial^2 f_4}{\partial x_6 \partial x_4} = \frac{\partial^2 f_4}{\partial x_{11} \partial x_4} = -\eta \frac{\beta_2}{N}$,

$\frac{\partial^2 f_5}{\partial x_5 \partial x_4} = \frac{\partial^2 f_5}{\partial x_7 \partial x_4} = \frac{\partial^2 f_5}{\partial x_8 \partial x_4} = \frac{\partial^2 f_5}{\partial x_9 \partial x_4} = \frac{\beta_2}{N}$, $\frac{\partial^2 f_5}{\partial x_6 \partial x_4} = \frac{\partial^2 f_5}{\partial x_{11} \partial x_4} = \eta \frac{\beta_2}{N}$,

$\frac{\partial^2 f_5}{\partial x_5 \partial x_1} = \frac{\partial^2 f_5}{\partial x_7 \partial x_1} = \frac{\partial^2 f_5}{\partial x_8 \partial x_1} = \frac{\partial^2 f_5}{\partial x_9 \partial x_1} = \frac{\beta_2}{N}$, $\frac{\partial^2 f_5}{\partial x_6 \partial x_1} = \frac{\partial^2 f_5}{\partial x_{11} \partial x_1} = \eta \frac{\beta_2}{N}$,

$\frac{\partial^2 f_5}{\partial x_3 \partial x_5} = \frac{\partial^2 f_5}{\partial x_8 \partial x_5} = \frac{\partial^2 f_5}{\partial x_{12} \partial x_5} = -\theta \frac{\beta_1}{N}$,

$\frac{\partial^2 f_6}{\partial x_3 \partial x_6} = \frac{\partial^2 f_6}{\partial x_8 \partial x_6} = \frac{\partial^2 f_6}{\partial x_{12} \partial x_6} = -\omega_2 \frac{\beta_1}{N}$,

$\frac{\partial^2 f_7}{\partial x_5 \partial x_2} = \frac{\partial^2 f_7}{\partial x_7 \partial x_2} = \frac{\partial^2 f_7}{\partial x_8 \partial x_2} = \frac{\partial^2 f_7}{\partial x_9 \partial x_2} = \epsilon \frac{\beta_2}{N}$, $\frac{\partial^2 f_7}{\partial x_6 \partial x_2} = \frac{\partial^2 f_7}{\partial x_{11} \partial x_2} = \eta \epsilon \frac{\beta_2}{N}$,

$\frac{\partial^2 f_7}{\partial x_3 \partial x_5} = \frac{\partial^2 f_7}{\partial x_8 \partial x_5} = \frac{\partial^2 f_7}{\partial x_{12} \partial x_5} = \theta \frac{\beta_1}{N}$,

$\frac{\partial^2 f_8}{\partial x_5 \partial x_2} = \frac{\partial^2 f_8}{\partial x_7 \partial x_2} = \frac{\partial^2 f_8}{\partial x_8 \partial x_2} = \frac{\partial^2 f_8}{\partial x_9 \partial x_2} = \epsilon_2 \frac{\beta_2}{N}$, $\frac{\partial^2 f_8}{\partial x_6 \partial x_2} = \frac{\partial^2 f_8}{\partial x_{11} \partial x_2} = \eta \epsilon_2 \frac{\beta_2}{N}$,

$\frac{\partial^2 f_{12}}{\partial x_3 \partial x_6} = \frac{\partial^2 f_{12}}{\partial x_8 \partial x_6} = \frac{\partial^2 f_{12}}{\partial x_{12} \partial x_6} = \omega \frac{\beta_1}{N}$.

Then $a = v_2 u_1 u_3 \frac{\beta_1}{N} + v_2 u_1 u_8 \frac{\beta_1}{N} + v_2 u_1 u_{12} \frac{\beta_1}{N} + v_2 u_2 u_5 \frac{-\epsilon_1 \beta_2}{N} + v_2 u_2 u_7 \frac{-\epsilon_1 \beta_2}{N} + v_2 u_2 u_8 \frac{-\epsilon_1 \beta_2}{N} +$
$v_2 u_2 u_9 \frac{-\epsilon_1 \beta_2}{N} + v_2 u_2 u_6 \frac{-\eta \epsilon_1 \beta_2}{N} + v_2 u_2 u_{11} \frac{-\eta \epsilon_1 \beta_2}{N} + v_3 u_3 u_5 \frac{-\epsilon_2 \beta_2}{N} + v_3 u_3 u_7 \frac{-\epsilon_2 \beta_2}{N} + v_3 u_3 u_8 \frac{-\epsilon_2 \beta_2}{N} + v_3 u_3 u_9 \frac{-\epsilon_2 \beta_2}{N} +$
$v_3 u_3 u_6 \frac{-\eta \epsilon_2 \beta_2}{N} + v_3 u_3 u_{11} \frac{-\eta \epsilon_2 \beta_2}{N} + v_4 u_4 u_5 \frac{-\beta_2}{N} + v_4 u_4 u_7 \frac{-\beta_2}{N} + v_4 u_4 u_8 \frac{-\beta_2}{N} + v_4 u_4 u_9 \frac{-\beta_2}{N} + v_4 u_4 u_6 \frac{-\eta \beta_2}{N} +$
$v_4 u_4 u_{11} \frac{-\eta \beta_2}{N} + v_5 u_4 u_5 \frac{\beta_2}{N} + v_5 u_4 u_7 \frac{\beta_2}{N} + v_5 u_4 u_8 \frac{\beta_2}{N} + v_5 u_4 u_9 \frac{\beta_2}{N} + v_5 u_4 u_6 \frac{\eta \beta_2}{N} + v_5 u_4 u_{11} \frac{\eta \beta_2}{N} + v_5 u_1 u_5 \frac{\beta_2}{N} +$
$v_5 u_1 u_7 \frac{\beta_2}{N} + v_5 u_1 u_8 \frac{\beta_2}{N} + v_5 u_1 u_9 \frac{\beta_2}{N} + v_5 u_1 u_6 \frac{\eta \beta_2}{N} + v_5 u_1 u_{11} \frac{\eta \beta_2}{N} + v_5 u_5 u_3 \frac{-\theta \beta_1}{N} + v_5 u_5 u_8 \frac{-\theta \beta_1}{N} + v_5 u_5 u_{12} \frac{-\theta \beta_1}{N} +$
$v_6 u_6 u_3 \frac{-\omega_2 \beta_1}{N} + v_6 u_6 u_8 \frac{-\omega_2 \beta_1}{N} + v_6 u_6 u_{12} \frac{-\omega_2 \beta_1}{N} + v_7 u_5 u_3 \frac{\theta \beta_1}{N} + v_7 u_5 u_8 \frac{\theta \beta_1}{N} + v_7 u_5 u_{12} \frac{\theta \beta_1}{N} + v_{12} u_6 u_3 \frac{\omega \beta_1}{N} +$
$v_{12} u_6 u_8 \frac{\omega \beta_1}{N} + v_{12} u_6 u_{12} \frac{\omega \beta_1}{N} + v_7 u_2 u_5 \frac{\epsilon \beta_2}{N} + v_7 u_2 u_7 \frac{\epsilon \beta_2}{N} + v_7 u_2 u_8 \frac{\epsilon \beta_2}{N} + v_7 u_2 u_9 \frac{\epsilon \beta_2}{N} + v_7 u_2 u_6 \frac{\epsilon \eta \beta_2}{N} +$
$v_7 u_2 u_{11} \frac{\epsilon \eta \beta_2}{N} + v_8 u_2 u_5 \frac{\epsilon_2 \beta_2}{N} + v_8 u_2 u_7 \frac{\epsilon_2 \beta_2}{N} + v_8 u_2 u_8 \frac{\epsilon_2 \beta_2}{N} + v_8 u_2 u_9 \frac{\epsilon_2 \beta_2}{N} + v_8 u_2 u_6 \frac{\epsilon_2 \eta \beta_2}{N} + v_8 u_2 u_{11} \frac{\epsilon_2 \eta \beta_2}{N}$.
We considered the case when $R_T > R_H$ i.e., $R_0 = R_T$ and $R_0 = 1$. Choose $\beta_1 = \beta_1^*$ as the

bifurcation parameter.

Now, $b = \sum_{k,i=1}^{n} v_k u_i \frac{\partial^2 f_k}{\partial x_i \partial \beta_1}(\varepsilon_0) = v_2 u_3 + v_2 u_8 + v_2 u_{12}$
$= v_2(u_3 + u_8 + u_{12}) > 0.$

Again, $a = (v_2 u_1 - v_6 u_6 \omega_2 - v_{12} u_6 \omega)(u_3 + u_8 + u_{12})\frac{\beta_1}{N} + \Delta \frac{\beta_2}{N}(u_5 + u_7 + u_8 + u_9 + \eta(u_6 + u_{11}))$, where $\Delta = -v_2 u_2 - v_3 u_3 \epsilon_2 - v_4 u_4 - v_5 u_5 + v_5 u_1 + v_5 u_4 + v_7 u_5 \theta + v_7 u_2 \epsilon + v_8 u_2 \epsilon_2$. Since u_1 is negative and the sign of a is determined by the sign of Δ.

As a result, the model (5.1) displays forward or backward bifurcation at $R_0 = 1$ in keeping with the sign of Δ.

5.4 Model with optimal control

We used the following four (two preventive and two controlling) efforts.

1. The preventive effort of TB disease, $u_1(t)$, implies the effort of protecting susceptible individuals from becoming infectious. The mechanisms such as health educational campaigns and early detection as well as isolation of infectious individuals are associated with u_1(t).

2. The preventive effort of HIV/AIDS disease, $u_2(t)$, implies the effort of protecting contacting susceptible from HIV/AIDS infected individuals. The mechanisms such as HIV/AIDS educational campaign and early detection of HIV infected individuals are associated with u_2(t).

3. The case finding for TB disease ($u_3(t)$). The effort, $u_3(t)$, illustrates the screening and then treatment of high- risk latent TB. The risk that TB infection will progress to TB disease is greatly reduced by treatment of latent TB. Since finite groups are at a high risk of growing TB disease once infected. This effort is a key mechanism for a TB control strategy.

4. The treatment effort for HIV/AIDS disease ($u_4(t)$). This strategy, $u_4(t)$, refers to treating HIV infected people with Antiretroviral Therapy (ART). This can decrease the individuals infectiousness level by reducing their viral load and helping them to recapture their immunity to obtain a better life. This treatment can also curtail HIV-TB co-infection rate.

Thus incorporating the above strategies in the model (5.1), we get the following optimal control model of HIV-TB co-epidemics.

$$
\begin{cases}
\frac{dS}{dt} = \pi - ((1-u_2)\lambda_H + (1-u_1)\lambda_T + \mu)S, \\
\frac{dE}{dt} = (1-u_1)\lambda_T S + \gamma p I + \sigma L - (k + \alpha + \epsilon_1\lambda_H + \mu)E, \\
\frac{dI}{dt} = kE - (\gamma + \epsilon_2\lambda_H + d_1 + \mu)I, \\
\frac{dL}{dt} = (1-p)\gamma I + \alpha E - (\sigma + \lambda_H + \mu)L, \\
\frac{dH}{dt} = (1-u_2)\lambda_H S + \lambda_H L - (\theta\lambda_T + \delta + \omega_1(1+u_4) + \mu)H, \\
\frac{dA}{dt} = \delta H + \varphi T - (\omega_2(1+u_4) + \omega\lambda_T + \mu + d_2)A, \\
\frac{dH_E}{dt} = \epsilon_1\lambda_H E + \theta\lambda_T H + \psi\gamma H_I + \theta_1 H_L - (\epsilon + \omega_3(1+u_4) + \\
\qquad \theta_2(1+u_3) + \sigma_1 + \delta_1 + \mu)H_E, \\
\frac{dH_I}{dt} = \epsilon_2\lambda_H I + \epsilon H_E - (\psi\gamma + (1-\psi)\gamma\phi + (1-\phi)\omega_4(1+u_4) + \\
\qquad \psi_1 + \mu + d_1)H_I, \\
\frac{dH_L}{dt} = (1-\psi)\phi\gamma H_I + \theta_2(1+u_3)H_E - (\theta_1 + \theta_3 + \omega_5(1+u_4) + \mu)H_L, \\
\frac{dT}{dt} = \omega_1(1+u_4)H + \omega_2(1+u_4)A + \omega_3(1+u_4)H_E + \omega_4(1+u_4)(1-\phi)H_I + \\
\qquad \omega_5(1+u_4)H_L + \omega_6(1+u_4)A_L + \omega_7(1+u_4)A_I - (\varphi + \mu)T, \\
\frac{dA_L}{dt} = (\tau)A_I + \theta_3 H_L - (\omega_6(1+u_4) + \mu + d_2)A_L, \\
\frac{dA_I}{dt} = (\sigma_1 + \delta_1)H_E + \psi_1 H_I + \omega\lambda_T A - (\omega_7(1+u_4) + \mu + d_3 + \tau)A_I.
\end{cases}
\tag{5.30}
$$

The optimal controls are defined in the set $U = \{u_i(t) : 0 \leq u_i(t) \leq 1, 0 \leq t \leq T\}$, where $i = 1, 2, 3, 4$.

Let the objective function be expressed as [PRL$^+$15, BLVDL14]:

$$
J(t) = \int_0^{t_f} [b_1 H_E(t) + b_2 H_I(t) + b_3 H_L(t) + b_4 A_L(t) + b_5 A_I(t) + \frac{1}{2}\sum_{i=1}^{4} c_i u_i^2(t)]dt, \tag{5.31}
$$

where b_1, b_2, b_3, b_4, and b_5 are the cost associated with a number of H_E, H_I, H_L, A_L, and A_I compartments respectively, whereas $c_i, i = 1, 2, 3, 4$ are the costs of executing the strategies from u_1 up to u_4 respectively [Mar15]. We have taken a quadratic form for determining the cost of intervention [MO11, OMT13].

Thus, we try to find the optimal controls u_1^*, u_2^*, u_3^*, and u_4^* satisfying:
$J(u_1^*, u_2^*, u_3^*, u_4^*) = \min\{J(u_1, u_2, u_3, u_4) | (u_1, u_2, u_3, u_4) \in U\}$, where U is the set expressed above.

Theorem 25 *(Existence of solutions). There exists an optimal control $u_1^*(t)$, $u_2^*(t)$, $u_3^*(t)$, $u_4^*(t)$ and solutions (S, E, I, L, H, A, H_E, H_I, H_L, A_L, T, A_I) such that the function $J(u_i(t)), i = 1, 2, 3, 4$*

over U. For given these optimal solutions, there exist adjoint variables, $\lambda_1(t), ..., \lambda_{12}(t)$, satisfying.

$$
\begin{cases}
\frac{d\lambda_1}{dt} = (1-u_1)(\lambda_1-\lambda_2)\frac{\beta_1(I+H_I+A_I)}{N} + (1-u_2)(\lambda_1-\lambda_5)\frac{\beta_2(H+H_E+H_I+H_L+\eta(A+A_L))}{N},\\
\frac{d\lambda_2}{dt} = \lambda_2(k+\alpha+\mu) - \lambda_3 k - \lambda_4\alpha + (\lambda_2-\lambda_7)\epsilon_1(\frac{\beta_2(H+H_E+H_I+H_L+\eta(A+A_L))}{N}),\\
\frac{d\lambda_3}{dt} = (1-u_1)(\lambda_1-\lambda_2)\frac{\beta_1 S}{N} - \lambda_2\gamma p + \lambda_3(\gamma + \epsilon_2\frac{\beta_2(H+H_E+H_I+H_L+\eta(A+A_L))}{N} + d_1 + \mu)\\
\quad -\lambda_4(1-p)\gamma + \frac{\theta\beta_1 H}{N}(\lambda_5-\lambda_7) + \frac{\omega\beta_1 A}{N}(\lambda_6-\lambda_{12}),\\
\frac{d\lambda_4}{dt} = -\lambda_2\sigma + \lambda_4(\sigma+\mu) + (\lambda_4-\lambda_5)\frac{\beta_2(H+H_E+H_I+H_L+\eta(A+A_L))}{N},\\
\frac{d\lambda_5}{dt} = \lambda_1(1-u_2)\frac{\beta_2 S}{N} + \epsilon_1\frac{\beta_2 E}{N}(\lambda_2-\lambda_7) + \epsilon_2\frac{\beta_2 I}{N}(\lambda_3-\lambda_8) + \frac{\beta_2 L}{N}(\lambda_4-\lambda_5)\\
\quad +\lambda_5(1-u_2)\frac{\beta_2 S}{N} - \sigma\lambda_6 - \lambda_7\theta(\frac{\beta_1(I+H_I+A_I)}{N}) - \lambda_{10}\omega_1(1+u_4),\\
\frac{d\lambda_6}{dt} = \lambda_1(1-u_2)\frac{\eta\beta_2 S}{N} + \epsilon_1\frac{\eta\beta_2 E}{N}(\lambda_2-\lambda_7) + \epsilon_2\frac{\eta\beta_2 I}{N}(\lambda_3-\lambda_8) + \frac{\eta\beta_2 L}{N}(\lambda_4-\lambda_5)\\
\quad +\lambda_5(1-u_2)\frac{\eta\beta_2 S}{N} + \lambda_6(d_2+\mu) + (\lambda_6-\lambda_{10})\omega_2(1+u_4) + (\lambda_6-\lambda_{12})\omega(\frac{\beta_1(I+H_I+A_I)}{N}),\\
\frac{d\lambda_7}{dt} = -b_1 + \lambda_1(1-u_2)\frac{\beta_2 S}{N} + \epsilon_1\frac{\beta_2 E}{N}(\lambda_2-\lambda_7) + \epsilon_2\frac{\beta_2 I}{N}(\lambda_3-\lambda_8) + \frac{\beta_2 L}{N}(\lambda_4-\lambda_5)\\
\quad +\lambda_5(1-u_2)\frac{\beta_2 S}{N} + \lambda_7(\epsilon+\mu) + (\lambda_7-\lambda_9)\theta_2(1+u_3)+\\
\quad (\lambda_7-\lambda_{10})\omega_3(1+u_4) + (\lambda_7-\lambda_{12})(\sigma_1+\delta_1),\\
\frac{d\lambda_8}{dt} = -b_2 + \lambda_1(1-u_2)\frac{\beta_2 S}{N} + \epsilon_1\frac{\beta_2 E}{N}(\lambda_2-\lambda_7) + \epsilon_2\frac{\beta_2 I}{N}(\lambda_3-\lambda_8) + \frac{\beta_2 L}{N}(\lambda_4-\lambda_5)\\
\quad +\lambda_5(1-u_2)\frac{\beta_2 S}{N} + \lambda_6\frac{\omega\beta_1 A}{N} + (\lambda_8-\lambda_7)\psi\gamma + \lambda_8(1-\psi)\gamma\phi+\\
\quad \psi_1(\lambda_8-\lambda_{12}) + (\lambda_8-\lambda_{10})\omega_4(1+u_4)(1-\phi),\\
\frac{d\lambda_9}{dt} = -b_3 + \lambda_1(1-u_2)\frac{\beta_2 S}{N} + \epsilon_1\frac{\beta_2 E}{N}(\lambda_2-\lambda_7) + \epsilon_2\frac{\beta_2 I}{N}(\lambda_3-\lambda_8) + \frac{\beta_2 L}{N}(\lambda_4-\lambda_5)\\
\quad +\lambda_5(1-u_2)\frac{\beta_2 S}{N} + (\lambda_9-\lambda_7)\theta_1 + (\lambda_9-\lambda_{11})\theta_3 + (\lambda_9-\lambda_{10})\omega_5(1+u_4) + \lambda_9\mu,\\
\frac{d\lambda_{10}}{dt} = -\lambda_6\varphi + \lambda_{10}(\varphi+\mu),\\
\frac{d\lambda_{11}}{dt} = -b_4 + \lambda_1(1-u_2)\frac{\eta\beta_2 S}{N} + \epsilon_1\frac{\eta\beta_2 E}{N}(\lambda_2-\lambda_7) + \epsilon_2\frac{\eta\beta_2 I}{N}(\lambda_3-\lambda_8) + \frac{\eta\beta_2 L}{N}(\lambda_4-\lambda_5)\\
\quad +\lambda_5(1-u_2)\frac{\eta\beta_2 S}{N} + (\lambda_{11}-\lambda_{10})\omega_6(1+u_4) + \lambda_{11}(d_2+\mu),\\
\frac{d\lambda_{12}}{dt} = -b_5 + (\lambda_1-\lambda_2)(1-u_1)\frac{\eta\beta_1 S}{N} + (\lambda_1-\lambda_5)(1-u_2)\frac{\eta\beta_2 S}{N} + \epsilon_1\frac{\eta\beta_2 E}{N}(\lambda_2-\lambda_7)+\\
\quad \epsilon_2\frac{\eta\beta_2 I}{N}(\lambda_3-\lambda_8) + \frac{\eta\beta_2 L}{N}(\lambda_4-\lambda_5) + (\lambda_5-\lambda_7)\frac{\theta\beta_1\eta H}{N} + \lambda_6)\frac{\omega\beta_1\eta A}{N} + (\lambda_{12}-\lambda_{10})\omega_7(1+u_4)\\
\quad +(\lambda_{12}-\lambda_{11})(\tau) + \lambda_{12}(d_3+\mu),
\end{cases}
\tag{5.32}
$$

with the transversality conditions $\lambda_i(t_f) = 0, i = 1, 2, 3, ..., 12$. Moreover, we get the control set $(u_1^*(t), u_2^*(t), u_3^*(t), u_4^*(t))$ characterized by:

$$u_1^*(t) = max\{0, min(1, u_1^*)\}, \qquad u_2^*(t) = max\{0, min(1, u_2^*)\},$$
$$u_3^*(t) = max\{0, min(1, u_3^*)\}, \qquad u_4^*(t) = max\{0, min(1, u_4^*)\}; \text{ where}$$

$$u_1^* = \frac{\beta_1 S(\lambda_2-\lambda_1)(I+H_I+A_I)}{c_1 N}, \qquad u_2^* = \frac{\beta_2 S(\lambda_5-\lambda_1)(H+H_E+H_I+H_L+\eta(A+A_I)}{c_2 N},$$
$$u_3^* = \frac{(\lambda_7-\lambda_9)\theta_2 H_E}{c_3}, \qquad \text{and}$$
$$u_4^* = \frac{(\lambda_5-\lambda_{10})\omega_1 H+(\lambda_6-\lambda_{10})\omega_2 A+(\lambda_7-\lambda_{10})\omega_3 H_E+(\lambda_8-\lambda_{10})\omega_4(1-\phi)H_I+(\lambda_9-\lambda_{10})\omega_5 H_L+(\lambda_{11}-\lambda_{10})\omega_6 A_L+(\lambda_{12}-\lambda_{10})\omega_7 A_I}{c_4}.$$

Proof:

Look the following three conditions are verified thanks to Fleming and Rishel's theorem.

1. The set of solutions of (5.30) and the associated control variables in U is non-empty.

2. The system of (5.30) is a linear combination of control functions with coefficients are state functions or functions depending of time.

3. The integrand L in (5.31) becomes $L(x,u,t) = b_1H_E(t) + b_2H_I(t) + b_3H_L(t) + b_4A_L(t) + b_5A_I(t) + \frac{1}{2}\sum_{i=1}^{4} c_iu_i^2(t)$ is convex on U and it also fulfills $L(x,u,t) \geq \delta_1 \mid (u_1,u_2,u_3,u_4) \mid^{\beta} -\delta_2$, where $\delta_1 > 0$ and $\beta > 1$.

Firstly to proof 1, we mentioned to [CL55, GCF$^+$08]. In fact if the solutions of (5.30)–(5.31) are bounded and Lipschitz, then they are unique.
Thus $N(t)$ also bounded above by $\frac{\pi}{\mu}$ and below by $N_0 \neq 0$. Here, each compartment in $N(t)$ is bounded. In that case the state variables are bounded and continuous. Hence, this displays that there is the boundedness of the partial derivatives with respect to the state variables with in the system [Cod12].
This accomplishes that proof 1 holds.
Secondly, 2 is confirmed by simply looking the state equations which are linear combinations of the controls u_i, for $i = 1,2,3,4$.
Lastly to verify condition 3, we refer to [BP12, Ped06] any constant, linear and quadratic functions are convex. Hence, $L(x,u,t)$ is convex on U. Hereafter, to prove the boundedness on L, as shown below.
$c_3u_3^2 \leq c_3$, since $u_3 \in [0,1]$.
$\Rightarrow \frac{1}{2}c_3u_3^2 \leq \frac{c_3}{2} \Rightarrow \frac{1}{2}c_3u_3^2 - \frac{c_3}{2} \leq 0.$
Then $L(x,u,t) = b_1H_E(t)+b_2H_I(t)+b_3H_L(t)+b_4A_L(t)+b_5A_I(t)+\frac{1}{2}\sum_{i=1}^{4} c_iu_i^2(t) \geq \frac{1}{2}\sum_{i=1}^{4} c_iu_i^2 - \frac{c_3}{2}$,
$\Rightarrow L(x,u,t) \geq \min(\frac{c_1}{2}, \frac{c_2}{2}, \frac{c_3}{2}, \frac{c_4}{2})(u_1^2 + u_2^2 + u_3^2 + u_4^2) - \frac{c_3}{2}$,
$\Rightarrow L(x,u,t) \geq \min(\frac{c_1}{2}, \frac{c_2}{2}, \frac{c_3}{2}, \frac{c_4}{2}) \mid\mid (u_1,u_2,u_3,u_4) \mid\mid^2 -\frac{c_3}{2}$.
Therefore, $L(x,u,t) \geq \delta_1 \mid\mid (u_1,u_2,u_3,u_4) \mid\mid^{\beta} -\delta_2$, where $\delta_1 = \min(\frac{c_1}{2}, \frac{c_2}{2}, \frac{c_3}{2}, \frac{c_4}{2})$, $\delta_2 = \frac{c_4}{2}$ and $\beta = 2$.
By using PMP [PM86], we found a Hamiltonian ($\mathbb{H}$) stated as:
$\mathbb{H}(S,E,I,L,H,A,H_E,H_I,H_L,A_L,T,A_I,u,t) = L(x,u,t) + \lambda_1\frac{dS}{dt} + \lambda_2\frac{dE}{dt} + \lambda_3\frac{dI}{dt} + \lambda_4\frac{dL}{dt} + \lambda_5\frac{dH}{dt} + \lambda_6\frac{dA}{dt} + \lambda_7\frac{dH_E}{dt} + \lambda_8\frac{dH_I}{dt} + \lambda_9\frac{dH_L}{dt} + \lambda_{10}\frac{dT}{dt} + \lambda_{11}\frac{dA_L}{dt} + \lambda_{12}\frac{dA_I}{dt}$,
where $\lambda_i, i = 1,2,...,12$ are the co-state variables.
We refereed [FR82] to show the existence of optimal control pairs.
In addition to this, we applied the next procedure to show the system (5.32) and optimal control functions .
The Hamiltonian function $\mathbb{H}$ is described by:
$\mathbb{H} = b_1H_E(t) + b_2H_I(t) + b_3H_L(t) + b_4A_L(t) + b_5A_I(t) + \frac{1}{2}(c_1u_1^2 + c_2u_2^2 + c_3u_3^2 + c_4u_4^2) + \lambda_1[\pi -$

$((1-u_2)\lambda_H+(1-u_1)\lambda_T+\mu)S]+\lambda_2[(1-u_1)\lambda_T S+\gamma pI+\sigma L-(k+\alpha+\epsilon_1\lambda_H+\mu)E]+\lambda_3[kE-(\gamma+\epsilon_2\lambda_H+d_1+\mu)I]+\lambda_4[(1-p)\gamma I+\alpha E-(\sigma+\lambda_H+\mu)L]+\lambda_5[(1-u_2)\lambda_H S+\lambda_H L-(\theta\lambda_T+\delta+\omega_1(1+u_4)+\mu)H]+\lambda_6[\delta H+\varphi T-(\omega_2(1+u_4)+\omega\lambda_T+\mu+d_2)A]+\lambda_7[\epsilon_1\lambda_H E+\theta\lambda_T H+\psi\gamma H_I+\theta_1 H_L-(\epsilon+\omega_3(1+u_4)+\theta_2(1+u_3)+\sigma_1+\delta_1+\mu)H_E]+\lambda_8[\epsilon_2\lambda_H I+\epsilon H_E-(\psi\gamma+(1-\psi)\gamma\phi+(1-\phi)\omega_4(1+u_4)+\psi_1+\mu+d_1)H_I]+\lambda_9[(1-\psi)\phi\gamma H_I+\theta_2(1+u_3)H_E-(\theta_1+\theta_3+\omega_5(1+u_4)+\mu)H_L]+\lambda_{10}[\omega_1(1+u_4)H+\omega_2(1+u_4)A+\omega_3(1+u_4)H_E+\omega_4(1+u_4)(1-\phi)H_I+\omega_5(1+u_4)H_L+\omega_6(1+u_4)A_L+\omega_7(1+u_4)A_I-(\varphi+\mu)T]+\lambda_{11}[(\tau)A_I+\theta_3 H_L-(\omega_6(1+u_4)+\mu+d_2)A_L]+\lambda_{12}[(\sigma_1+\delta_1)H_E+\psi_1 H_I+\omega\lambda_T A-(\omega_7(1+u_4)+\mu+d_3+\tau+u_4)A_I]$.

Hereafter, the second condition of the PMP sates that, $\exists$ adjoint variables $\lambda_i, i=1,2,...,12$ which fulfill the next equalities.

$$\frac{d\lambda_1}{dt}=-\frac{d\mathbb{H}}{dS},\quad \frac{d\lambda_2}{dt}=-\frac{d\mathbb{H}}{dE},\quad \frac{d\lambda_3}{dt}=-\frac{d\mathbb{H}}{dI},\quad \frac{d\lambda_4}{dt}=-\frac{d\mathbb{H}}{dL},$$
$$\frac{d\lambda_5}{dt}=-\frac{d\mathbb{H}}{dH},\quad \frac{d\lambda_6}{dt}=-\frac{d\mathbb{H}}{dA},\quad \frac{d\lambda_7}{dt}=-\frac{d\mathbb{H}}{dH_E},\quad \frac{d\lambda_8}{dt}=-\frac{d\mathbb{H}}{dH_I},$$
$$\frac{d\lambda_9}{dt}=-\frac{d\mathbb{H}}{dH_L},\quad \frac{d\lambda_{10}}{dt}=-\frac{d\mathbb{H}}{dT},\quad \frac{d\lambda_{11}}{dt}=-\frac{d\mathbb{H}}{dA_L},\quad \frac{d\lambda_{12}}{dt}=-\frac{d\mathbb{H}}{dA_I}.$$

We obtained the result of these derivations like below:

$$
\begin{cases}
\frac{d\lambda_1}{dt} = (1-u_1)(\lambda_1-\lambda_2)\frac{\beta_1(I+H_I+A_I)}{N} + (1-u_2)(\lambda_1-\lambda_5)\frac{\beta_2(H+H_E+H_I+H_L+\eta(A+A_L))}{N},\\
\frac{d\lambda_2}{dt} = \lambda_2(k+\alpha+\mu) - \lambda_3 k - \lambda_4\alpha + (\lambda_2-\lambda_7)\epsilon_1(\frac{\beta_2(H+H_E+H_I+H_L+\eta(A+A_L))}{N}),\\
\frac{d\lambda_3}{dt} = (1-u_1)(\lambda_1-\lambda_2)\frac{\beta_1 S}{N} - \lambda_2\gamma p + \lambda_3(\gamma + \epsilon_2\frac{\beta_2(H+H_E+H_I+H_L+\eta(A+A_L))}{N} + d_1 + \mu)\\
\quad -\lambda_4(1-p)\gamma + \frac{\theta\beta_1 H}{N}(\lambda_5-\lambda_7) + \frac{\omega\beta_1 A}{N}(\lambda_6-\lambda_{12}),\\
\frac{d\lambda_4}{dt} = -\lambda_2\sigma + \lambda_4(\sigma+\mu) + (\lambda_4-\lambda_5)\frac{\beta_2(H+H_E+H_I+H_L+\eta(A+A_L))}{N},\\
\frac{d\lambda_5}{dt} = \lambda_1(1-u_2)\frac{\beta_2 S}{N} + \epsilon_1\frac{\beta_2 E}{N}(\lambda_2-\lambda_7) + \epsilon_2\frac{\beta_2 I}{N}(\lambda_3-\lambda_8) + \frac{\beta_2 L}{N}(\lambda_4-\lambda_5)\\
\quad +\lambda_5(1-u_2)\frac{\beta_2 S}{N} - \sigma\lambda_6 - \lambda_7\theta(\frac{\beta_1(I+H_I+A_I)}{N}) - \lambda_{10}\omega_1(1+u_4),\\
\frac{d\lambda_6}{dt} = \lambda_1(1-u_2)\frac{\eta\beta_2 S}{N} + \epsilon_1\frac{\eta\beta_2 E}{N}(\lambda_2-\lambda_7) + \epsilon_2\frac{\eta\beta_2 I}{N}(\lambda_3-\lambda_8) + \frac{\eta\beta_2 L}{N}(\lambda_4-\lambda_5)\\
\quad +\lambda_5(1-u_2)\frac{\eta\beta_2 S}{N} + \lambda_6(d_2+\mu) + (\lambda_6-\lambda_{10})\omega_2(1+u_4) + (\lambda_6-\lambda_{12})\omega(\frac{\beta_1(I+H_I+A_I)}{N}),\\
\frac{d\lambda_7}{dt} = -b_1 + \lambda_1(1-u_2)\frac{\beta_2 S}{N} + \epsilon_1\frac{\beta_2 E}{N}(\lambda_2-\lambda_7) + \epsilon_2\frac{\beta_2 I}{N}(\lambda_3-\lambda_8) + \frac{\beta_2 L}{N}(\lambda_4-\lambda_5)\\
\quad +\lambda_5(1-u_2)\frac{\beta_2 S}{N} + \lambda_7(\epsilon+\mu) + (\lambda_7-\lambda_9)\theta_2(1+u_3) +\\
\quad (\lambda_7-\lambda_{10})\omega_3(1+u_4) + (\lambda_7-\lambda_{12})(\sigma_1+\delta_1),\\
\frac{d\lambda_8}{dt} = -b_2 + \lambda_1(1-u_2)\frac{\beta_2 S}{N} + \epsilon_1\frac{\beta_2 E}{N}(\lambda_2-\lambda_7) + \epsilon_2\frac{\beta_2 I}{N}(\lambda_3-\lambda_8) + \frac{\beta_2 L}{N}(\lambda_4-\lambda_5)\\
\quad +\lambda_5(1-u_2)\frac{\beta_2 S}{N} + \lambda_6\frac{\omega\beta_1 A}{N} + (\lambda_8-\lambda_7)\psi\gamma + \lambda_8(1-\psi)\gamma\phi +\\
\quad \psi_1(\lambda_8-\lambda_{12}) + (\lambda_8-\lambda_{10})\omega_4(1+u_4)(1-\phi),\\
\frac{d\lambda_9}{dt} = -b_3 + \lambda_1(1-u_2)\frac{\beta_2 S}{N} + \epsilon_1\frac{\beta_2 E}{N}(\lambda_2-\lambda_7) + \epsilon_2\frac{\beta_2 I}{N}(\lambda_3-\lambda_8) + \frac{\beta_2 L}{N}(\lambda_4-\lambda_5)\\
\quad +\lambda_5(1-u_2)\frac{\beta_2 S}{N} + (\lambda_9-\lambda_7)\theta_1 + (\lambda_9-\lambda_{11})\theta_3 + (\lambda_9-\lambda_{10})\omega_5(1+u_4) + \lambda_9\mu,\\
\frac{d\lambda_{10}}{dt} = -\lambda_6\varphi + \lambda_{10}(\varphi+\mu),\\
\frac{d\lambda_{11}}{dt} = -b_4 + \lambda_1(1-u_2)\frac{\eta\beta_2 S}{N} + \epsilon_1\frac{\eta\beta_2 E}{N}(\lambda_2-\lambda_7) + \epsilon_2\frac{\eta\beta_2 I}{N}(\lambda_3-\lambda_8) + \frac{\eta\beta_2 L}{N}(\lambda_4-\lambda_5)\\
\quad +\lambda_5(1-u_2)\frac{\eta\beta_2 S}{N} + (\lambda_{11}-\lambda_{10})\omega_6(1+u_4) + \lambda_{11}(d_2+\mu),\\
\frac{d\lambda_{12}}{dt} = -b_5 + (\lambda_1-\lambda_2)(1-u_1)\frac{\eta\beta_1 S}{N} + (\lambda_1-\lambda_5)(1-u_2)\frac{\eta\beta_2 S}{N} + \epsilon_1\frac{\eta\beta_2 E}{N}(\lambda_2-\lambda_7) +\\
\quad \epsilon_2\frac{\eta\beta_2 I}{N}(\lambda_3-\lambda_8) + \frac{\eta\beta_2 L}{N}(\lambda_4-\lambda_5) + (\lambda_5-\lambda_7)\frac{\theta\beta_1\eta H}{N} + \lambda_6)\frac{\omega\beta_1\eta A}{N} + (\lambda_{12}-\lambda_{10})\omega_7(1+u_4)\\
\quad +(\lambda_{12}-\lambda_{11})(\tau) + \lambda_{12}(d_3+\mu),
\end{cases}
\tag{5.33}
$$

with the final conditions $\lambda_i(t_f) = 0, i = 1, 2, 3, ..., 12$.

By optimality conditions we get:

$$\frac{d\mathbb{H}}{du_1}\Big|_{u_1=u_1^*} = 0, \qquad \frac{d\mathbb{H}}{du_2}\Big|_{u_2=u_2^*} = 0,$$
$$\frac{d\mathbb{H}}{du_3}\Big|_{u_3=u_3^*} = 0, \qquad \frac{d\mathbb{H}}{du_4}\Big|_{u_4=u_4^*} = 0.$$

So, $u_1^* = \frac{\beta_1 S(\lambda_2-\lambda_1)(I+H_I+A_I)}{c_1 N}$, $u_2^* = \frac{\beta_2 S(\lambda_5-\lambda_1)(H+H_E+H_I+H_L+\eta(A+A_I))}{c_2 N}$,
$u_3^* = \frac{(\lambda_7-\lambda_9)\theta_2 H_E}{c_3}$ and

$$u_4^* = \frac{(\lambda_5-\lambda_{10})\omega_1 H+(\lambda_6-\lambda_{10})\omega_2 A+(\lambda_7-\lambda_{10})\omega_3 H_E+(\lambda_8-\lambda_{10})\omega_4(1-\phi)H_I+(\lambda_9-\lambda_{10})\omega_5 H_L}{c_4}+ \frac{(\lambda_{11}-\lambda_{10})\omega_6 A_L+(\lambda_{12}-\lambda_{10})\omega_7 A_I}{c_4}.$$

These results can be expressed in U likes below.

$$u_1(t) = \begin{cases} 0, & \text{if} \quad u_1^* \leq 0 \\ u_1^*, & \text{if} \quad 0 < u_1^* < 1 \\ 1, & \text{if} \quad u_1^* \geq 1 \end{cases}, \qquad u_2(t) = \begin{cases} 0, & \text{if} \quad u_2^* \leq 0 \\ u_2^*, & \text{if} \quad 0 < u_2^* < 1 \\ 1, & \text{if} \quad u_2^* \geq 1 \end{cases},$$

$$u_3(t) = \begin{cases} 0, & \text{if} \quad u_3^* \leq 0 \\ u_3^*, & \text{if} \quad 0 < u_3^* < 1 \\ 1, & \text{if} \quad u_3^* \geq 1 \end{cases}, \qquad u_4(t) = \begin{cases} 0, & \text{if} \quad u_4^* \leq 0 \\ u_4^*, & \text{if} \quad 0 < u_4^* < 1 \\ 1, & \text{if} \quad u_2^* \geq 1 \end{cases}.$$

5.5 Numerical simulations

Till now, the TB-HIV co-infection model with or without optimal control is analysed analytically. Here, we will discuss the numerical results to confirm our analytical findings. It also gives a clear image about the involvement of control functions on the disease transmission dynamics. We shall propose two or more intervention strategies at a time to minimize both the disease and the cost burden.

Hence, we will execute this section based on the initial value of each compartment and values of parameters. The populations in classes $E = 1.19 \times 10^6, I = 3.73 \times 10^5$, and $L = 2.18 \times 10^7$, collected from National TB and Leprosy strategic plan in Ethiopia [vvv22]. Again, we estimated H =890 311, A= 305 770, H_E = 213 451, H_I = 250 853, H_L = 290 008, T = 1 253 420, A_L = 207 457, A_I = 120 598 collected from Federal health ministry of Ethiopia, WHO annual report, and CDC.

The susceptible people is obtained by $S = N - (E + I + L + H + A + H_E + H_I + H_L + A_L + A_I)$ where N=102 468 037, then S = 75 573 169. The recruitment people enter to class S is calculated by $\pi = b \times N$, where the birth rate b =30.97 /1 000 . Hence, the value π =3 173 435.1 .

Some of the parameters in model (5.1) are estimated via similar technique with in Chapter 3. We presented the value of the parameters in Table [5.2] as well as we fixed the time duration of our study as $t_f = 10$ years.

In addition, we assessed the value of the coefficient parameters ($b_1 = 0.65, b_2 = 0.55, b_3 = 0.28, b_4 = 1$, and $b_5 = 1.72$) depend on the way of constants found in [MLV16]. Furthermore, we assumed that the value of weight constants based on the importance level of one intervention over the other. These are $c_1 = 10^4, c_2 = 10^4, c_3 = 2 \times 10^4$, and $c_4 = 2 \times 10^4$. Some data may also taken as just for numerical purpose. Nevertheless, obtaining sufficient data about the vital elements

Parameters	Values	References	Parameters	Values	References
π	3.1734×10^6	Calculated	β_2	0.18	[AGM21]
β_1	0.00151	[cgt21b]	ϕ	0.701	Assumed
μ	0.0058	Estimated	σ	0.0013	[KMW19]
θ	0.3	Estimated	γ	0.546	[KMW19]
ϵ_1	0.004	[vvv22]	ϵ_2	0.001	Calculated
ϵ	0.5	Calculated	d_2	0.016	Estimated
p	0.168	[cgt21b]	δ	0.62	Estimated
d_1	0.0003	[vvv22]	d_3	0.002	[Yoh21]
α	0.153	Calculated	k	0.023	Estimated
ω	1.17	[ST15]	σ_1	0.015	Estimated
δ_1	0.03	Estimated	θ_1	0.0026	Assumed
ψ	0.336	Assumed	θ_2	0.153	Estimated
ψ_1	0.88	[Mer20]	φ	0.08	Assumed
τ	0.6	Estimated	θ_3	0.1	Estimated
η	1.05	[KO11]	ω_4, ω_7	0.4	Estimated
ω_3	0.302	Estimated	$\omega_i, i = 1, 2, 5, 6$	0.2	Estimated

Table 5.2: Symbols and values of parameters.

of the TB-HIV/AIDS co-infection model is one big challenge of this study.

We used MATLAB software to validate the analytical results. Here, we discussed the features of state trajectories with or without control. The control profiles of each strategy are also plotted. We propose four strategies based on the suggested intervention approaches. They designed as combination of two or more strategies at a time. However, only one intervention at a time is not effective [AGM21]. Thus, we have seen these strategies can highly minimize TB-HIV co-infection disease in our country Ethiopia and the elaborations are continuing in the next part.

5.5.1 Preventive effort of TB disease and treatment of HIV/AIDS disease

We used prevention of TB disease combined with HIV/AIDS treatment as an alternative intervention strategy (i.e.$u_i \neq 0$, for $i = 1, 4$,whereas $u_2 = 0$, and $u_3 = 0$). The plot (A-E) of Figure (5.2–5.4) illustrates the impact of this optimal approach on HIV/AIDS-TB co-infected individuals. This strategy can be used to decreases the number of low risk latent TB individuals co-infected by HIV with pre-AIDS and AIDS symptoms dramatically rather than without control.

As shown in the Figure (5.2)- A and B, If no optimal control is applied, the co-infected individuals in H_L and A_L classes increased at the beginning of the year and reached at a peak value at 3.2999×10^5 and 3.1217×10^5 respectively. Hereafter, the disease burden decreased significantly. However, in case of optimal control the prevention effort has an impact on individuals under H_L class, because it reduces the high risk latent individuals. In addition, the more co-infected people

are moved to the treated class due to HIV treatment.
In Figure (5.3)-C, when no optimal control is used the co-infectious people decreased in H_I class due to the influence of constant treatment rate w_4 for HIV and successful TB treatment rate of $1-\psi$. Conversely, in Figure (5.3)-D, the co-infectious people increased at the beginning of the years and reached at a peak value 1.5322×10^4. Hereafter, the disease burden decreased significantly. This is because more TB infected people co-infected with HIV completed their TB treatment at a constant rate τ and with constant HIV treatment rate w_7 . However, the time-based optimal approach seems negligible in the H_I compartment but later one can observe its impact. This combination strategy has a high effect on the co-infected people by active TB and HIV with AIDS symptoms. This shows, the prevention effort can minimize the susceptible individuals become TB infected. Consequently, individuals will decrease from high-risk latent stage progress to active stage. Additionally, the more co-infectious people are joined to treated class due to HIV treatment.
In Figure (5.4)-E, when no optimal control is used the co-infected people decreased in H_E class due to the influence of constant treatment rate w_3 for HIV and treatment rate of high risk latent TB θ_2. Nevertheless, when optimal control is used the disease burden decreased rather than without control. The impact of this strategy is visible around five years but seems negligible after a while. Therefore, this strategy can minimize/eradicate the HIV-TB co-infection disease burden in our country, Ethiopia.

5.5.2 Preventive effort of HIV/AIDS disease and case finding TB

We used prevention of HIV/AIDS disease combined with case finding effort of TB as optimal intervention (i.e.$u_i \neq 0$, for $i = 2, 3$, whereas $u_1 = 0$, and $u_4 = 0$). The plot (A-E) of Figure (5.5–5.7) illustrates the impact of this optimal approach on HIV/AIDS-TB co-infected individuals. As shown in the Figure (5.5)- A and B, if no time-based control is used, the co-infected individual in H_L and A_L increased at the beginning of the year. The disease burden decreased dramatically after a while. Nevertheless, in case of optimal control, the co-infected individuals in these two sub-classes are not decreased more as compared from the first strategy. Since, there are more HIV-infected people who have recovered from TB but remain low-risk latent due to case-finding effort. Hence, the co-infected populations in the H_L class are increased and reached a peak value 3.6876×10^5. Conversely, the optimal strategy seems negligible for the first around 1 year in A_L class but it shows a significant influence far ahead.
In Figure (5.6)-C, the impact of optimal control strategy seems negligible in the H_I class but it has a visible impact to some extent. While, in Figure (5.6)-D, the co-infected people in A_I compartment are raised for the first few months and reached a high value 1.5322×10^5. Afterwards, the co-infected individuals in A_I class decreased radically.

In Figure (5.7)-E, the co-infected people in H_E class are decreased when optimal control is used. In this compartment, the influence of this strategy is better than the first approach. Since, the number of HIV people co-infected with TB at a high-risk latent stage are decreased more because of case-finding effort.
Hence, this strategy can minimize/eradicate the HIV-TB co-infection disease burden.

5.5.3 Case finding for TB disease and HIV treatment

We used case finding for TB disease combined with HIV/AIDS treatment as elective optimal control (i.e.$u_i \neq 0$, for $i = 3, 4$, whereas $u_1 = 0$, and $u_2 = 0$). The plot (A-E) of Figure (5.8 –5.10) illustrates the impact of this optimal approach on HIV/AIDS-TB co-infected individuals. Each plot shows that the model with and without optimal control plays a great role to minimize the disease burden.
In the Figure (5.8)- A, the numerical results displayed that this strategy is better than the second strategy due to HIV treatment effort. The disease burden seems raised at the first of a few months, but decreased intensely later. The optimal strategy is more effective approach on the co-infected class A_I as shown in the Figure (5.8)- B. The graphical result shows the combination optimal approach can reduce the disease load effectively.
In Figure (5.9)-C, one can observe that this combination optimal control has enhanced the impact on the co-infected class H_I rather than the second strategy. The same effect is shown in the sub-population A_I (5.9)-D. For the reason that, the more co-infected people are moved to the treated class as a result of HIV treatment effort.
In Figure (5.10)-E, the number of co-infected people in H_E class are reduced when optimal control is used. In this class, the effect of this strategy is also better than the first approach.
Thus, the optimal control of case finding effort of TB and HIV/AIDS treatment has great impact to reduce the disease burden.

5.5.4 Using all the intervention efforts

We used all intervention efforts optimally as an alternative mechanism (i.e.$u_i \neq 0$, for $i = 1, 2, 3, 4$). The plot (A-E) of Figure (5.11) –(5.13) displays the effect of this approach on HIV/AIDS TB co-infected people. All graphical results show that the model with and without optimal control plays a great role to minimize the disease burden. The effect of this mechanism on co-infected individuals seems like to the third strategy, but the visible differences appear on the cost needed for implementation. This will be discussed in the cost-effectiveness section.
The control profiles that generate this simulation result are as shown in the Figure (5.13) (F). Figure (F) displays that, the pink color of the trajectory u_1 is concealed by the cyan color of the trajectory

u_2. The control plots u_1 and u_2 display the maximum efforts required for the entire duration. The control plot u_3 shows that high case-finding for TB is needed for the first around 1 year and extremely reduced later. The control plot u_4 shows high treatment of HIV is required for around 7.8 year and reduced after a while. Finally, all controls are dropped to zero due to the proposed strategies being expected to be over at the end of the time forecast.

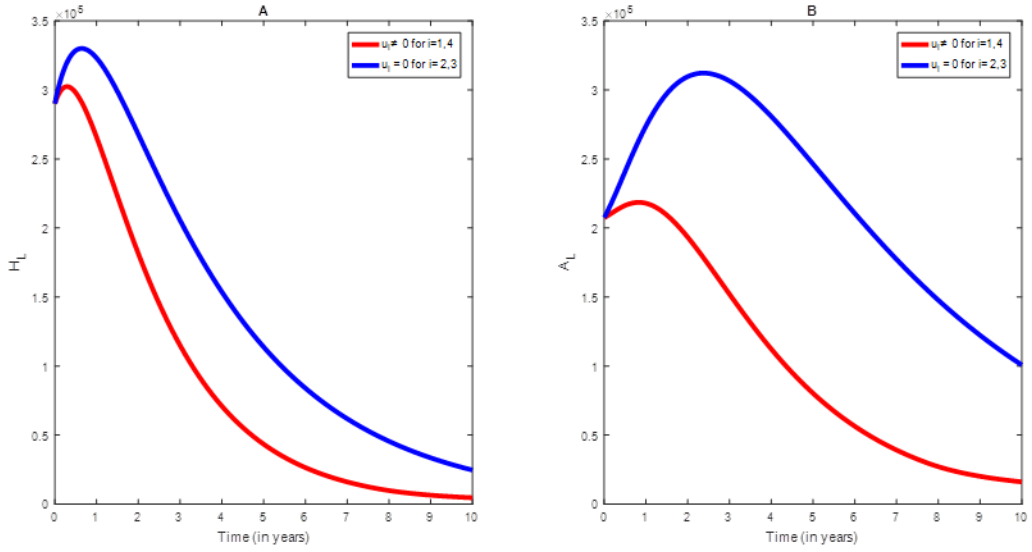

Figure 5.2: Infected individuals in H_L and A_L class when applying combined efforts of prevention of TB and treatment of HIV/AIDS optimally.

5.6 Cost-effectiveness analysis

Here, we presented the cost-effectiveness rank of one implemented strategy over the other. We achieved this by (Baba and Makinde, 2014); they had declared that
Incremental Cost-Effectiveness Ratio (ICER)= $\frac{\text{Difference in costs between strategies}}{\text{Difference in health effects between strategies}}$.
We get the total number of infected averted which is the difference between the total infected without and with control. We applied this technique by ranked increasing order of effectiveness with respect to infected averted. Besides, the total cost is also mentioned in Table [5.3].
We compare the strategy of B and C by computing the $ICER$:

$ICER(B) = \frac{6.0870\times10^6}{9.661\times10^5} = 6.3$ and ICER (C)$= \frac{8.6911\times10^6 - 6.0870\times10^6}{1.0603\times10^6 - 9.661\times10^5} = 27.64$.

The comparison displayed that $ICER(C) > ICER(B)$, which shows that strategy C is strongly dominated and does not consume limited resource.

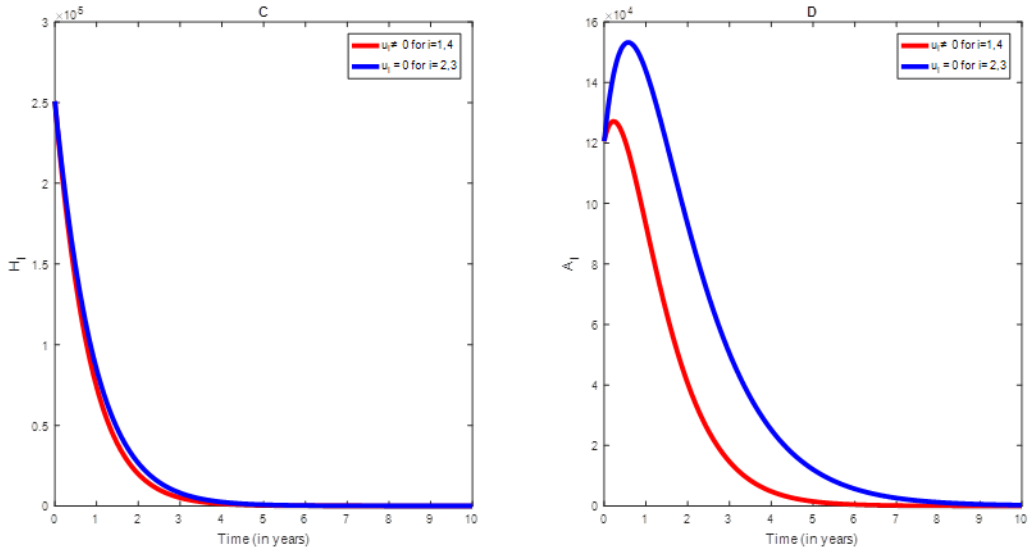

Figure 5.3: Infected individuals in H_I and A_I class when applying combined efforts of prevention of TB and treatment of HIV/AIDS optimally.

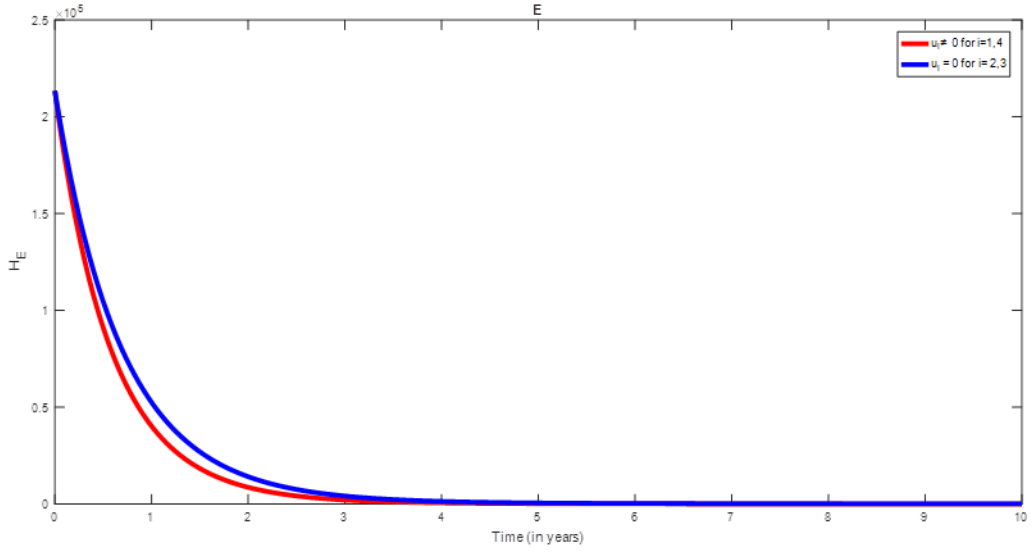

Figure 5.4: Infected individuals in H_E class when applying combined efforts of prevention of TB and treatment of HIV/AIDS optimally.

Hence, we should remove strategy C from the set of choices.

Next, we compare strategy B and D.

Already we calculated $ICER(B) = 6.3$ $ICER(D) = \frac{1.7715\times10^7 - 6.0870\times10^6}{1.0613\times10^6 - 9.661\times10^5} = 122.14.$

The comparison showed that strategy D is more costly and less effectiveness than strategy B. Hence,

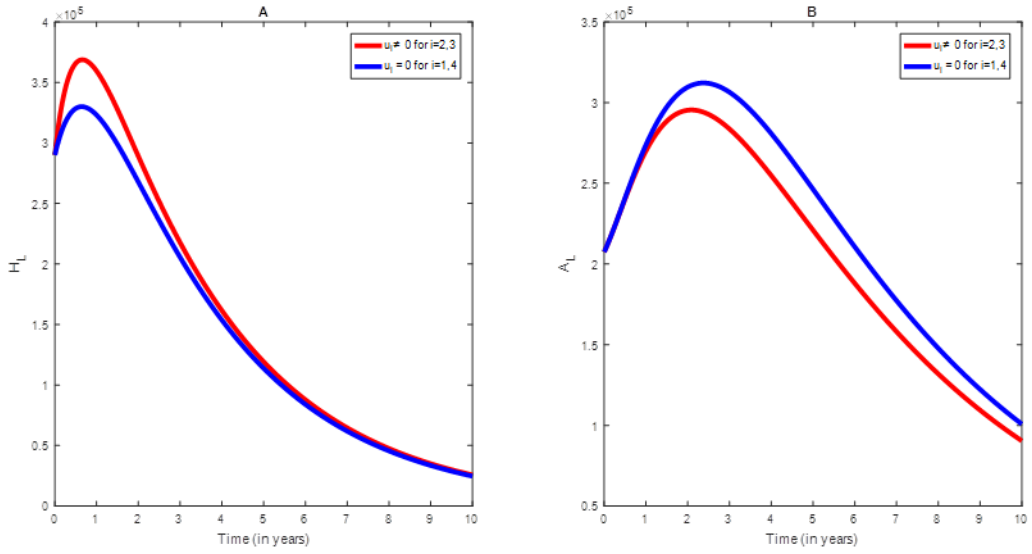

Figure 5.5: Infected individuals in H_L and A_L class when applying combined efforts of prevention of HIV/AIDS and case finding TB optimally.

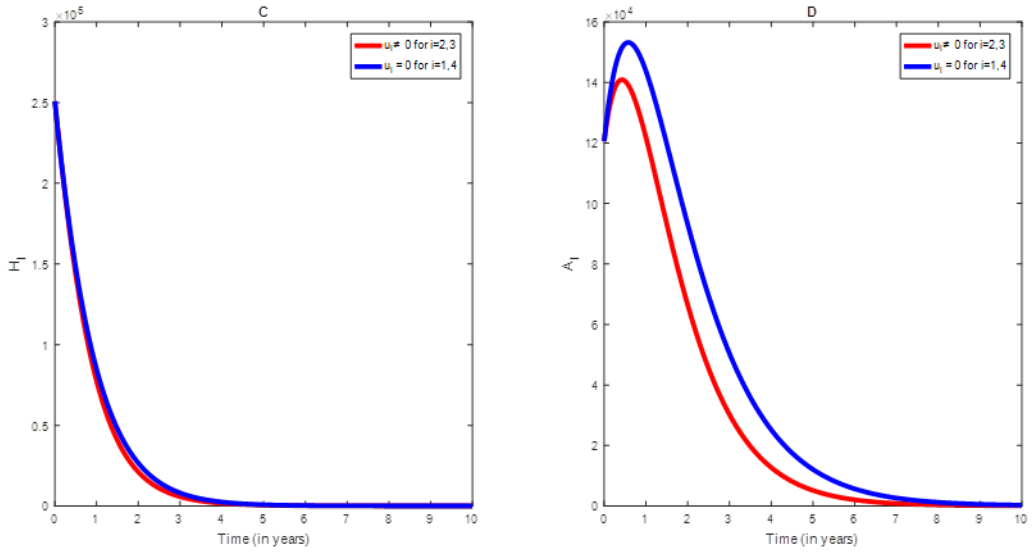

Figure 5.6: Infected individuals in H_I and A_I class when applying combined efforts of prevention of HIV/AIDS and case finding TB optimally.

we should remove strategy D from the set of alternatives.

Finally, we compare strategy B and A.

Now, $ICER(A) = \frac{1.2038\times10^7 - 6.0870\times10^6}{1.0616\times10^6 - 9.661\times10^5} = 62.314.$

This implies that, we should remove strategy A from alternative approaches.

Therefore, strategy B is the most cost-effective strategy rather than the rest choices.

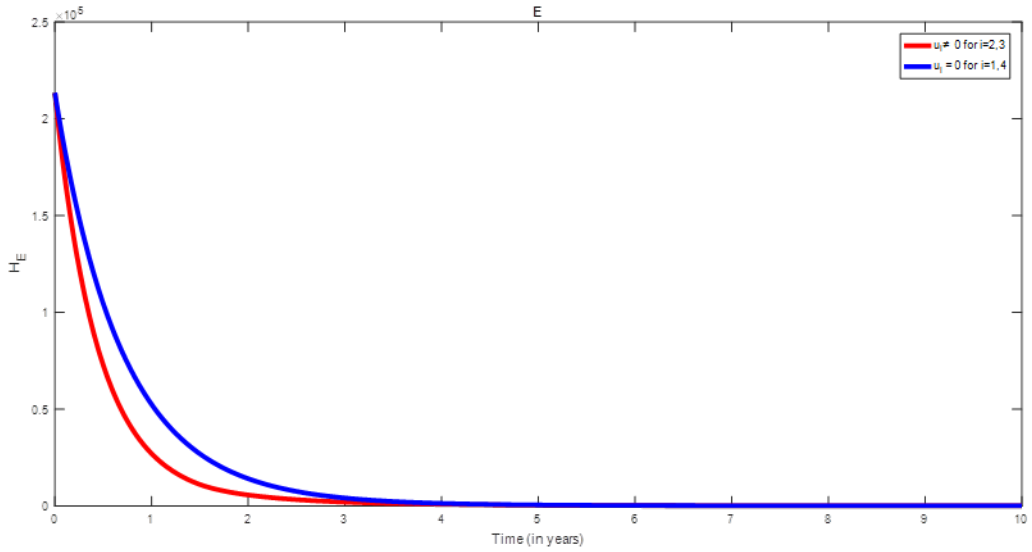

Figure 5.7: Infected individuals in H_E class when applying combined efforts of prevention of HIV/AIDS and case finding TB optimally.

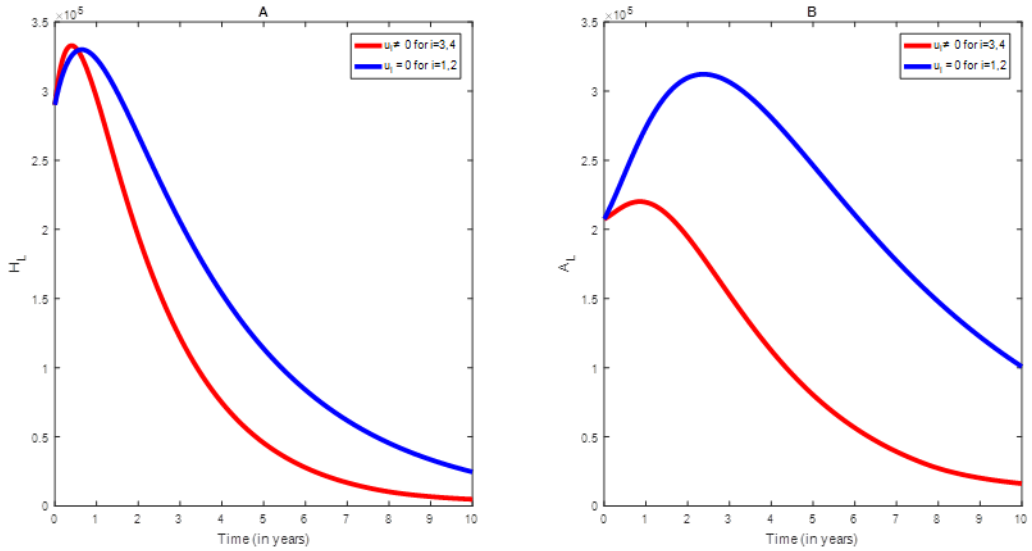

Figure 5.8: Infected individuals in H_L and A_L class when applying combined efforts of case finding TB and HIV treatment optimally.

Plans	Description	Total infected averted	Total cost (USD)
B	Preventive of HIV & case finding TB	9.661×10^5	6.0870×10^6
C	Case finding TB & HIV treatment	1.0603×10^6	8.6911×10^6
D	All interventions	1.0613×10^6	1.7715×10^7
A	Preventive of TB & HIV treatment	1.0616×10^6	1.2038×10^7

Table 5.3: Total infected averted (increasing order) and total cost.

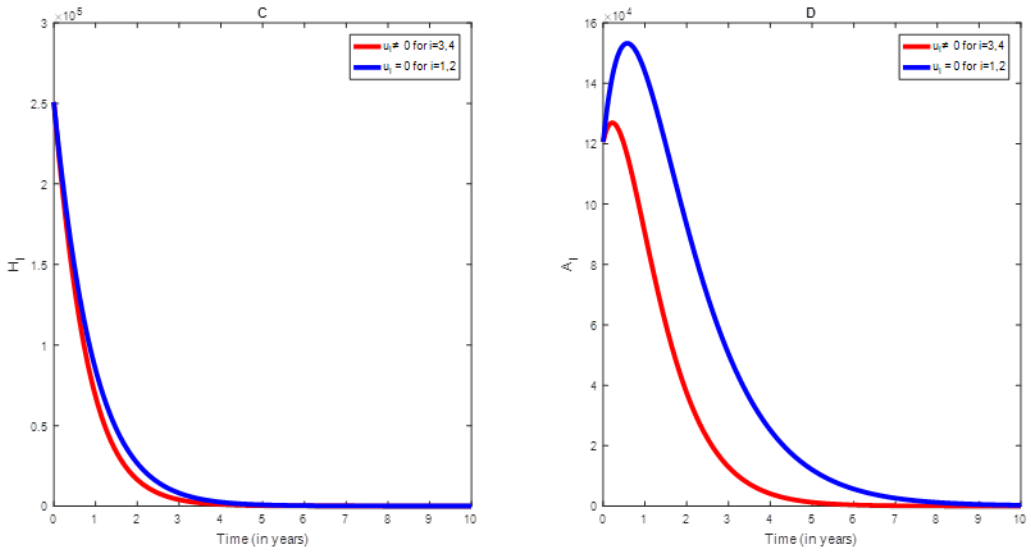

Figure 5.9: Infected individuals in H_I and A_I class when applying combined efforts of case finding TB and HIV treatment optimally.

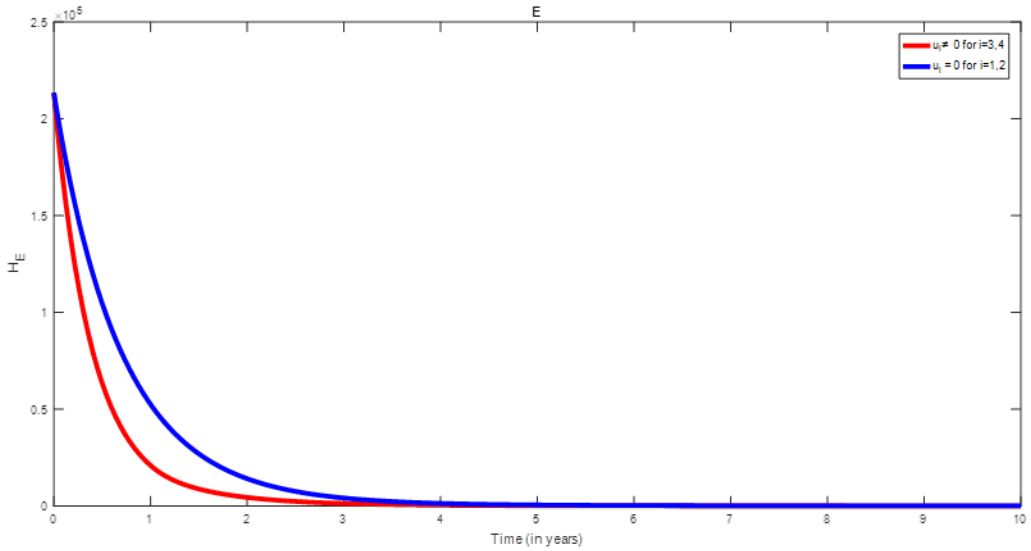

Figure 5.10: Infected individuals in H_E class when applying combined efforts of case finding TB and HIV treatment optimally.

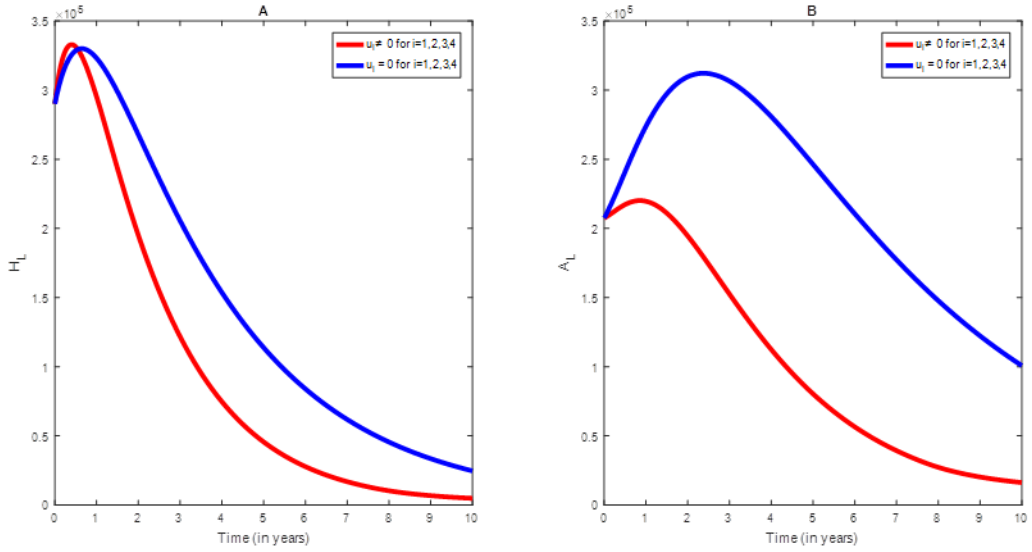

Figure 5.11: Infected individuals in H_L and A_L class when applying all strategies optimally.

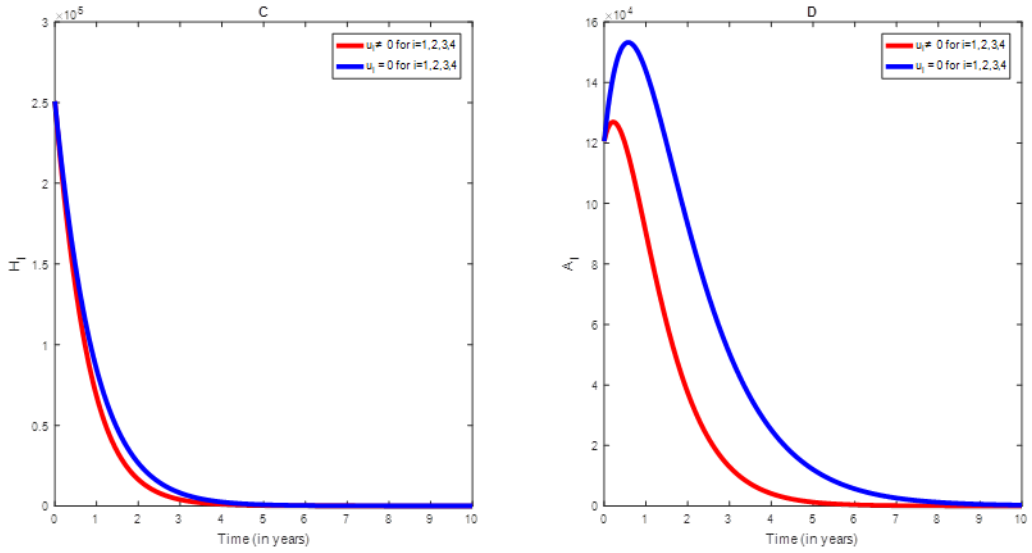

Figure 5.12: Infected individuals in H_I and A_I class when applying all strategies optimally.

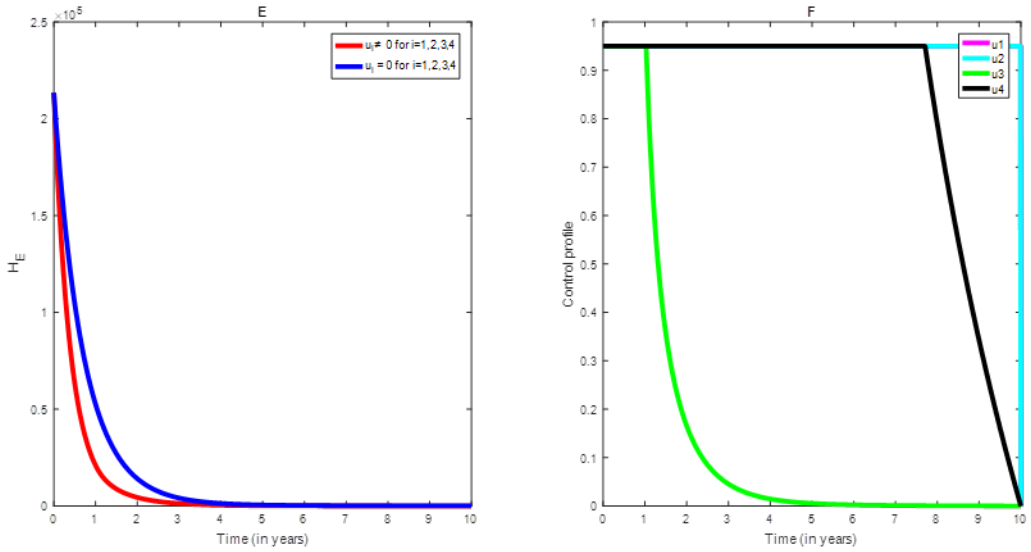

Figure 5.13: Infected individuals in H_E class when applying all strategies optimally and control profiles.

Chapter 6

Conclusions, future work and recommendations

6.1 Conclusions

Mathematical models play a vital role in exploring infectious diseases. They are founded on certain plausible assumptions. In the absence of sufficient epidemiological data, models are required to produce some evidence for future disease situations and possibility of interventions. Epidemic models are very crucial to study contagious diseases because the statistical analysis with repeated trials is infeasible in outbreak settings and randomized controlled trials of diseases are logically challenging.

In this study, new mathematical models have been developed in order to explore the transmission dynamics of HIV/AIDS, tuberculosis and their co-dynamics in Ethiopia. Tuberculosis (TB) and HIV/AIDS are still serious diseases in Ethiopia. Their co-evolution is also a danger which is highly expanded in the country. If one is infected by co-epidemics, one infection accelerates the rate of infection of the other and vice versa. This burden is a cause in Ethiopia which means having health and economic challenges. Thus, we expect that a lot of new research findings would be incorporated into the body of knowledge. This study addressed mathematical models and its exploration for each disease dynamics. In each model optimal control theory is well explored. This theory helps to find an optimal control for these infectious diseases over a given period of time. The proposed models with or without optimal control are analyzed analytically and numerically. Additionally, the cost-benefit analysis is incorporated to ensure the optimal resource utilization. The models and its analysis are summarized in the following way.

In chapter 3, we described and proposed a deterministic HIV/AIDS model, which considers undiagnosed infectious people (who transfer the disease fast and easily) as one big challenge in Ethiopia. On the basis of the SIA model, our formulated model is also founded on aware and unaware sus-

ceptible individuals. In Ethiopia, the two classes (undiagnosed infected and unaware susceptible people) have great contributions to disease transmission. The function of recruitment campaign $f(M$ from unaware susceptible to aware susceptible and the function $g(M)$ from aware to unaware are incorporated in the model. We discussed numerous qualitative properties of the model such as positivity of the solution, feasible region, stability of equilibrium points, and possibility of bifurcation. The DFE point is locally asymptotically stable when the control reproduction number ($R_e < 1$) and unstable when $R_e > 1$, whereas the endemic equilibrium point is stable when $R_e > 1$ and does not exist otherwise. The model has a bifurcation at $R_e = 1$. The type of bifurcation is forward which is confirmed by the sign of a and b formulated by Castillo-Chaveze and Song [CCS04]. The occurrence of this type of bifurcation justifies that the two equilibrium points does not co-exist. This shows there is an exchange of stability at $R_e = 1$. In this model, the sensitivity analysis of the control reproduction number has been carried out. As a result, R_e is most sensitive to the parameters $\beta_1, a_1, a_2, \epsilon, \eta_1$, and η_2. Hence, increasing these parameters would raise the value R_e, consequently, the expansion of disease transmission. However, increasing the parameters $\rho, k, \gamma, \sigma, d,$ and μ would reduce the value of R_e when keeping others constant. This shows us HIV treatment rate, screening rate, proportion rate to infectious stage, and death rate have an inversely proportional relationship with R_e. In addition, the model is extended to an optimal control model via incorporated control variables such as preventive, screening, and treatment. The adjoint variables and the optimality controls are derived from Hamiltonian, which is a combination of optimal control problem and integrand parts of cost function. The numerical results are investigated by considering two intervention strategies at a time and finally applying all the three control variables using classical forward Runge-Kutta method of order four (FRK4-method) using MATLAB software. This showed that combinations of optimal control strategies greatly helps to reduce the number of unaware susceptible, undiagnosed infectious, diagnosed infectious, and diagnosed infectious with AIDS symptoms. Moreover, these strategies can also reduce the cost burden. Using the ICER metric, we assessed which combination of approaches is the most cost effective in the fight against HIV/AIDS. We observed that the combination of preventive and screening strategies at a time is the best cost effective strategy.

In chapter 4, we formulated a new tuberculosis (TB) model from [WCJ11] considering drug resistance TB transmission dynamics. The model is analyzed analytically and the model properties like positivity of the solution, stability nature of equilibria points, and probability of bifurcation are discussed. The model has two control reproduction numbers R_1 and R_2. The value R_1 is when only drug sensitive TB infectious people are responsible for the disease transmission and R_2 is when only drug resistant TB infectious individuals are responsible for the disease transmission. The two equilibra (DFE and EE) points are calculated. The nature of stability of equlibra points is determined by the condition of the reproduction index $R_0 = max\{R_1, R_2\}$. The DFE point is both

locally and globally asymptotically stable if $R_0 < 1$ and unstable if $R_0 > 1$, whereas the EE point is both locally and globally asymptotically stable if $R_0 > 1$. A bifurcation occurred in the model at $R_0 = 1$. The type of bifurcation is forward due to the value of $a < 0$ and $b > 0$ [CCS04]. The sensitivity analysis of the model suggest that, an increase in $\beta_1, \beta_2, a_1, a_2, \theta$ and ϕ has the greatest effect on rising the value of R_1 or R_2. However, an increase in $\epsilon, \gamma, \rho, \delta, \sigma, d_1, d_2$, and μ has the greatest effect on reducing the value of R_1 or R_2. Hence, an increment in the parameter which has negative sensitivity indices would result reduce the reproduction index $R_0 = max\{R_1, R_2\}$. Based on the sensitivity result, the model is developed further in to a new model with optimal control. The model incorporated control variables such as prevention, case finding, and case holding for both drug-sensitive TB (DS-TB) and drug-resistant TB (DR-TB). The existence of an optimal control solution is presented using [FR12] and the necessary condition for an optimal pair is determined by the PMP [PM86]. To validate the analytical results, the model with and without optimal control is investigated numerically. In the numerical simulation, we used MATLAB software similar to the HIV/AIDS model. The numerical analysis shows that the four proposed strategies (prevention and case finding, prevention and case holding, case holding and case finding, and all three strategies) at a time reduce the disease burden. Throughout the simulation, coupling of optimal control schemes significantly helps to minimize the number of high risk latent (E_1), high risk latent (E_2), drug sensitive TB (I), and drug resistance TB (I_D) people. Likewise, the cost function is high at the beginning of the year and continues constantly for years subject to the suggested approach. This function is decreased left before dropping to zero. Furthermore, the cost-effectiveness analysis is carried out. The analysis suggest that, the combination of case-finding and case-holding strategies at a time is the best cost-effective mechanism.

In chapter 5, we developed the new TB-HIV co-infection model by coupling HIV/AIDS (susceptible, HIV infection with and without AIDS symptoms, and treating individuals from HIV infection) with the TB model [WCJ11]. The model is expressed by a system of first order differential equations by 12 state variables. We discussed the points such as positivity of the solution, stability of equilibria points, and bifurcation analysis. We calculated the control reproduction numbers R_H for the HIV sub-model and R_T for the TB sub-model. The reproduction index R_0 of the co-dynamics model is addressed by $R_0 = max\{R_H, R_T\}$. The number R_0 determined the stability region of DFE and EE points of the HIV-TB co-infection model. At the threshold value $(R_0 = 1)$, the bifurcation can be forward or backward governed by the sign value of a [CCS04]. Furthermore, the model is extended to a new TB-HIV co-epidemics model by taking into account time-based controlling efforts such as TB disease prevention (u_1), HIV disease prevention (u_2), TB disease case-finding (u_3), and HIV/AIDS treatment (u_4). The technique used to analyze this optimal model is also similar to the preceding models discussed so far. We proposed four coupling strategies in the co-infection model and analyzed numerically. The result suggest that all strategies can reduce

the co-infected individuals within H_E, H_I, H_L, A_L, A_I classes. Likewise, these interventions can also decrease the cost burden. Additionally, using the ICER metric, the best proposed method is identified. As a result, combining HIV/AIDS prevention efforts with TB case finding at a time is the most cost-effective strategy to curtail the co-dynamics disease.
Generally, in this study, the concept of optimal control theory plays a vital role to identify the best optimal measure to control the disease burden. All the results found in each model have significant public health lessons. As a result, they can predict the outcomes of tuberculosis, HIV/AIDS, and their co-evolution. Moreover, the study will help to fight against HIV/AIDS, TB, and their co-infection by policy-makers, NGOs, and other concerned organizations.

6.2 Future work

As HIV/AIDS, TB and their co-dynamics are continuously living; then several extraordinary studies will be claimed. Based on the models' result in the thesis and the limitations appeared, we propose the following few areas for further research.

- ♠ Expanding each model via considering immigrants, thus assessing their role on each disease dynamics.
- ♠ The vertical transmission of HIV could be studied based on the HIV/AIDS formulated model in the thesis.
- ♠ Integrating the vaccination cohort could be explored for the TB disease model.
- ♠ All developed models in our study are not exhaustive. COVID-19 disease dynamics could be investigated due to the fact that it can emerge with all diseases discussed in the thesis.

6.3 Recommendations

Nowadays, controlling the transmission of a communicable disease is challenging. This actual problem needs multidimensional study. Investigating epidemic diseases from a mathematical point of view can address remarkable notions about the disease situation and public health policies. In this study, the diseases TB, HIV/AIDS and their co-epidemics are well explored. Controlling these diseases is challenging in a country with limited resource like Ethiopia. This thesis recommends to government policy makers or stakeholders to increase the implementation of prevention efforts like health educational campaigns, screening or diagnosis tests, and follow-up the patients to complete their treatment. Likewise, an integrative intervention strategy is suggested for TB- HIV co-infection. Early screening is a best suggestion for everyone that shows symptoms timely qualm

towards such diseases.

Ever since identifying and forecasting the best cost-effective intervention strategy is the primary goal of policy makers and healthy sector administrators. Interdisciplinary research between healthy experts and mathematicians is highly recommended. A professional healthy worker can provide a framework for complex phenomena. It is very important for a mathematical modeler to construct a model and confirm its validity.

As a big challenge of our study, we suggest that all infectious diseases data should be collected and well-organized in most health institutions such as regional health bureau, federal ministry of health, and further WHO. The well-organized data can solve the researchers' difficulties as well as the health ministry to manage the disease in time. Despite all its limitations, the models provided valuable information and insights for choosing the proper intervention with available costs.

Finally, the thesis recommends that more emphasis should be given to mathematical modelling of infectious diseases.

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