Modeling, analysis and numerical method for HIV-TB co-infection with TB treatment in Ethiopia

by

Abdella Arega Tessema

Submitted in accordance with the requirements
for degree of

DOCTOR OF PHILOSOPHY

in the subject

APPLIED MATHEMATICS

in the

Department of Mathematical Sciences

at the

University of South Africa

Supervisor: Prof. E.F. Doungmo Goufo

Co-supervisor: Dr. Amos Kubeka

(July 2018)

Declaration Student number: 50841343

I declare that "**Modeling, analysis and numerical method for HIV-TB co-infection with TB treatment in Ethiopia**" is my own work and that all the sources that I have used or quoted have been indicated and acknowledged by means of complete references.

I further declare that I have not previously submitted this work, or part of it, for examination at Unisa for another qualification or at any other higher education institution.

Abstract

In this thesis, a mathematical model for HIV and TB co-infection with TB treatment among populations of Ethiopia is developed and analyzed. The TB model includes an age of infection. We compute the basic reproduction numbers R_{TB} and R_H for TB and HIV respectively, and the overall reproduction number R for the system. We find that if $R < 1$ and $R > 1$, then the disease-free and the endemic equilibria are locally asymptotically stable, respectively. Otherwise these equilibria are unstable. The TB-only endemic equilibrium is locally asymptotically stable if $R_{TB} > 1$, and $R_H < 1$. However, the symmetric condition, $R_{TB} < 1$ and $R_H > 1$, does not necessarily guarantee the stability of the HIV-only equilibrium, but it is possible that TB can coexist with HIV when $R_H > 1$. As a result, we assess the impact of TB treatment on the prevalence of TB and HIV co-infection.

To derive and formulate the nonlinear differential equations models for HIV and TB co-infection that accounts for treatment, we formulate and analyze the HIV only sub models, the TB-only sub models and the full models of HIV and TB combined. The TB-only sub model includes both ODEs and PDEs in order to describe the variable infectiousness and effect of TB treatment during the infectious period.

To analyse and solve the three models, we construct robust methods, namely the numerical nonstandard finite difference methods (NSFDMs). Moreover, we improve the order of convergence of these methods in their applications to solve the model of HIV and TB co-infection with TB treatment at the population level in Ethiopia. The methods developed in this thesis work and show convergence, especially for individuals with small tolerance either to the disease free or the endemic equilibria for first order mixed ODE and

PDE as we observed in our models.

Keywords and expressions: HIV, TB, Nonstandard finite difference methods, Basic reproduction number, Stability, Co-infection.

Acknowledgements

First of all, I am glad to thank almighty ALLAH (the Most Gracious, the Most Merciful) who petered me for this result. I would like to express my deepest heartfelt gratitude to my supervisor, Prof. E.F. Doungmo Goufo, for his excellent and continued guidance, caring, patience, and providing me with helpful advice for doing this thesis. Without his encouraging support and advice, the fruitfulness of my thesis is impossible to reach in this stage. First and foremost, my deepest gratitude goes to my first supervisor, Prof. Riette Maritz. She helped, encouraged and advised me for a long time, starting from the joining of the University of South Africa (UNISA) with helpful suggestions and comments until she retired. In addition to this, I gratefully thank my co-supervisor Dr. Amos Kubeka for his continuous help and comment to the thesis.

I also thank Wollo University that funded me to continue my PhD programme in UNISA.

Next to this my deeply felt thanks goes to my respected and beloved wife Nesib Seid for all her lovely support as well as her continues follow up of our children in place of me. Next to her, I would like to thank my sons Mohammed, Mahir, Muaz and my daughter Meryem Abdella for their beloved smile that gives energy for my work.

Last, but not least I would like to thank all of my families and relatives who encourage me to complete my thesis.

Notations and definitions of some terms

- AIDS: Acquired Immunodeficiency Syndrome;
- ARV: Antiretroviral Virus;
- CPT: Cotrimoxazole prophylactic treatment;
- DOTS: Directly Observed Treatment, Short-Course;
- DR-TB: drug resistant TB;
- DS-TB: drug-sensitive TB;
- EDHS: Ethiopian Demographic Health Survey;
- IPT: Isoniazid Preventive Therapy;
- MOH: Federal Ministry of Health;
- MTB: Mycobacterium tuberculosis;
- NSFDMs: Nonstandard finite difference methods;
- ODEs: ordinary differential equations;
- PDEs: partial differential equations;
- PLWHA: People Living with HIV/AIDS;
- TB: Tuberculosis;
- UNAIDS: United Nations Joint Program on HIV and AIDS;
- WHO: World Health Organization;
- SI: susceptible, infectious;

- SIS: susceptible, infectious, susceptible epidemiological compartments;
- SEE: stable epidemic equilibrium;
- SDFE: stable disease free equilibrium;
- UEE: unstable epidemic equilibrium;
- UDFE: unstable disease free equilibrium;
- Age of infection is the time lapsed since infection;
- Antiretroviral therapy (ART) is the recommended treatment for HIV infection. ART involves taking a combination (regimen) of three or more anti-HIV medications daily. ART prevents HIV from multiplying and destroying infection-fighting CD4 cells. This helps the body fight off life-threatening infections and cancer. ART can not cure HIV, but anti-HIV medications help people infected with HIV live longer, healthier lives;

- Co-infection is the infection of a host by at least two different types of pathogens. TB and HIV dynamics have a correlation, as HIV weakens the immune system of the host, which creates a proper medium for MTB to infect the host. Therefore, in areas with high HIV prevalence, TB is one of the main causes of death;

- Drug resistant TB (DR-TB) is a disease (usually pulmonary) caused by Mycobacterium Tuberculosis strains resistant to one or more anti-TB drugs. TB organisms resistant to the antibiotics used in its treatment are widespread and occur in all countries surveyed. Drug resistance

emerges as a result of inadequate treatment and once TB organisms acquire resistance. They can spread from person to person in the same way as drug-sensitive TB;

- Human Immunodeficiency Virus (HIV) is the virus that causes HIV infection. During HIV infection, the virus attacks and destroys the infection-fighting CD4 cells of the bodys immune system. Loss of CD4 cells makes it difficult for the immune system to fight infections;

- HIV-1 is a type of HIV which has been classified into three groups: M (major), O (outlier) and N (non-M and non-O). The global AIDS epidemic is currently dominated by the group M HIV-1 virus. Group M can further be divided into subtypes or clades, of which nine have been designated A to K (M clades) and O. M and O show 55-70;

- Macrophages- are white blood cells within tissues, produced by the division of monocytes;

- Multi-drug-resistant TB (MDR-TB) is caused by organisms that are resistant to the most effective anti-TB drugs (isoniazid and rifampicin). MDR-TB results from either infection with organisms which are already drug-resistant or may develop in the course of a patient's treatment. This form of TB does not respond to the standard six month treatment with first-line anti-TB drugs and can take two years or more to treat with drugs that are less potent, more toxic and much more expensive;

- Resistant strains are those that differ from sensitive strains in their capacity to grow in the presence of higher concentrations of a drug;

- Sensitive strains (sensitive strains of Mycobacterium TB) are those that have never been exposed to the main anti-tuberculosis drugs (wild strains) and respond to these drugs, generally in a remarkably uniform manner;

- TB incidence and prevalence are central to the rate of tuberculosis transmission. TB incidence is defined as the rate of appearance of new TB cases per unit time. TB prevalence is the proportion of infected individuals at one point in time, or over a short time period. The measurement of incidence and prevalence is often based on stratification of the population by a variety of factors, such as age, ethnicity, etc;

- Treatment: control of tuberculosis is managed by two types of treatment. The treatment of latent TB is called chemoprophylaxis and treatment of active TB is called therapeutics. Treatment of TB lasts long; therefore control strategies have been developed for compliance to TB treatment. DOTS (Directly Observed Treatment, Short-Course) are a treatment program used for compliance with treatment of drug-sensitive TB. Another control program is DOTS-plus, which is developed for compliance with treatment of drug-resistant TB. A good public health treatment strategy combines different control strategies to control all types of TB infections.

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Chapter 1

General introduction

The spread of human immunodeficiency virus/acquired immune deficiency syndrome (HIV/AIDS), tuberculosis (TB) and malaria across the world poses major global health challenges of this time [29, 56, 60].

In [52], according to the recent estimates by the United Nations Program on HIV/AIDS (UNAIDS) global report, 35.3 (32.2–38.8) million people were living with HIV/AIDS, worldwide in 2012; more than a half of them in Sub-Saharan Africa and nearly about a fifth in South and South-East Asia. According to MOH office report [23, 28], the overall prevalence of HIV infection was 2.4 percent and 1, 216, 908 people were living with HIV/AIDS in Ethiopia.

Globally, in 2013, an estimated nine million people developed TB and 1.5 million died from the disease [59]. In Ethiopia, TB has been recognized as a major public health problem for more than half a century, and claiming the lives of thousands of Ethiopians every year. In 2011 WHO global TB report, Ethiopia ranks 7^{th} among the 22 high TB burden countries in the world and one of the top three in Africa, with regard to the prevalence of TB [58, 60].

MDR-TB is an emerging challenge for TB control globally. Ethiopia is among

these countries, at the end of February 2012, a total of 437 cases of MDR-TB patients were enrolled on treatment in three MDR-TB centers in Ethiopia. Regarding their outcome of treatment, success was documented in 72 patients while 43 died and 6 defaulted from treatment [26, 29, 30, 58, 59, 60].
An estimated 1.1 million (13 percent) of the nine million people who developed TB were HIV-positive. The African region accounts for about four out of every five HIV-positive TB cases and TB deaths among people who were HIV positive [56, 59]. Among people with active TB, more than 22 percent of them are HIV positive. Co-infection of HIV with TB greatly increases the probability for an individual to progress from latent to active TB and TB is also the most common cause of AIDS-related deaths [45, 61].
In this thesis; firstly, we focus on considering the age of infection in TB when modeling the dynamics of TB with treatment from a mathematical point of view. Lastly, we include the age of infection on the dynamics of HIV and TB co-infections with TB treatment. Hence, the mathematical models considered or developed are described by autonomous systems of non-linear partial and ordinary differential equations. Therefore, we design a special class of numerical methods, known as Nonstandard Finite Difference Methods (NSFDMs) as is mentioned in [32] and others fail to investigate the applicability of such methods for non-linear PDE models and to improve the order of convergence of these methods (both for ODE and PDE models) in biology and ecology.
As far as possible, most of the terminologies considered in this thesis are adopted from MOH, WHO and UNAIDS in Ethiopia. We have been working in collaboration with the staffs of MOH to access the data made.
A concise background for HIV-TB co-infection with TB treatment is presented in the next section.

1.1 HIV-TB co-infection with TB treatment in Ethiopia

The global adoption of WHO has enabled more than 55 million people infected with TB to receive treatment. It also prevented up to 7 million deaths between 1995 and 2010. In 2013, an estimated 9.0 million people developed TB and 1.5 million died from the disease in this year alone and 2.5 million new HIV infections annually [4, 39, 56, 58].

In Ethiopia, the number of notified TB cases has been steadily increasing since 1996 from 79,095 to reach a peak of 159,017 cases in 2011. However, the number of notified TB cases has shown a marked decline over the last three successive years as shown in the table 1.1 below. It is shown a decline of 8 percent and 13 percent over the next two successive years (2012 and 2013) and the last one year, respectively [26, 29].

Number of notified TB cases in Ethiopia: 1996 - 2014			
year	Number of notified TB	year	Number of notified TB
1996	79,095	2005	125,135
1997	59,611	2006	123,009
1998	70,714	2007	129,743
2000	92,759	2008	141,909
2001	95,826	2009	149,146
2002	110,998	2010	154,406
2003	118,276	2011	159,017
2004	124,223	2012	146,367
2013	130,614	2014	115,821

Table 1.1: Trend in the number of notified TB cases over 19 years, Ethiopia.

In 2011, a total of 159,017 cases of TB were registered for treatment. The

TB cure rate for new smear positive pulmonary TB registered is 66.5 percent in 2011. A death rate of 2.6 percent among TB patients registered for treatment in a year would imply the need to strength quality of TB patient care along with fostering early diagnosis and treatment. Similarly the death rate (proportion of TB cases who died while on anti-TB treatment among TB cases registered for treatment during same time period) among the notified new smear positive pulmonary TB (PTB+) cases in 2012 is 2.8 percent at national level. In 2013, a total of 130,614 TB cases were reported with a TB case notification rate of 152 per 100,000 populations. Out of 130,614 cases reported in the year; 33.4 percent were smear positive pulmonary TB, 34.5 percent were smear negative pulmonary TB and 32.1 percent were extra pulmonary TB [26, 29]. The HIV pandemic presents a massive challenge to the control of tuberculosis at global and national level. It is evidenced that the synergy between TB and HIV/AIDS is strong, especially in high HIV prevalence settings. TB is the leading cause of morbidity and mortality, and HIV is driving the TB epidemic in many countries, especially in Sub-Saharan Africa including Ethiopia [29].

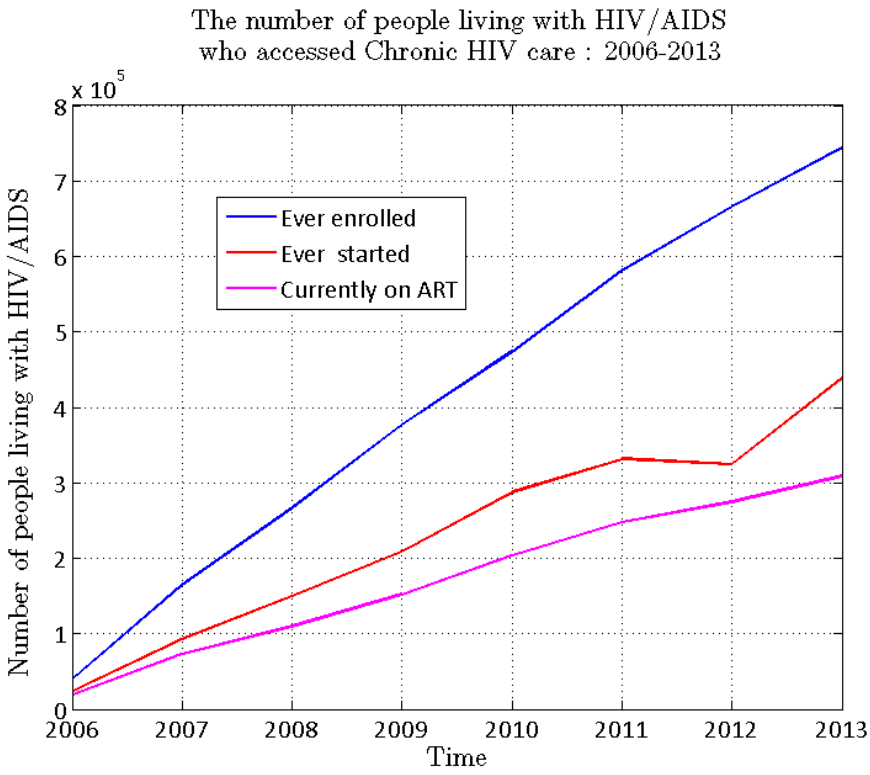


Figure 1.1: Trend in the number of people living with HIV/AIDS who accessed chronic HIV care (2006-2013) [26,29].

From the above figure, a linear increase has been observed in the number of people living with HIV/ADIS (PLWHA) ever enrolled, ever started and currently on ART over the past seven years; in particular, there was an increase between Ethiopian fiscal year (EFY) 2004 and EFY 2005 from 666,147 to 744,339 for PLWHA ever enrolled in HIV/AIDS care (+78,192), from 379,190 to 439,301 for those ever started (+60,111), and from 274,708 to 308,860 for those currently on ART (+34,152).

To understand the epidemiology of TB and HIV co-infection in Ethiopia,we cross-matched incident TB cases reported to routine surveillance data during 2007-2010 with cases in the HIV/AIDS registry [4]. Of 176,739 TB case-

patients 35,140 (20 percent) had known HIV infection. TB rates for persons with HIV declined from 31 to 15 percent for the first four years and slightly increased fom 17 to 20 percent for the last two years during 2007-2012. In 2010, 69 and 39 percent of patients co-infected with TB-HIV were put on CPT and ART respectively in the same registry [10, 11, 12]. In Ethiopia, the overall prevalence of HIV infection is 2.4 percent and Minister of Health office reported 1,216, 908 people were living with HIV/AIDS.

In 2010, of 66,955 TB cases 9,809 (15 percent) patients had known HIV infection [21, 26]. Of 68,169 TB cases 9,285 (14 percent) patients had known HIV infection in 2013/2014. When a person is infected with HIV, they are at an increased risk of also contracting TB. Co-infection with TB can also mean an accelerated progression to AIDS. Most leading international bodies, such as the WHO and UNAIDS, agree on the importance of a collaborative approach to dealing with TB-HIV co-infection, including testing and treatment [33]. TB/HIV collaborative activities are essential to reduce the burden of TB among people living with HIV/AIDS and to reduce the burden of HIV among TB patients. These activities include establishing mechanisms for collaboration between TB and HIV programs; infection control in healthcare and congregate settings; HIV testing and counseling of TB patients and to refer TB patients infected with HIV to HIV services such as CPT and ART [8, 26, 41].

In 2011, among people with active TB, more than 22 percent of them are HIV positive. Co-infection of HIV with TB increases greatly the probability of progressing from latent to active TB [23].

The following table shows the number/proportion of TB patients tested for HIV, HIV-TB co-infection and their co-infection rate 2007-2014.

Number of people tested for TB and co-infected with HIV			
Year	TB patients tested for HIV	HIV-TB co-infected	co-infection rate
2007	20,723	6,342	31
2008	33,021	7,891	24
2009	56,040	11,098	20
2010	66,955	9,809	15
2011	68,169	9,285	14
2012	75,137	11,271	15
2013	82,802	11,592	14
2014	90,034	11,705	13

Table 1.2: Sources [8, 26, 41].

Some of the important associations between the epidemiology of HIV and TB co-infections are:

- TB is harder to diagnose and treat in HIV positive people,
- TB facilitates the progression of HIV to AIDS,
- TB progresses faster in HIV positive infected people,
- HIV accelerates TB from latent to active and had impact on the prevalence of TB diseases,

- HIV facilitates the progression of TB to MDR-TB.

1.2 Literature review

Many literatures relevant to this research were reviewed, developed and analyzed through mathematical models by different researchers. The NSFD methods were explored by many researchers to solve problems in the biological sciences and other areas. This section gives an overview on some chosen models on HIV, TB (including drug resistant TB) and their co-infections.
Maliyoni [41] formulated and analyzed a two-strain TB model with diagnosis, treatment, and health education. Their theoretical study was assessed the impact of the control strategies on the transmission dynamics of MDR-TB (with Malawi as a case study). They noted that the results presented were general and could be applied to other settings because neither the model, nor the parameters values represent characteristics unique of Malawi. The effective reproduction number was computed and used to compare the effect of each intervention strategy on the MDR-TB dynamics.
In [31, 76] as most traditional compartmental models in mathematical epidemiology descend from the classical Susceptible Infecected Recovered(SIR) model and epidemic model with fractional derivative and non-linear incidence advance in difference equations of Kermack-McKendrick, where the population is divided into the classes of susceptible, infected, and recovered individuals. All of the models cited assumed the homogeneity of the infected class and individuals in that compartment share the same epidemiological parameters. In reality, however, as time elapses and the disease develops within the host, its infectivity might continuously change. The purpose of their paper was to incorporate this feature into the Susceptible Exposed Infecected Re-

covered (SEIR) model. Models keeping track of an individuals infection age had existed for particular diseases, for instance TB and HIV/AIDS. However, their general SEIR was formulated as a system of delay differential equations with infinite delay. The novelty of their model was that they allowed varying infectivity of the infected individuals as a function of the age of infection. This assumption leads to a system of differential equations with distributed infinite delay. They have shown that several standard theorems in mathematical epidemiology can be extended to this kind of SEIR model, and the basic reproduction number has been calculated. In the future, it would be interesting to prove the global stability of the endemic equilibrium.

Phillips [36] explained, TB infection can be latent or active. In the latent form it was held at bay by the immune system, did not cause illness, and could not be spread from one person to another. In the active state it can be transmitted to others, and severe illness and death could result if it was not diagnosed and effectively treated. Anyone who is latently infected is at risk of developing active TB later in life if his or her immune system fails. Unlike HIV infection, which is not spread by casual contact, TB infection can be acquired by healthy individuals who inhale mycobacterium tuberculosis. TB is more likely to be spread in crowded living conditions (such as homeless shelters, prisons, or crowded homes) and areas of high prevalence in which uninfected individuals were in close proximity with persons with active TB. Several studies [9, 10] have presented a two-strain model, in which the drug-resistant strain was not treated, and latent, infectious and treated individuals might be re-infected with the drug-resistant strain. Each strain has a different basic reproduction number, and there were three equilibrium points (no disease, coexistence of both strains, and only the drug-resistant strain). Without acquisition of drug resistance, there was an additional equilibrium with only

the drug-sensitive strain. The authors discussed stability of the equilibria and found, interestingly, areas of parameter space of positive measure where coexistence of the strains was possible; they reported that coexistence was rare when drug resistance was mainly primary (resulting from transmission) but almost certain if the resistant strain was the result of acquisition, for example under poor treatment. Neglecting disease-induced death and setting the transmission parameter equal for the two strains, they were able to prove that the disease-free equilibrium is globally asymptotically stable if both basic reproduction numbers are less than unity.

Although TB is currently well-controlled in most countries, recent data indicated that the overall global incidence of TB was rising as a result of resurgence of disease in Africa and parts of Eastern Europe and Asia (Dye, 2006). In these regions, the emergence of drug-resistant TB and the convergence of the HIV and TB epidemics have created substantial new challenges for disease control.

TB treatment was long and hard to complete. Therefore, there was a need for a program to force tuberculosis patients to complete their treatment. For this purpose, DOTS (Directly Observed Treatment, Short-Course) was used as an effective strategy for controlling TB epidemics [7].

Blower et al [6]. developed a model for designing effective control strategies to determine levels of eradication of TB. Treatment failure can lead to drug resistance, which is a challenge to control programs, as these drug-resistant strains are more difficult to treat. One-strain models account only for drug-sensitive cases only. To account for drug resistance, Blower et al [6]. built a two-strain model, a linked control model, by integrating drug resistance.

Mathematical models for the dynamics of multi-drug resistant tuberculosis in Mali; assessing the impact of control strategies was developed by Maliyoni

[40]. In their thesis, they have presented and analyzed a basic tuberculosis model which was modified into a two-strain TB model with diagnosis, treatment and health education in Malawi. The main objective of their study was to assess the impact of the control strategies mentioned above on the transmission dynamics of MDR-TB only in Malawi. Qualitative analysis of the models shows that the model has two equilibria; the disease free equilibrium and endemic equilibrium. It was found out that whenever reproductive number is less than unity, the disease free equilibrium is locally asymptotically stable and becomes unstable whenever the reproductive number becomes greater than unity.

There were a lot of mathematical models describing tuberculosis, but only few of them concerning drug resistance. They were often deterministic although some stochastic models, such as Markov chain models, were also used in general cases. Two leading experts in this field, Castillo-Chavez and Song [9], contributed to a better understanding of the tuberculosis dynamics and drug resistance. In transmission model, several authors [6, 8, 9, 11, 57] have developed ordinary differential equation models with drug-sensitive and drug-resistant strains.

E.F. du Toit [19] proposed a linear differential equations model for showing the co-infection dynamics of HIV-1 and Mycobacterium tuberculosis. In the research, a model is proposed to indicate the populations of both pathogen as well as key information factors, such as the overall infected cell population and antigen-presenting cells. Their treatment simulation showed both the effect that changes in HIV has on TB, and the effect that changes in TB has on HIV. Finally, they listed new research possibilities stem from this co-infection model that can be extended as to be the latest knowledge on TB and HIV. For TB, this would mean the effect of drug resistant TB would

have to be considered and the model must be adjusted for the specific types of TB accordingly.

Santosh Ramkissoon et.al. [50] developed a modeling HIV and MTB co-infection including combined treatment strategies. They had presented a new model which was able to simulate HIV and TB co-infection and test various combined treatment strategies. They also tested combined treatment with different timings for each therapy. In their conclusion, they recommended that further work could address mechanisms of HIV disease progression, suppressed, latent and active MTB infection, and tubercle formation and TB of drug resistant could be modeled. As a step toward multi-scale simulation the host pathogen model could be embedded in a population-level of epidemiological model.

Kirschner [16] designed Dynamics of Mycobacterium tuberculosis and HIV-1 co-infection. Here a simple mathematical model was developed to describe the interaction of the immune system's key players, T cells and macrophages, with the pathogens HIV and Mycobacterium tuberculosis. It showed that the presence of Mycobacterium tuberculosis in the HIV-infected individual worsens the clinical picture and therefore, treatment of TB in HIV-infected individuals could have been a profound effect on their progression to AIDS. When designing treatment, a drug that suppresses bacterial growth, as opposed to enhancing the bacterial death rate, would likely be more effective. They recommended screening HIV-infected individuals at high risk for TB (or showing any clinical signs of TB), and then initiation of a complete course of treatment for TB positive individuals. They concluded that further investigation will be needed to examine the role of development of drug-resistance in both TB (MDR-TB) and TB-HIV infections.

Roeger [38] proposed mathematical modeling of TB and HIV co-infections.

Their model consisted of a system of eight differential equations that was introduced to model the joint dynamics of TB and HIV by dividing the total population in to different epidemiological subgroups, which allowed the incorporation of both infections. The simulation results showed that the progression of latent to active TB is faster in people with HIV than in people without. The presence of HIV could lead to the co-existence of TB and HIV. The numerical results suggested that to reduce (control) the impact of TB, investing more in reducing the prevalence of HIV could be an effective option. In the conclusions, they recommended that detailed models that take into accounts various forms of TB treatment (latent and active TB), the danger of increasing the prevalence of antibiotic resistant TB and their relation to HIV treatment must be incorporated into models of HIV/TB co-infection if further progress is to be made.

The mathematical analysis of the transmission dynamics of HIV and TB co-infection in the presence of treatment was developed by Sharomi et al [44]. By combining some assumptions and definitions, the realistic deterministic model for the transmission dynamics of HIV and TB in a population is designed and rigorously analyzed using fifteen linear ordinary differential equations with treatment strategies using burification methods. Their study showed that the prospect of effectively controlling the spread of HIV and TB in a community, using effective treatment for both diseases, is bright.

Villanueva et al. [56] developed NSFD schemes to solve the numerical solution of a mathematical model of infant obesity with constant population size. Their model consists of a system of coupled nonlinear ordinary differential equations. The numerical results showed that their methods have better convergence properties as compared to the classical Euler or the fourth-order Runge-Kutta methods and the Matlab routines in the sense that these rou-

tines give negative values for some of the state variables.

Construction and analysis of efficient numerical methods to solve mathematical models of TB and HIV co-infection was conducted by Obaid Ahmed [32]. In his study competitive unconditionally stable NSFDMs were proposed for solving a TB-only sub-model and a full HIV-TB co-infection model represented by a nonlinear system of ordinary differential equations. Numerical results presented, confirmed the applicability of the proposed NSFDMs for the biological systems. These methods preserved the positivity of solutions and converging to stability properties of the equilibria for arbitrary step-sizes while the solutions obtained by other numerical methods experience difficulties in either preserving the positivity of the solutions or in converging to the correct equilibria. Finally they suggested that investigating the applicability of their methods for partial differential equation models in biology, and improving the order of convergence of these NSFDMs (both for ODE and PDE models) still needs further study.

According to the best of our knowledge, we could hardly find research on mathematical modeling of HIV and TB co-infections that incorporate TB treatment in nonlinear ordinary and partial differential equations models. But from biological and medical perspectives, the reader who wishs to look at the work of HIV and TB co-infections may refer to the works in [14, 19, 31, 32, 34, 36, 38, 39, 43, 44, 45, 51, 50, 56, 92, 96, 97, 98, 99, 100, 101, 102, 104] and the reference there in.

Some other works dealing with the dynamics of TB only can be found in [4, 5, 6, 7, 8, 9, 10, 11, 15, 17, 18, 34, 35, 39, 40, 41, 42, 43, 52, 53, 54, 57, 65, 90, 91, 93, 94, 95, 103] whereas works dealing with the dynamics of HIV only are available in [1, 34, 39, 40, 43, 61].

From this background our study investigates the applicability of NSFD meth-

ods for partial differential equation models in epidemiology and improves its order of convergence by improving the mathematical model of [32].

1.3 Outline of the thesis

This thesis deals with the construction and analysis of nonstandard finite difference numerical methods for solving HIV-TB co-infection with TB treatment models. The case of Ethiopian population is considered. At the beginning, we studied the sub-models (HIV-only and TB-only) and then the full model (HIV-TB co-infection). More specific details are provided in the following lines.

Chapter 1 deals with the general introduction on the main goal of this thesis where a global literature review on HIV /TB co-infection with TB treatment and the NSFD methods have been thoroughly detailed. In chapter 2, we develop and analyze a mathematical model describing the dynamics of TB with age of infection. The model accounts for one-strain distributed-delay model at the age of infection with drug sensitive TB. The analysis presented in this chapter introduces a function $p(\alpha)$ $(0 \leq p(\alpha) \leq 1$) as the small proportion of the sensitive strain that is active at the infection age α to distinguish active TB and inactive TB. The drug resistant strain accounts for active TB only. Drug-resistant and drug-sensitive strains are modeled, but only the age of the infection with drug-sensitive strain is considered. Here, the density function $i_s(\alpha, t)$ is a function of two independent continuous variables that has a PDE in the model which makes the model more complicated than the models based on ODE. In this chapter, we also try to analyse the effect of $p(\alpha)$ and the per-capita contact rate on the dynamics of the TB model in both strains.

Chapter 3 investigates the above approach by studying a co-infection of the HIV-TB model. In this chapter, the TB model developed in chapter 2 is combined with the HIV model to formulate the model of the HIV-TB co-infection. Therefore, we study the stability of the steady states. In particular, we study the stability of the disease-free equilibria, and the endemic equilibria. To this end, the effects of TB treatment on the dynamics of HIV-TB co-infections are investigated.

In chapter 4, we propose effective numerical methods (NSFDMs) that solve the TB models with both TB strains as proposed in chapter 2. We also construct and analyze the NSFDMs that solve the HIV-TB co-infection model presented in chapter 3. We show the stability and applicability of the methods for biological systems and for the systems presented here.

Finally some conclusions are drawn from this study. These are also mentioned in chapter 5 where scope of some future research are indicated.

Chapter 2

Analysis of the TB model with the age of infection

In this chapter, we develop and analyze a mathematical model describing the dynamics of TB with the age of infection. In this model, the dynamics of both drug-sensitive and resistant strains of TB are considered. The model accounts for a one-strain distributed-delay model at the age of infection with drug sensitive TB.

2.1 Introduction

Mathematical models have played a key role in the formulation of TB control strategies and the establishment of interim goals for intervention programs. Most of these models are of the SEIR or SIS type in which ndividuals in the host population are categorized by their infection status such as susceptible, exposed (infected but not yet infectious), infectious and recovered (here a recovered individual can become susceptible again). One of the main attributes of these models is that the force of infection (the rate at which a susceptible

individual leaves the susceptible class and moves into an infected category, i.e. become infected) is a function of the number of infectious hosts in the population at any time t and is thus a nonlinear term. Other transitions, such as the recovery of infectious individuals and the death of others, are modeled as linear terms with constant coefficients [9, 10].

Globally, 3.5 percent of new TB infections and 20.5 percent of previously treated TB cases were estimated to have had MDR-TB in 2013. However, much higher levels of resistance and poor treatment outcomes are of major concern in some parts of the world. There is a case of MDR-TB that is resistant to the first two lines of drugs, namely: isoniazid and rifampicin. For most patients diagnosed with MDR-TB, the WHO recommends treatment for 20 months with a regimen that includes second line anti-TB drugs. Hence, among the estimated 480 000 people having developed MDR-TB that year, a total of 97 000 patients were put on MDR-TB treatment [59].

In [52], M.R. Silvia's analysis provides new insights for the interpretation of epidemiological estimates of fitness of MDR-TB strains. Their results implied that the potential for the spreading of the drug-resistant strain cannot be evaluated simply by measuring its relative fitness value, but should be evaluated within the context of several others factors, including the treatment, healing rates, treatment efficacy and relative fitness.

Zhilan Feng, Wenzhang Huang, and Carlos Castillo-Chavez proved the global stability of the endemic equilibrium of an ODE model of TB that were developed previously (see Castillo-Chavez and Feng, 1997a) [8, 65] . They also constructed a TB model with a distributed delay to study the effect of variable periods of latency on the transmission dynamics of TB at the population level. The purpose of their paper was to look at the effects of variable (rather than exponentially distributed) periods of latency on the dynamics of TB.

M. Maliyoni [41] formulated and analyzed a two-strain TB model in Malawi with diagnosis, treatment, and health education as their main objective was the theoretical study (as a case study). They noted that the results presented were general and could be applied to other settings because neither the model nor the parameter values did not represent characteristics unique to Malawi. The effective reproduction number was computed and used to compare the effect of each intervention strategy on the MDR-TB dynamics. Traditional compartmental models in mathematical epidemiology descend from the classical SIR model of Kermack and McKendrick, where the population is divided into the classes of susceptible, infected, and recovered individuals as already mentioned here above. Most of the model used assumed the homogeneity of the infected class and individuals in that compartment share the same epidemiological parameters [31]. In reality, however, as time elapses and the disease develops within the host, its infectivity might continuously change. The purpose of their paper was to incorporate this feature into the SEIR model. Models that keep track of an individual's infection age had existed for some particular diseases, for instance TB and HIV/AIDS. However, their general SEIR model was formulated as a system of delay differential equations with infinite delay. The novelty of the model was to consider varying infectivity of the infected individuals as a function of the age of infection. They had shown that several standard theorems in mathematical epidemiology can be extended to this kind of SEIR model, and the basic reproduction number was calculated. In the future, it would be interesting to prove the global stability of the endemic equilibrium.

Moualeu in their thesis [15] presented a nonlinear extended deterministic model for the transmission dynamics of TB, based on realistic assumptions and data collected from the WHO. This model enables a comprehensive qual-

itative analysis of various aspects in the outbreak and control of TB in Sub-Saharan Africa countries and successfully reproduces the epidemiology of TB in Cameroon for the period of 1994 to 2010. Some particular properties of the model and its solution have been presented using the comparison theorem applied to the theory of differential equations. The existence and the stability of a disease free equilibrium has been discussed using the Perron-Frobenius theorem and Metzler matrices.

The drug-resistant phenotype may be acquired among those treated for drug-sensitive active disease, or directly transmitted to susceptible individuals. TB is affecting everyone no matter the sex or age group. Poverty is a risk factor for developing TB, which places Ethiopia as a high-risk environment. The country is one of the least developed in the world. Among the total smear positive TB cases reported in 2009-2010, 55.5 percent were males, 7.5 percent were children of age less than 14 years old, and 2 percent were above the age of 65. The group age between 15 to 34 was found to be the most affected with TB, accounting for 62 percent of notified new smear positive TB cases [54]. The disproportionately large burden of TB in this age group, which comprises a large part of the total workforce in the country, could be contributing to poverty. Some people of the same age group are parent of young children and this can also be heavily contributing to the transmission of TB in the household and to the overall burden of childhood TB in the country [28, 54]. C. Colijn reviewed the literature on the mathematical modeling of tuberculosis dynamics [10]. Multiple models exist, encapsulating different assumptions about the dynamics of progression from latent infection to active disease, the nature of re-infection and the subsequent partial immunity, and the complexities of different TB strains as well as HIV. They described results from two new models of TB: a spatial stochastic model and

a delay differential equation model. The stochastic model indicates that if the disease transmission is indeed local, this may reduce the effectiveness of widely applied preventative treatment. Both models allow us to examine the portion of new disease that is due to exogenous re-infection without having to specify the portion of new infections destined to be fast progressors. The specific implementation of partial immunity does not affect the estimated contribution of re-infection to disease levels, but spatial effects do.

Although TB is currently well-controlled in most countries, recent data indicated that the overall global incidence of TB is rising as a result of resurgence of disease in Africa and parts of Eastern Europe and Asia (Dye, 2006). In these regions, the emergence of drug-resistant TB and the convergence of the HIV (human immunodeficiency virus) and TB epidemics have created substantial new challenges for disease control. TB treatment is long and hard to complete. Therefore, there is a need for a program to force TB patients to complete their treatment. For this purpose, DOTS (Directly Observed Treatment, Short-Course) is used as an effective strategy for controlling TB epidemics [7]. One-strain models account only for drug-sensitive cases only. Blower et al. developed a model for designing effective control strategies to determine levels of eradication of TB. Treatment failure can lead to drug resistance, which is a challenge to control programs, as these drug-resistant strains are more difficult to treat. To account for drug resistance, Blower et al. built a two-strain model, a linked control model, by integrating drug resistance [7, 53].

There were a lot of mathematical models describing tuberculosis, but only few of them concerning drug resistant. They were often deterministic although some stochastic models, such as Markov chain models, were also used in general cases. Two leading experts in this field, Castillo-Chavez and

Song, contributed a review. In transmission model several authors developed ordinary differential equation models with drug-sensitive and drug resistant strains, such as Blower et al, Castillo-Chavez and Feng in [6, 9, 11, 57].
In [9], drug sensitive and resistant strains were modeled, but only the age of the infection with drug sensitive strain was considered. They introduce a function $p(\alpha)$ as the proportion of the sensitive strain that is active at the infection age α to distinguish TB and inactive TB. For the drug resistant strain, they only account active TB. MDR-TB is an emerging challenge for TB control programs globally; Ethiopia ranks the 7^{th} among the 22 high burden countries in the world and one of the top three in Africa, with regard to the prevalence of TB [26, 58]. At the end of February 2012, from a total of 870 cases of MDR-TB only 437 patients were enrolled on treatment in three MDR-TB centers in Ethiopia. Regarding their outcome of treatment, success was documented in 72 patients while 43 died and 6 defaulted from treatment. The estimated annual number of MDR-TB patients was 1500-2500 cases in 2013-2014. The prevalence of MDR-TB is increasing at an alarming rate from a baseline rate of 1.6 percent among new TB cases in 2005 to current level of 2.3 percent in 2014 [30].

The following table shows the prevalence, incidence and mortality rate of TB in Ethiopia for 19 years from 1990 to 2014.

Number of notified TB cases per 100,000 in Ethiopia: 1996 - 2014			
Year	Incidence of TB	Prevalence of TB	Mortality rate of TB
1990	425	367	49
1995	480	419	48
2000	430	421	41
2005	330	342	29
2006	314	324	27
2007	296	308	25
2008	280	293	23
2009	265	280	21
2010	251	261	20
2011	237	258	18
2012	172	181	24
2013	154	170	29
2014	200	210	30

Table 2.1: Number of notified TB cases per 100,000 in Ethiopia: 1996 - 2014 [26, 29, 58].

The following figure shows that the prevalence, incidence and mortality rate of TB (sensitive strain) cases in Ethiopia.

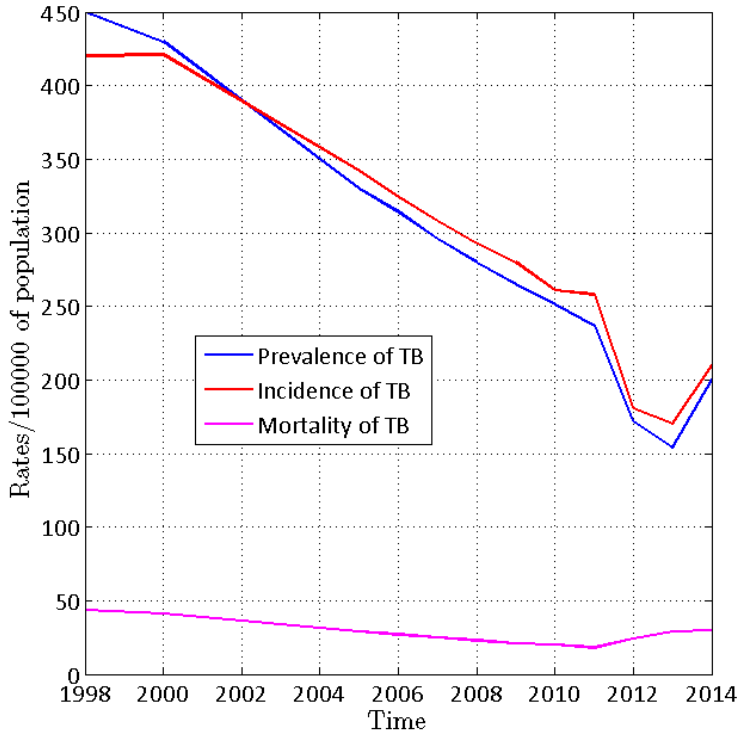


Figure 2.1: Trend of TB prevalence, incidence and mortality rates in Ethiopia: 1990-2014 [26, 29].
This figure shows the prevalence, incidence, and mortality rate of TB per 100,000 of population.

The estimates of TB prevalence rate in Ethiopia had increased during the first five years and declined for the second 18 years and start to increasing the last one year since 1990 from 425 per 100,000 population per year and reached a peak value of 482 per 100,000 population per year in 1994. Since 1995 onwards however, the estimates for TB prevalence rate have shown a steady decline at an average rate of 4 percent per year, with an increased rate of decline for the last 5 years (5.5 percent per year) and reached a level of 154/100,000 population and increased rate 30 percent for the last year that reached a level of 200/100,000 population.

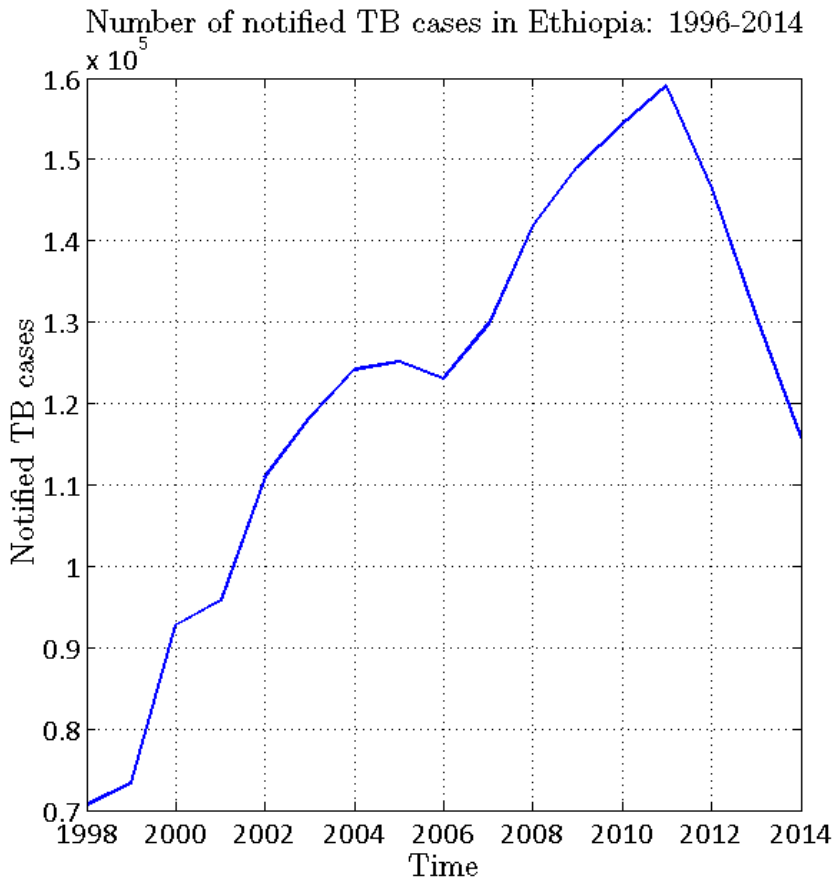


Figure 2.2: Number of notified TB cases in Ethiopia (1996-2014).

The above figure shows that the number of TB cases has been steadily increasing since 1996 from 79,095 to reach a peak of 159,017 cases in 2011. However; the number of notified TB cases has shown a marked decline over the last three successive years and reach a level of 115,821 cases in 2014 which as shown in this figure.

According to the Federal Democratic republic of Ethiopia Ministry of Health, the documented MDR-TB patients for years shown below [26, 29, 58].

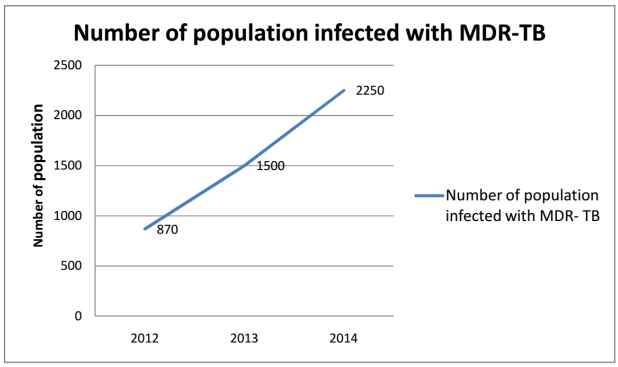


Figure 2.3: The trend of notified MDR-TB for three successive years.

In the view of the above discussion, we develop and analyze a mathematical model (2.2.1) below describing the dynamics of TB with age of infection. This model accounts for the data obtained from the Federal Democratic Republic of Ethiopia Ministry of Health, in particular, from Health Promotion and Diseases Prevention Directorate, Ministry of Health Directorate and Police Planning Offices. The data indicated that both drug sensitive TB and drug resistant TB strains did recover in Ethiopia. Epidemiological modeling led to the analysis of ordinary differential, discrete/stochastic/ or partial differential systems. Age-structured models comprise partial differential equations models whose dynamics depend on whether the age of the population and the age of infection are taken to account or not.

We show that the stability of the system equilibria is completely determined by the basic reproduction number of TB, R_{TB}. The system is shown to exhibit the existence of a disease free and the endemic equilibria.

2.2 Description of a TB model with age of infection

The total population in our model is divided into three epidemiological classes SIS-model according to their diseases status as in [73]: Susceptible class $S_T(t)$, infectious class with drug sensitive strain $I_s(t)$ and infectious class with drug resistant strain $I_r(t)$. Susceptible individuals are recruited into the population at a contact rate c. These individuals are infected with the force of infections λ_s and λ_r respectively for drug sensitive and drug resistant TB and due to their contact with active TB. Drug sensitive and resistant strains were modeled, but only the age of the infection with drug sensitive strain was considered [9, 73].

The flow diagram is expressed as:

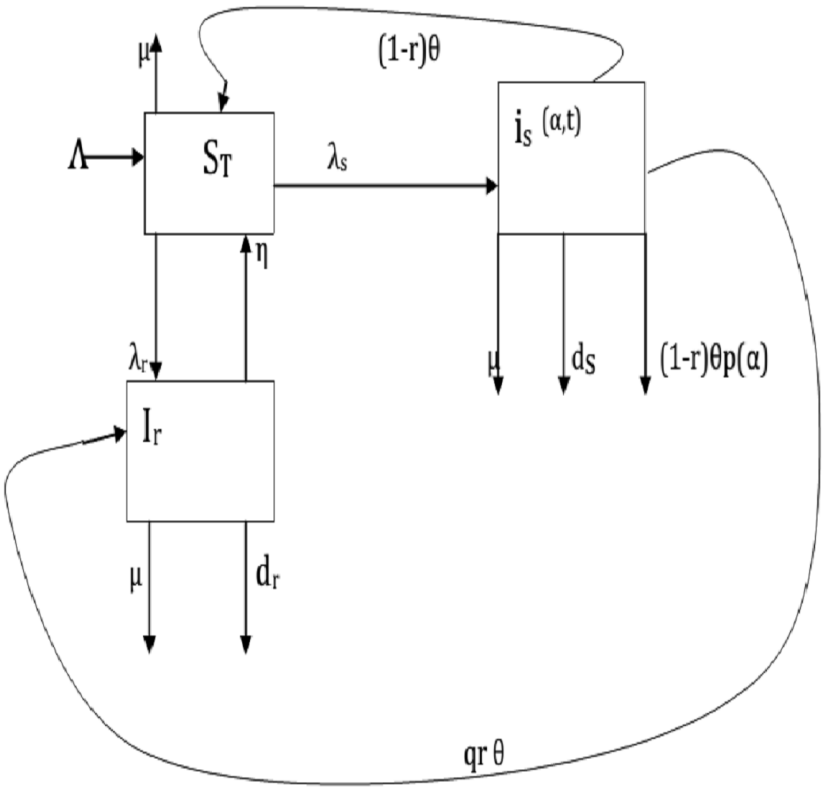


Figure 2.4: Flow diagram of the SIS compartments of the TB with treatment model.

Letting $i_s(\alpha, t)$ be the infection density of infected individuals of age α with the drug sensitive strain at the current time t, the model framework indicates the following system of nonlinear ordinary and partial differential equations:

$$\begin{aligned}
&\tfrac{dS_T}{dt} = \Lambda - (\lambda_s + \lambda_r + \mu)S_T + \eta I_r + (1-r)\theta I_s^a, \\
&\tfrac{\partial i_s}{\partial \alpha}(\alpha, t) + \tfrac{\partial i_s}{\partial t}(\alpha, t) = -((1 - r + qr)p(\alpha)\theta + \mu + d_s)i_s(\alpha, t) \\
&\tfrac{dI_r}{dt} = \lambda_r S_T - (d_r + \mu + \eta)I_r + qr\theta I_s^a
\end{aligned} \tag{2.2.1}$$

where, $I_s^a = \oint_0^\infty p(\alpha) i_s(\alpha, t) d\alpha$ is the total number of active TB with drug

sensitive strain. These are infected individals individuals with the strain that can transmit the disease only to others at the age of their infection. $I_s(t) = \int_0^\infty i_s(\alpha, t)d\alpha$ is the total number of infected individuals with drug sensitive TB. These include the infectious individuals that transmit the disease (active TB) and the latent individuals that do not transmit it. Here, as already pointed in the introduction most of the infected individuals with drug-sensitive TB remains latent, but only a small portion of them develop and show the disease, becoming infective. To account for this, we assume the function $p(\alpha)$ ($0 \leq p(\alpha) \leq 1$) as the proportion of sensitive -strain-infected individuals which are active at infection-age α. In the case of drug resistant TB, it accounts for active TB only. Other related parameters are defined as follows: $\lambda_s = \beta_s c\frac{I_s}{N_T}$ is the force of infection of drug sensitive TB,

$\lambda_r = \beta_r c\frac{I_r}{N_T}$ is the force of infection of drug resistant TB,

c=per-capita contact rate,

θ=per-capita TB treatment rates for infected(infectious),

β_s =the probability that a susceptible individual becomes infected by one infectious individual with drug sensitive,

β_r =the probability that a susceptible individual becomes infected by one infectious individual with drug resistant TB,

d_s= The disease induced mortalities for drug-sensitive,

d_r=the disease induced mortalities drug-resistant TB.

It is assumed that a fraction r of the treated individuals with drug-sensitive strain does not recover due to incomplete treatment, and the remaining $(1-r)$ is successfully treated and become susceptible again. It is also assumed that a fraction q of those who do not finish their treatment will generate drug resistant TB and the remaining fraction $(1-q)$ of them will keep as infectious. The data obtained from ministry of health in Ethiopia indicated that drug

resistant TB strains were cured and then treated like drug-sensitive strain TB [23, 26, 28]. Therefore, according to our assumptions the cured strains become susceptible again. Hence we introduce that η is the fraction of treated individuals with drug resistant TB that is cured and becomes susceptible again and that the remaining fraction $(1-\eta)$ does not recover nor become latent since individuals who are not cured die after acquiring drug resistant TB. The total population considered for this compartment model is given by

$$N_T = S_T + I_r + \int_0^{\infty} i_s(\alpha, t)d\alpha = S_T + I_r + I_s \tag{2.2.2}$$

The following table gives the values of the parameters used in our analysis. $S_T(0) = 178,445$, Ethiopia total population=87,989,000.

Symbol	Value	Sources
Λ	33.3/1000	[46, 56, 59]
μ	0.0165	[46, 56, 59]
c	0.7	[32, 69]
$(1-r)$	0.921	[26, 56]
β_s	0.653	[26, 46, 58]
d_s	0.024	[58, 59]
q	0.270	[26, 58, 59]
η	0.178	[26]
β_r	0.013	[26, 46, 59]
d_r	0.011	[26, 58]

Table 2.2: The values of the parameters used in the system (2.2.1) [12, 13, 48].

2.3 A Well-posed problem

2.3.1 Definition: (Well-posed problem)

A mathematical problem is said to be a well-posed problem if its solution exits, is unique and depends continuously on the data, initial conditions on the (finite) boundary of the domain.
The other most important concepts in epidemiological models is the basic reproduction number (R) for a given parasite strain that is defined below.

2.3.2 Definition: (Basic reproduction number)

The basic reproduction number is defined as the expected number of new infections from one infected individual in a fully susceptible population through the entire duration of the infectious period. If $R < 1$, then on average an infected individual produces less than one new infected individual over the course of its infectious period, and the infection cannot grow. Conversely, if $R > 1$, then each infected individual produces, on average, more than one new infection, and the disease can invade the population in [1, 32, 37, 39, 43, 51].
We can now move to the mathematical analysis of the model.

2.4 Analysis of the model

In this section, we discuss the mathematical analysis of the TB model given in the systems (2.2.1) to show the stability equilibria of the system according to the basic reproduction number we computed. We determine all these things first by considering the models well-posed and its positivity of solutions.
In this analysis, we consider the drug resistant only sub-model when $I_s = 0$.

This is done in the following section.

2.4.1 Analysis of drug resistant TB only sub-model

Here, we highlighted the drug resistant TB sub-model with simple concepts but more details are shown in the next subsection. when $I_s = 0$, the systems of equations (2.2.1) reduces to:

$$\begin{aligned} \frac{dS_T}{dt} &= \Lambda - (\lambda_r + \mu)S_T + \eta I_r, \\ \frac{dI_r}{dt} &= \lambda_r S_T - (\eta + d_r + \mu)I_r. \end{aligned} \tag{2.4.1}$$

where, $N_T = S_T + I_r$ which implies that $S_T = N_T - I_r$.

Hence we have

$$\begin{aligned} \frac{dN_T}{dt} &= \Lambda - \mu N_T - d_r I_r, \\ \frac{dI_r}{dt} &= \beta_r c(1 - \frac{I_r}{N_r})I_r - (\mu + d_r + \eta)I_r \end{aligned} \tag{2.4.2}$$

For this system of equation, by applying the next generation matrix approach [82], where F and V are represented as matrices respectively for the new infections generated and the transition terms is then obtained as,

$\mathcal{F} = \beta_r c I_r$ and

$\vartheta = (\mu + d_r + \eta)I_r$.

Here, $F = (\beta_r c)$ and

$V = (\mu + d_r + \eta)$.

R_r, the basic reproduction number of drug resistant TB only sub-model is given by spectral radius, ρ of FV^{-1}, i e $R_r = \rho(FV^{-1}) = \frac{\beta_r c}{(\mu + d_r + \eta)}$.

Before showing the proofs of the theorems stated below, it it better to recall Routh Hurwitz Criteria [86] are used to determine local asymptotic stability of an equilibrium for nonlinear systems of differential equations. The Routh-Hurwitz Criteria are stated in the next theorem.

Theorem 2.4.1. *([86]) Routh-Hurwitz Criteria. Given the polynomial,*

$$P(\lambda) = \lambda^n + a_1\lambda^{n-1} + a_2\lambda^{n-2} + ... + a_{n-1}\lambda + a_n,$$

where the coefficients a_i are real constants, $i = 1, 2, ..., n$, define the n Hurwitz matrices using the coefficients a_i of the characteristic polynomial:

$H_1 = \begin{pmatrix} a_1 \end{pmatrix}$,

$H_2 = \begin{pmatrix} a_1 & 1 \\ a_3 & a_2 \end{pmatrix}$,

$H_3 = \begin{pmatrix} a_1 & 1 & 0 \\ a_3 & a_2 & a_1 \\ a_5 & a_4 & a_3 \end{pmatrix}$,

$$\begin{pmatrix} a_1 & 1 & 0 & 0 & . & . & . & 0 \\ a_3 & a_2 & a_1 & 1 & . & . & . & 0 \\ a_5 & a_4 & a_3 & a_2 & . & . & . & 0 \\ a_7 & a_6 & a_5 & a_4 & . & . & . & 0 \\ . & . & . & . & . & . & . & . \\ . & . & . & . & . & . & . & . \\ . & . & . & . & . & . & . & . \\ 0 & 0 & 0 & 0 & . & . & . & a_n \end{pmatrix},$$

where $a_j = 0$ if $j > n$. All of the roots of the polynomial $P(\lambda)$ are negative or have negative real part if and only if the determinants of all Hurwitz matrices are positive:

$$\det H_j > 0,\ j = 1, 2, ..., n.$$

When $n = 2$, the Routh-Hurwitz criteria simplify to

$$\det H_2 = \det \begin{pmatrix} a_1 & 1 \\ 0 & a_2 \end{pmatrix} = a_1 a_2 > 0 \text{ or } a_1 > 0 \text{ and } a_2 > 0.$$

For polynomial of degree $n = 2, 3, 4$ and 5, the Routh-Hurwitz criteria are summarized as shown below.

For

$n = 2 : a_1 > 0$ *and* $a_2 > 0$.

$n = 3 : a_1 > 0, a_2 > 0$ *and* $a_1 a_2 > a_3$.

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

$n = 5 : a_i > 0, i = 1, 2, 3, 4, 5, a_1 a_2 a_3 > a_3^2 + a_1^2 a_4$, *and*

$(a_1 a_4 - a_5)(a_1 a_2 a_3 - a_3^2 - a_1^2 a_4) > a_5(a_1 a_2 - a_3)^2 + a_1 a_5^2$.

Proof. For $n = 2$, the Routh-Hurwitz criteria are just $a_1 > 0$ and $a_2 > 0$. The characteristic polynomial in the case $n = 2$ is

$$P(\lambda) = \lambda^2 + a_1 \lambda + a_2.$$

The eigenvalues satisfy

$$\lambda_{1,2} = \frac{-a_1 \pm \sqrt{a_1^2 - 4a_2}}{2}.$$

Suppose a_1 and a_2 are positive, it is easy to see that if the roots are real, they are both negative, and if they are complex conjugates, they have negative real part.

Next, to prove the converse, suppose the roots are either negative or have negative real part. Then it follows that $a_1 > 0$. If the roots are complex conjugates, $0 < a_1^2 < 4a_2$, which implies that a_2 is also positive. If the roots are real, then since both of the roots are negative it follows that $a_2 > 0$. □

Corollary 2.4.2. *Suppose the coefficients of the characteristic polynomial are real. If all of the roots of the characteristic polynomial*

$$P(\lambda) = \lambda^n + a_1\lambda^{n-1} + a_2\lambda^{n-2} + ... + a_{n-1}\lambda + a_n,$$

are negative or have negative real part, then the coefficients $a_i > 0$ *for* $i = 1, 2, ..., n$.

Proof. The corollary is a direct consequence of the Routh-Hurwitz criteria but can be verified separately. The characteristic equation can be factored into the form

$$(\lambda + r_1)...(\lambda + r_{k_1})(\lambda^2 + 2c_1\lambda + c_1^2 + d_1^2)...(\lambda^2 + 2c_{k_2}\lambda + c_{k_2}^2 + d_{k_2}^2) = 0,$$

where the roots are $-r_i < 0$ for $i = 1, 2, ..., k_1$ and the complex roots are $c_j \pm d_j$ for $j = 1, 2, ..., k_2$ and $k_1 + k_2 = n$. If all the roots are either negative or have negative real part, then $r_i > 0$ and $c_j > 0$ for all i and j. Thus the coefficients in the factored characteristic equation are positive. □

The disease free equilibrium of the system in (2.4.1) is given by $E^0 = (\frac{\Lambda}{\mu}, 0)$ is locally asymptotically stable if $R_r < 1$ and otherwise unstable if $R_r > 1$.
By considering the following theorems, we investigate whether the system (2.4.1) is stable or not.

Theorem 2.4.3. *([32, 66]) Drug resistant TB dies out whenever* $R_r < 1$ *and persists whenever* $R_r > 1$.

Proof. By substituting the disease free equilibrium of the system in (2.4.1) and using next generation matrix methods [82] for:

$$\digamma = \beta_r c I_r$$
$$\text{and } \vartheta = \begin{pmatrix} \beta_r c \frac{I_r}{N_T} I_r + (\mu + d_r + \eta) I_r \\ \mu N_T + d_r I_r \end{pmatrix}.$$

We obtained $F = (\beta_r c)$,

$V = (\mu + d_r + \eta)$,

$R_r = \rho(FV^{-1}) = \frac{\beta_r c}{(\mu+\eta)+d_r}$.

We found the corresponding Jacobian matrix as follows:

$$J(E^0) = \begin{pmatrix} -\mu & -d_r \\ 0 & \beta_r c - (\mu + \eta + d_r) \end{pmatrix}$$

.

Hence, the eigenvalues of the matrix are:

$\lambda_1 = -\mu$,

$\lambda_2 = \beta_r c(1 - \frac{1}{R_r})$.

Thus, the first eigenvalue, λ_1 is always negative. The second eigenvalue, λ_2 is negative if $R_r < 1$ and is positive if $R_r > 1$.

Hence, the disease free equilibria is stable if $R_r < 1$ and unstable if $R_r > 1$.

Thus , this completes the proof this theorem. Similarly, the endemic equilibrium theorem stated as follows. □

Theorem 2.4.4. *([32]) The endemic equilibrium of drug resistant TB is locally asymptotically stable if $R_r > 1$ and it is unstable if $R_r < 1$.*

Proof. We can denote the endemic equilibrium of the system in (2.4.1) as $E^1 = (N_T^1, I_r^1)$ is given by

$E^1 = (\frac{\Lambda}{\mu+d_r(1-\frac{1}{R_r})}, \frac{\Lambda(1-\frac{1}{R_r})}{\mu+d_r(1-\frac{1}{R_r})})$

Then its corresponding Jacobian matrices becomes

$$J(E^1) = \begin{pmatrix} -\mu & -d_r \\ \beta_r c(1 - \frac{1}{R_r})^2 & -\beta_r c(1 - \frac{1}{R_r}) \end{pmatrix}$$

.

The characteristic equation associated with the above matrix is given by

$$\lambda^2 + C_1\lambda + C_2 = 0.$$

Where,
$C_1 = \mu + \beta_r c(1 - \frac{1}{R_r})$,
$C_2 = \mu\beta_r c(1 - \frac{1}{R_r}) + \beta_r c d_r(1 - \frac{1}{R_r})^2$.

As we observed the coefficients C_1 and C_2 are both greater than zero if $R_r > 1$. And all the roots of the above characteristic equations are negatives or have negative real parts. Hence using these results and Routh Hurwitz Criteria:

- When $\lambda = -1$, $1 - C_1 + C_2 > 0$,
  $1 + C_2 > C_1$,
- When $\lambda = 1$, $1 + C_1 + C_2 > 0$,
- When $\lambda = 0$, $|C_2| < 1$.

Therefore, the endemic equilibrium is locally asymptotical stable if $R_r > 1$, and unstable if $R_r < 1$. □

2.4.2 Analysis of the full TB model

In this section, we discuss some of the highlights of the mathematical analysis of the TB model given in the systems of equations (2.2.1) to show positivity of solution, its existence of invariant set and the stability equilibria of the

system according to the basic reproduction number we computed.

To find the basic reproduction number of our model, first we rewrite the systems in (2.2.1) as a linear form and integrate both sides of the second equation using a Cauchy problem and compatibility condition in the system along the characteristics line $t - \alpha$=constant. After we linearize the system we can easily find the basic reproduction number as defined in different literatures.

The density age function which is given in (2.2.1) recalled as follows:

$$\frac{\partial i_s}{\partial \alpha}(\alpha, t) + \frac{\partial i_s}{\partial t}(\alpha, t) = -((1 - r + qr)p(\alpha)\theta + \mu + d_s)i_s(\alpha, t) \tag{2.4.3}$$

subject to the initial condition $i_s(0, t) = \lambda_s S_T(t)$. This is the PDE that has the cauchy problem form, can be solved by considering the rate of change of $i_s(\alpha, t)$ with arbitrary variable parameter-σ as we move along this curve has the form $\frac{di_s}{d\sigma} = \frac{\partial i_s}{\partial \alpha} + \frac{\partial i_s}{\partial t}$ and is equivalent to the equation in (2.4.3) at point (α, t) below, which is the solution of a quasi-linear first order partial differential equation involving unknown function $i_s(\alpha, t)$. Consequently it is only necessary to consider the solution of a Cauchy problem for quasi-linear equations that is written in the form:

$$U(\alpha, t, i_s)\frac{\partial i_s}{\partial \alpha} + V(\alpha, t, i_s)\frac{\partial i_s}{\partial t} = f(\alpha, t, i_s) \tag{2.4.4}$$

,

where U, V and f are assumed to be continuously differentiable functions of their arguments.

Let $i_s(\sigma) = i_s(\sigma, \alpha(\sigma), t(\alpha))$, the total derivative of $i_s(\alpha, t)$ in terms of arbitrary variable parameter-σ is

$$\frac{di_s}{d\sigma} = \frac{\partial i_s}{\partial \alpha}\frac{d\alpha}{d\sigma} + \frac{\partial i_s}{\partial t}\frac{dt}{d\sigma} \tag{2.4.5}$$

From equations of (2.4.4) and (2.4.5) above, we have the following:

$$\frac{d\alpha}{d\sigma} = U(\alpha, t, i_s) and \frac{dt}{d\sigma} = V(\alpha, t, i_s) \tag{2.4.6}$$

The PDE in (2.4.4) can be expressed as the ODE $\frac{di_s}{d\sigma} = f(\alpha, t, i_s)$ provided that α and t satisfy (2.4.6) with respect to σ.

From the equations (2.4.4) to(2.4.6) in the above, we have

$i_s(\alpha, t) = \lambda_s(t)S_T(t)e^{-(\mu+d_s)\alpha - \oint_0^\alpha \delta(s)ds}$,

where, $\delta(s) = (1-r+qr)\theta p(s)$ is obtained from the initial value in the system (2.2.1).

By letting $\lambda_s(t)S_T(t) = m(t)$ and considering the initial conditions of the above PDE, we have:

$$\begin{aligned} i_{so}(0, t) &= \lambda_s(t)S_T(t) = m(t) \\ i_{so}(\alpha, 0) &= i_{so}(\alpha) \end{aligned} \tag{2.4.7}$$

Therefore, we have

$$i_s(\alpha, t) = \begin{array}{ll} m(t-\alpha)e^{-(\mu+d_s)\alpha - \oint_0^\alpha \delta(s)ds}, & for \quad t > \alpha, \\ i_{so}(\alpha - t)e^{-(\mu+d_s)\alpha - \oint_{\alpha-t}^\alpha \delta(s)ds}, & for \quad \alpha > t. \end{array} \tag{2.4.8}$$

From equation (2.4.8), we computed that $\lim_{t\to\infty} i_s(\alpha, t) = 0$, since the function of α and t is non-increasing as observed above.

And again by integrating both sides of (2.4.3) with respect to α, we obtained

$$\frac{dI_s}{dt} = \lambda_s(t)S_T(t) - (\mu + d_s)I_s - \oint_0^t m(t-\alpha)p(\alpha)e^{-(\mu+d_s)\alpha - \oint_0^\alpha \delta(s)ds}d\alpha \tag{2.4.9}$$

After obtaining the derivatives of $m(t)$ in equations (2.4.7) and according to [73], we have:

$$\frac{dm}{dt} = \frac{\beta_s c}{N_T}(N_T - I_r - \oint_0^t m(t-\alpha)p(\alpha) \oint_0^t p_1(\alpha)m(t-\alpha)p_2(\alpha) = m(t) \tag{2.4.10}$$

where, the notations,
$p_1 = \oint_0^t e^{-(\mu+d_s)\alpha - \oint_0^\alpha \delta(s)ds} d\alpha$,
$p_2 = \oint_0^t p(\alpha) e^{-(\mu+d_s)\alpha - \oint_0^\alpha \delta(s)ds} d\alpha$.

Here we can get $p_2 m = \oint_0^\infty p_2(\alpha)m(t-\alpha)d\alpha$.

Let us consider the equilibrium at $E^*(N_T^*, m^*, I_r^*)$ at $\alpha = 0$ and when it exists , must be constant solution of the limiting system associated with it, thus from (2.4.10) and (2.2.1), the system of equations reduced to

$$\begin{aligned}
&\tfrac{dN_T}{dt} = \Lambda - \mu N_T - d_r I_r - d_s \oint_0^t m(t-\alpha) e^{-(\mu+d_s)\alpha - \oint_0^\alpha \delta(s)ds} d\alpha, \\
&\tfrac{dm}{dt} = \beta_s c(1 - \tfrac{p_1}{N_T} m - \tfrac{I_r}{N_t}) p_2 m, \\
&\tfrac{dI_r}{dt} = \beta_r c(1 - \tfrac{p_1}{N_T} m - \tfrac{I_r}{N_t}) I_r - (\mu + \eta + d_r) I_r + qr\theta p_2 m.
\end{aligned} \tag{2.4.11}$$

By taking the of the above system, we search for solutions at equilibrium (N_T^*, m^*, I_r^*) of the system,

$$\begin{aligned}
&\Lambda - \mu N_T^* - d_r I_r^* - d_s p_1 m^* = 0, \\
&\beta_s c(1 - \tfrac{p_1}{N_T^*} m^* - \tfrac{I_r^*}{N_t^*}) p_2 m^* = m^*, \\
&\beta_r c(1 - \tfrac{p_1}{N_T^*} m^* - \tfrac{I_r^*}{N_t^*}) I_r^* - (\mu + \eta + d_r) I_r^* + qr\theta p_2 m^* = 0.
\end{aligned} \tag{2.4.12}$$

The solutions of the systems are related to the distribution of infected individuals with drug-sensitive TB at the steady state as
$i_{so}(\alpha, 0) = i_{so}(\alpha) = p_1 m^*$.

Moreover, when we take $I_r = 0$ (the infected individuals do not develop drug-resistant TB, i.e$q = 0$). Thus, particularly, the above system of equations (2.4.12) becomes the mathematical model of drug-sensitive TB as follows:

$$\begin{aligned} &\Lambda - \mu N_T^* - d_s p_1 m^* = 0, \\ &\beta_s c(1 - \tfrac{p_1}{N_T^*} m^*) p_2 m^* = m^*. \end{aligned} \tag{2.4.13}$$

Hence from the systems equations (2.2.1) and (2.4.12), using next generation matrix methods [82] for:

$F = \beta_s c p_2 m^*$ and $\vartheta = m^*$, we obtained $F = (\beta_s c) p_2$,
$V = 1$,
$R_s = \rho(FV^{-1}) = (\beta_s c) p_2$ (the basic reproduction number of with drug-sensitive TB). In addition to this by solving the equations, we obtained the endemic equilibrium of drug-sensitive TB, denoted as $E^* = (N_T^*, m^*)$ as shown below:
$m^* = \frac{N_T^*(1 - \frac{1}{R_s})}{p_1}$,
$N_T^* = \frac{\Lambda}{\mu + d_s(1 - \frac{1}{R_s})}$.

Theorem 2.4.5. *([32, 66, 73]) Drug-sensitive TB dies out whenever $R_s < 1$ and persists whenever $R_s > 1$ given that $q = 0$.*

Proof. By substituting the disease free equilibrium of the drug-sensitive sys-

tem in (2.2.1) and (2.4.12), we found the corresponding Jacobian matrix as follows:

$$J(E^0) = \begin{pmatrix} -\mu & -d_s p_1 \\ 0 & \beta_s c p_2 - 1 \end{pmatrix}$$

.

Hence, the eigenvalues of the matrix are:
$\lambda_1 = -\mu$,
$\lambda_2 = \beta_s c p_2 (1 - \frac{1}{R_s})$.
Thus, the first eigenvalue, λ_1 is always negative. The second eigenvalue, λ_2 is negative if $R_s < 1$ and is positive if $R_s > 1$.
Hence, the disease free equilibrium of drug-sensitive TB dies out if $R_s < 1$ and persists if $R_s > 1$.
Similarly, the endemic equilibrium theorem stated as follows. □

Theorem 2.4.6. *([32]) The endemic equilibrium of drug-sensitive TB is locally asymptotically stable if $R_s > 1$ and it is unstable if $R_s < 1$.*

Proof. The proof of this theorem is direct since we obtained the endemic equilibrium as shown above. □

Hence,

$$R_s = \beta_s c p_2 = \beta_s c \int_0^\infty p(\alpha) e^{-(\mu+d_s)\alpha - \int_0^\alpha \delta(s) ds} d\alpha$$
$$and$$
$$R_r = \frac{\beta_r c}{\mu + \eta + d_r}$$

are the basic reproduction number of drug sensitive and drug-resistant TB of the system (2.2.1), respectively.

Therefore, for the total population, the basic reproduction number of TB of the model (2.2.1), denoted by R_{TB}, is given by $R_{TB} = max(R_s, R_r)$.

R_s is the product of the probability of a susceptible individual infected by one infectious individual with drug sensitive TB during his or her contact $\beta_s c$ and the total active drug-sensitive TB.

R_r is the product of the probability of susceptible individual infected by one drug-resistant TB infectious individual $\beta_r c$ and the average infectious period $\frac{1}{\mu+d_r+\eta}$.

Therefore, R_s measures the number of secondary drug-sensitive TB infectious cases produced by a TB infectious individuals during his or her effective contact when introduced in a susceptible population of TB. Similarly R_r gives the number of secondary drug-resistant TB infectious cases produced by TB infectious due to incomplete treatment of drug-sensitive TB individuals during his or her infectious period when introduced in a population of TB susceptible.

In the next section, we consider positivity of solutions and existence of invariant set model (2.2.1).

2.4.3 Positivity of solutions and existence of invariant set

Most delay differential equations that arise in population dynamics and epidemiology models logically have nonnegative quantities. It is important to establish that nonnegative initial data give rise to nonnegative solutions. The model system (2.2.1) above describes the dynamics of a human population. Therefore, it is important to prove that the state variables susceptible $S_T(t)$, infectious with drug sensitive $I_s(t)$, and drug-resistant TB $I_r(t)$, are nonnegative for all time $t \geq 0$. For this, we state and prove the next theorems.

Theorem 2.4.7. *The feasible region in the set* $D = \{(S_T, i_s, I_r)\epsilon R^3 / N_T \leq \frac{\Lambda}{\mu}\}$ *is positively-invariant for system (2.2.1).*

Proof. The rate of change of the total population computed from the equations of models (2.2.1), (2.2.2) and the first equation of (2.4.11) is given by

$$\frac{dN_T}{dt} = \Lambda - \mu N_T - d_r I_r - d_s \oint_0^t m(t-\alpha)p_1(\alpha)d\alpha \leq \Lambda - \mu N_T. \qquad (2.4.14)$$

Where, $p_1 = e^{-(\mu+d_s)\alpha - \oint_0^\alpha \delta(s)ds}$.
Which shows the feasible region $D = \{(S_T(t), i_s(\alpha,t), I_r(t))\epsilon R^3/(S_T(t) + \oint_0^\infty i_s(\alpha,t)d\alpha + I_r(t) = N_T \leq \frac{\Lambda}{\mu}\}$ and we observed that $\limsup_{t\to\infty} N_T \leq \frac{\Lambda}{\mu}\}$.
It is clear that $\frac{dN_T}{dt} \leq \frac{\Lambda}{\mu}$, since $N_T(0) \leq \frac{\Lambda}{\mu}$.
And also from equation (2.2.1) and equation (2.3.2.8), we find that
$\frac{dS}{dt} = \Lambda - (\lambda_s + \lambda_r + \mu)S_T + (1-r)\theta I_s^a + qr\eta\theta I_s^a \geq (\lambda_s + \lambda_r + \mu)S_T$,
which implies that $S_T(t) \geq S_T(0)e^{-(\lambda_s+\lambda_r+\mu)t}$, for all $t \geq 0$.
Similarly; $I_s(t) \geq I_s(0)e^{-(\mu+d_s)t}$ for all $t \geq 0$.
$I_r(t) \geq I_r(0)e^{-(\mu+d_r)t}$ for all $t \geq 0$.

Thus, all the above shows that the solution of the system (2.2.1) is greater or equal to zero for all $t \geq 0$.
Therefore, the limits of the system in (2.2.1) with initial conditions remain in D and all the variables and parameters of it are non-negative for all $t \geq 0$. Hence, D is positivity of invariant. And the mathematical model in (2.2.1) in the region D is epidemiologically well-posed.
In the next section, we study the equilibria and stability properties of our model in (2.2.1). □

2.4.4 Stability properties of the equilibria

In this section, we find the equilibria and determine the stability properties of the epidemiology model in (2.2.1). The details of the disease free and the endemic equilibria of the system (2.2.1) are shown in the following theorems (2.4.8) and (2.4.9) as stated.

Theorem 2.4.8. *([65, 66, 73]) The disease free equilibrium of both drug sensitive and drug resistant TB die out (locally asymptotically stable) whenever* $R_{TB} < 1$ *and persist whenever* $R_{TB} > 1$.

Proof. The disease free equilibrium, denoted by E^0 of the system (2.2.1) is $E^* = (\frac{\Lambda}{\mu}, 0, 0)$.

By substituting this to the system (2.2.1), we obtained the corresponding Jacobian matrix as follows:

$$J(E^*) = \begin{pmatrix} -\mu & -d_s p_1 & -d_r \\ 0 & p_2\beta_s c - 1 & 0 \\ 0 & qr\theta p_2 & \beta_r c - \mu - \eta - d_r \end{pmatrix}$$

.

Thus, the eigenvalues of the matrix are:

$\lambda_1 = -\mu$,

$\lambda_2 = p_2\beta_s c - 1 = R_s - 1$,

$\lambda_3 = \beta_r c - \mu - d_r = (\mu + \eta + d_r)(R_r - 1)$.

Hence, the first eigenvalue, λ_1 is always negative.

The second and third eigenvalues, λ_2 and λ_3 are negatives when both R_s and R_r are less than one , respectively. Otherwise they are positive if both R_s and R_r are greater than one.

Using Rouths stability criterion [84-86], we have $R_{TB} = max(R_s, R_r) < 1$

while all eigenvalues are negatives.

Therefore, the disease free equilibrium is locally asymptotically stable if $R_{TB} < 1$ and unstable if $R_{TB} > 1$.

The following theorem shows the stability of endemic equilibria of our model.

□

Theorem 2.4.9. *([32, 65, 66, 73]) The endemic equilibrium of the epidemic model (2.2.1) is locally asymptotically stable whenever $R_{TB} > 1$ and it is unstable whenever $R_{TB} < 1$.*

Proof. In our previous sections we had shown the endemic properties of drug-resistant TB while no drug-sensitive TB and vice versa. So showing when both TB strains are endemic is enough consideration of this case.

The endemic equilibrium denoted by $E^* = (N_T^*, m^*, I_r^*)$ of the model (2.2.1), which was further expressed and rewritten as in the system (2.4.12) solved below to investigate whether $R_s > 1$ and $R_r < 1$ or $R_s < 1$ and $R_r > 1$ or $R_s > 1$ and $R_r > 1$.

we obtained:

$N_T^* = \frac{\Lambda}{\mu+d_s\chi+\frac{d_r(1-\frac{1}{R_s})}{1+\chi}}$,

$m^* = \frac{\Lambda\chi(1-\frac{1}{R_s})}{\mu+d_s\chi+\frac{d_r(1-\frac{1}{R_s})}{1+\chi}} = N_T^*\chi\frac{(1-\frac{1}{R_s})}{(1+\chi)p_1}$,

$I_r^* = \frac{\Lambda(1-\frac{1}{R_s})}{(\mu+d_s\chi+\frac{d_r(1-\frac{1}{R_s})}{1+\chi})(1+\chi)} = N_T^*\frac{(1-\frac{1}{R_s})}{(1+\chi)}$.

Where,

$\chi = \frac{p_1(\mu+\eta+d_r)(1-\frac{R_r}{R_s})}{qr\theta p_2}$. However, when we checked the positivity of our solutions, we found the relationships of the basic reproduction numbers and other constants as follows:

- $\chi > 0$ implies that $(1 - \frac{R_r}{R_s}) > 0$ as a result $R_s > R_r$.

- The endemic equilibrium is positive when both $\chi > 0$ and $(1 - \frac{1}{R_s}) > 0$, which is equivalent to $R_s > 1$.

As we did the endemic equilibrium of drug-sensitive TB above (i.e when $I_r = 0$), it is true if there is no infected individuals who develop drug-resistant TB which is $q = 0$. But here, it is not the case we consider in our purpose. Therefore, from the these cases and with generally truth, our model is endemic at the endemic equilibrium when both R_s and R_r greater than one since $R_s > 1$ and $R_s > R_r$. □

2.5 Numerical results and simulations

In this section, we perform some numerical simulations in order to study the epidemiology model of the system (2.2.1). For our purpose we take the values of the parameters from the table 2.2.1 and the prevalence, incidence and notifications of drug-sensitive and MDR-TB considered in above sections. In the following sections, we consider the numerical simulations at the disease free and endemic equilibria.

2.5.1 The numerical simulations at the disease free equilibria

In the figures (2.5) and (2.6) below, the first two figures showed solutions of susceptible to TB on the left side and infected individual with drug-sensitive TB on the right side. But the last one shows the solution of infected individuals with drug-resistant TB of the disease free equilibrium of the model (2.2.1) at different initial values when $R_{TB} < 1$.

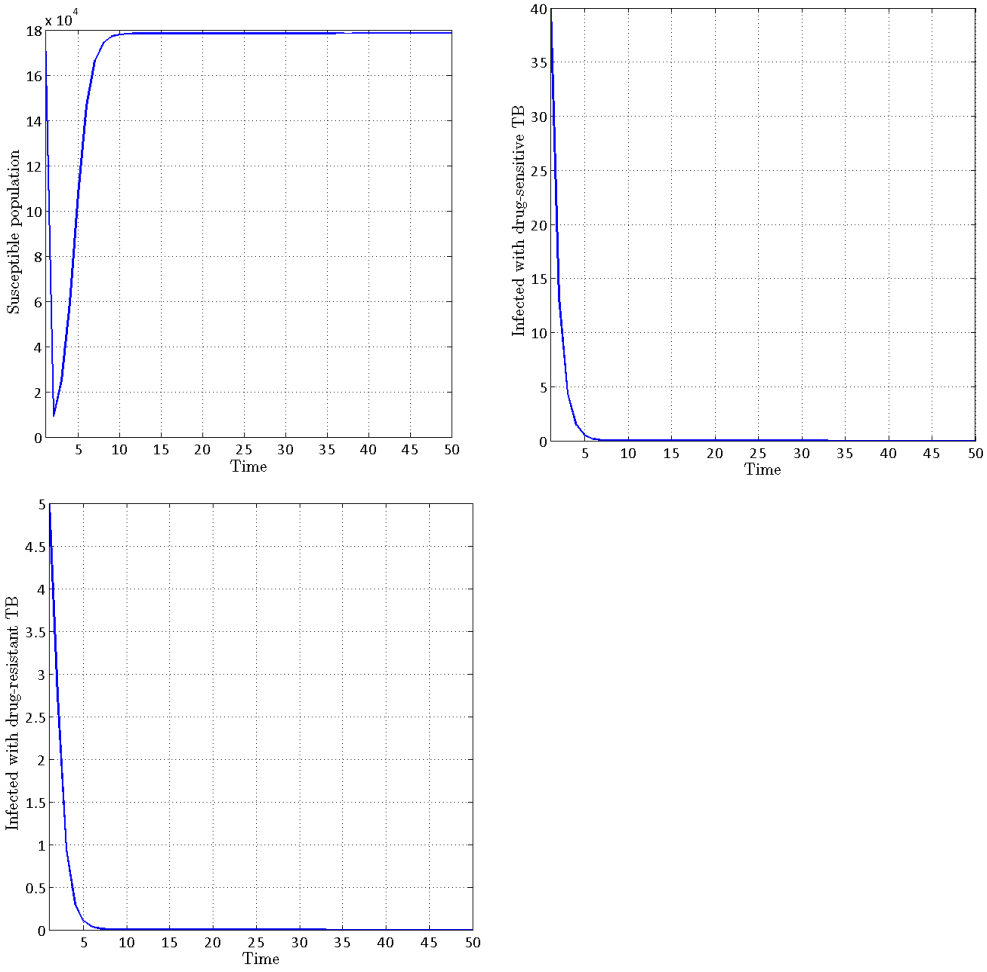


Figure 2.5: These are solutions of TB model with initial solutions $(S(0), I_s(0), I_r(0)) = (178000, 40, 5)$.

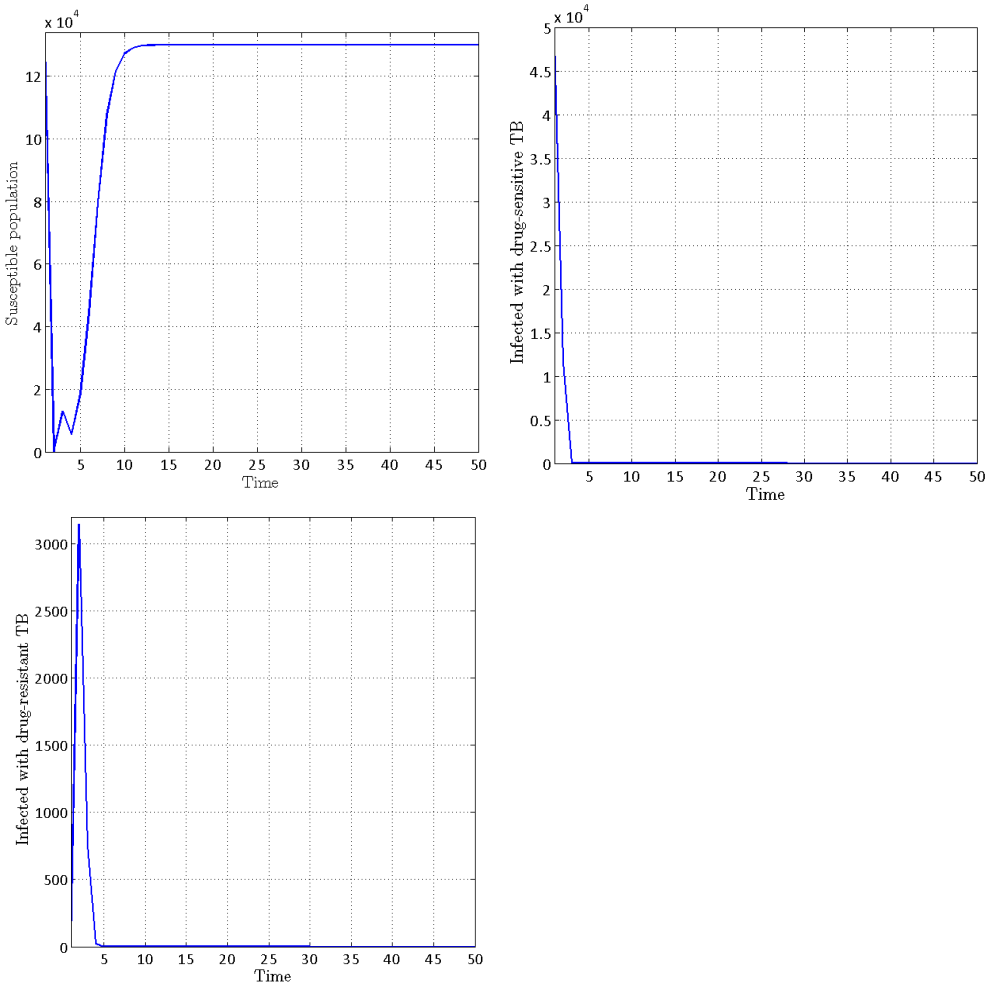


Figure 2.6: These are solutions of TB model with initial solutions $(S(0), I_s(0), I_r(0)) = (130000, 48400, 45)$.

2.5.2 The numerical simulations at endemic equilibria

Here, we discuss solutions of the endemic equilibrium of the model (2.2.1) at different initial values when $R_{TB} > 1$. The numerical simulations as shown in the following figures (2.7, 2.8 and 2.9), first two figures showed solutions of susceptible to TB on the left side and infected individual with drug-sensitive

TB on the right side. But the last one shows the solution of infected individuals with drug-resistant TB in all cases.

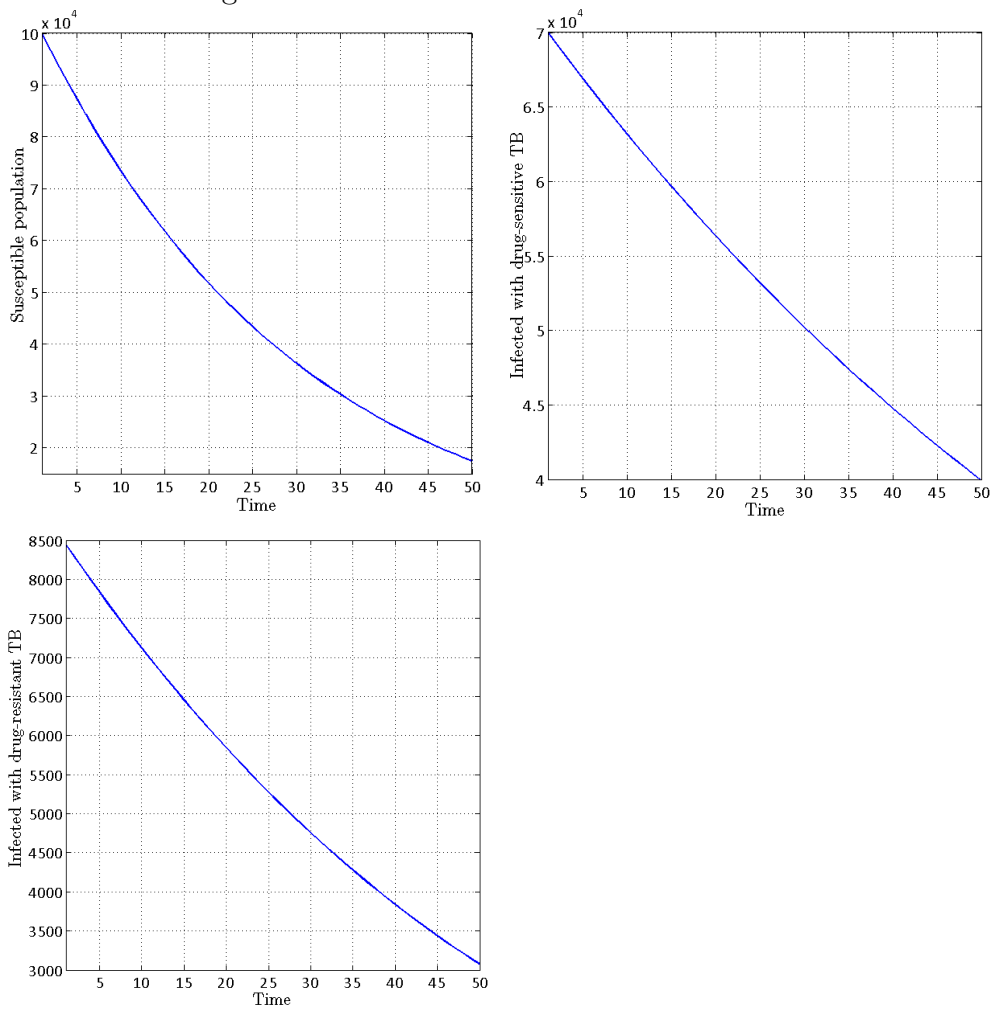


Figure 2.7: These are solutions of TB model with initial solutions $(S(0), I_s(0), I_r(0)) = (100000, 70000, 8445)$.

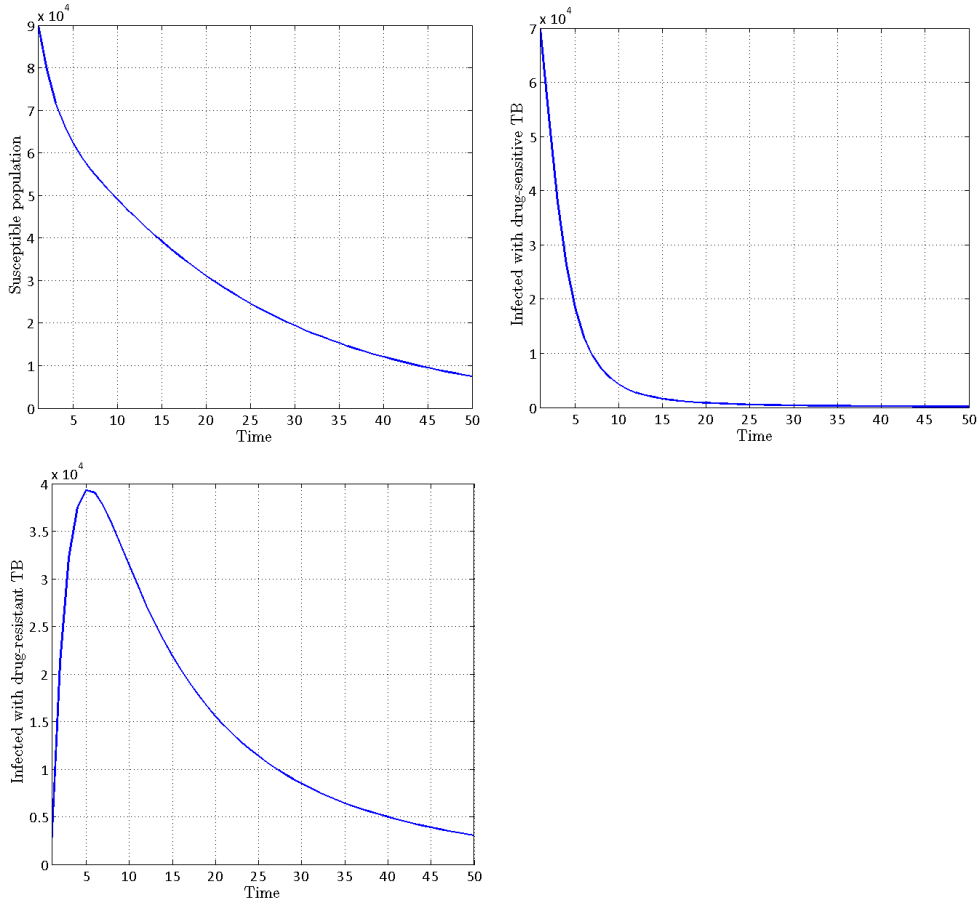


Figure 2.8: These are solutions of TB model with initial solutions $(S(0), I_s(0), I_r(0)) = (100000, 70000, 2000)$.

The following figure shows the region of equilibria stability of TB models discussed in our previous sections .

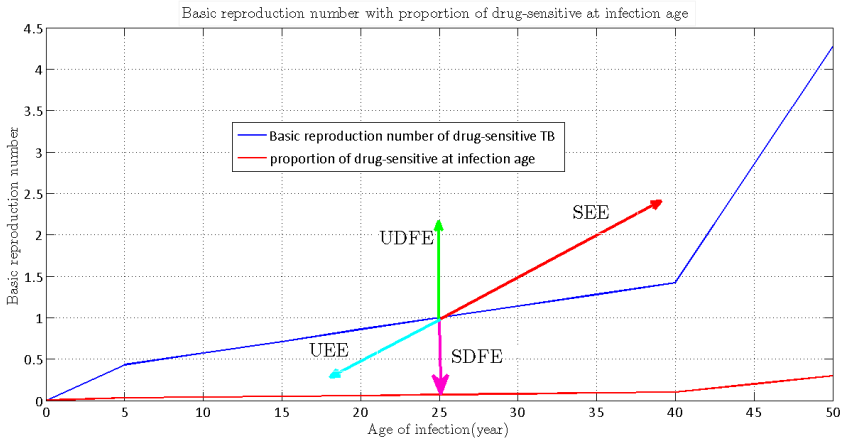


Figure 2.9: Basic reproduction number of drug-sensitive TB.

This figure shows the region of unstable disease free equilibrium and stable endemic equilibrium points lie when the basic reproduction number greater than unity, but the stable disease free equilibrium and unstable endemic equilibrium lie in the region when the basic reproduction number less than unity.

Chapter 3

Description of the HIV-TB co-infection model

We develop and analyze a mathematical model describing the dynamics of HIV-TB co-infection. In this model, the dynamics of both drug-sensitive and resistant strains TB discussed in chapter two and HIV are considered. It is the combination of the model presented in chapter 2 and the HIV model presents in this chapter. We develop and analyze a mathematical model describing the dynamics of HIV-TB co-infection. In this model, the dynamics of both drug-sensitive and resistant strains TB discussed in chapter two and HIV are considered. It is the combination of the model presented in chapter 2 and the HIV model presents in this chapter.

3.1 Introduction

In recent history, the paths of HIV and Tuberculosis have come to a critical intersection. Combined, these two diseases are the leading cause of mortality due to infectious disease [71]. In Sub Saharan African countries including

Ethiopia, there were 24.7 million people living with HIV and 1.1 million people died from AIDS-related causes in 2013 (UNAIDS, Fact sheet 2014). In 2013, the worldwide percentage of identified HIV-positive tuberculosis patients who started or continued the anti-retro-viral treatment reached 70 percent (up from 60 percent in 2012) [55, 59, 64].

It is estimated that one third of the worlds population is host to tuberculosis and among the estimated 9 million people who developed TB, an estimated 1.1 million (13 percent) were HIV positive. There were also 360,000 deaths from HIV associated TB equivalent to 25 percent of all TB deaths, and around 25 percent of the estimated 1.5 million deaths from HIV/AIDS in 2013 [59].

What links these two diseases so intimately is their common substrate of poverty; both are concentrated in resource-limited areas, exposing the social determinants of the diseases [69, 71]. Despite the fact that these diseases remain rampant in developing countries like Ethiopia, a lack of resources dedicated to co-infection has resulted in little progress being made at their intersection [55-68].

In the year 2012, the total number of new TB cases detected by TB DOST (Directly Observed Treatment, Short-Course) program represents a population of 92531. The data also described that 46869 of them were the number of new smear positive pulmonary TB cases detected by the program. In the same year, there were 74048 TB patients enrolled in DOST and tested for HIV in the quarter. From those population 9280 number of TB patients were co-infected with HIV (enrolled in DOTS who were HIV positive). In the year 2012, a total of 5641830 clients received HIV test and from them 81415 clients were testing positive for HIV. The number of PLWHA ever enrolled in HIV care who ever started the ART and who are currently receiving ART

were 432232, 244454 and 183249 respectively [21, 22, 29, 30].

HIV infection and infection with TB bacteria are though completely different infections. If you have HIV infection you will not be infected with TB bacteria unless you are in contact with someone who also is infected with TB bacteria. Although if you live in a country with a high prevalence of TB this may have happened without you realize it. Similarly if you have TB you will not be infected with HIV unless you carry out an activity with someone who already has HIV infection, which results in you getting the HIV from them. TB also occurs earlier in the course of HIV infection than many other opportunistic infections. The risk of death in co-infected individuals is also twice that of HIV infected individuals without TB, even when CD4 cell count and antiretroviral therapy are taken into account [69].

The figures and tables presented in the previous chapters showed the prevalence and incidence of TB as well as HIV-TB co-infection in Ethiopia. According to the best of our knowledge discussed at the general introduction of first chapter, we could hardly find research on mathematical modeling of HIV and TB co-infections that incorporate TB treatment in nonlinear ordinary and partial differential equations models. But from biological and medical perspectives, the reader who wishes to have more information on HIV and TB co-infections may consult the following works and also the references there in [14, 19, 31, 32, 34, 36, 38, 39, 43, 44, 45, 51, 50, 56]. Therefore, we will provide some concepts and models that fills these gaps in the following sections.

3.2 Formulation of HIV-sub model

Before we combine the models considered in this chapter, we first consider the HIV only sub model. The total population divided into S susceptible individuals, I_H HIV infectious individuals in the SI model.

$$\begin{aligned} \frac{dS}{dt} &= \Lambda - \lambda_H S - \mu S \\ \frac{dI_H}{dt} &= \lambda_H S - (\mu + d_H) I_H \end{aligned} \tag{3.2.1}$$

d_H =per-capita HIV-induced death rate.

β_H= probability of HIV infection per contact with a person who is HIV infectious and c is the per-capita contact rate for HIV,

$\lambda_H = c\beta_H \frac{I_H}{N}$ -the force of infection.

The above model is also expressed using diagram as follows:

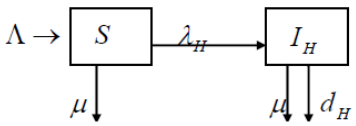


Figure 3.1: Flow diagram of the SI compartments of the HIV model.

Symbol	Value	Sources
β_H	0.28	[26]
d_H	0.05	[26]

Table 3.1: The values of the parameters used in (3.2.1)

The well-posed and positivity solution of this model is similar as we discussed in the previous chapter. In the next sections, we discuss the stability and epidemic equilibria of the the systems in (3.2.1).

3.2.1 Analysis of HIV sub-model

In this section, we discuss some of the points of mathematical analysis of the HIV sub-model given in the systems of equations (3.2.1) to obtain the basic reproduction number and to show the stability and unstably of the equilibria and epidemic of the system according to the basic reproduction number computed. The problems considered in our analysis are well-posed problem as observed in the second chapter and viewed in different literatures [32, 37, 39, 71].

3.2.2 Basic reproduction number

Recall that the basic reproduction number is defined as the expected number of new HIV infections from one infected individual in a fully susceptible population through the entire duration of the infectious period. If $R_H < 1$, then an infected individual produces, on average, less than one new infected individual over the course of its infectious period, and the infection cannot grow. Conversely, if $R_H > 1$, then each infected individual produces, on average, more than one new infection, and the disease can invade the population as we saw in the second chapter. By rearranging and substituting S in terms

of N ($S = N - I_H$)and I_H into the system in (3.2.1), we obtained

$$\begin{aligned} \frac{dN}{dt} &= \Lambda - \mu N - d_H I_H \\ \frac{dI_H}{dt} &= c\beta_H \frac{I_H}{N}(N - I_H) - (\mu + d_H) I_H \end{aligned} \tag{3.2.2}$$

For this system of equation, by applying the next generation method approach [82], F and V are represented as matrices respectively for the new infections generated and the transition terms is then obtained as,

$\digamma = \beta_H c I_H$ and

$\vartheta = (\mu + d_H) I_H$.

Here, $F = (\beta_H c)$ and

$V = (\mu + d_H)$.

R_H, the basic reproduction number of HIV only sub-model is given by spectral radius, ρ of FV^{-1}, i e $R_H = \rho(FV^{-1}) = \frac{\beta_H c}{\mu + d_H}$.

3.2.3 Positivity of solutions and existence of invariant set

Most delay differential equations that arise in population dynamics and epidemiology model intrinsically nonnegative quantities. It is important to establish that nonnegative initial data give rise to nonnegative solutions. The model system (3.2.1) above describes the dynamics of a human population. Therefore; it is important to prove that the state variables susceptible $S(t)$, and $I_H(t)$, HIV infected individuals are non-negative for all time $t \geq 0$.
For this, we state and prove the following proportion.

Theorem 3.2.1. *The feasible region in the set* $D = \{(S, I_H) \epsilon R^2 / N \leq \frac{\Lambda}{\mu}\}$ *is positivity-invariant for system (3.2.1).*

Proof. The proof of this theorem is the same as the theorem 2.4.7 proved in the previous chapter. □

3.2.4 Stability and equilibria properties of HIV

In this section, we find the equilibria and determine the stability properties of our model in (3.2.1).

Theorem 3.2.2. *The disease free equilibrium of HIV in (3.2.1) is locally asymptotically stable (will die out) if* $R_H < 1$ *while it is unstable if* $R_H > 1$.

Proof. By substituting the disease free equilibrium of the system in (3.2.1) is given by $E^0 = (\frac{\Lambda}{\mu}, 0)$ and using next generation matrix methods [82] for:

$$\digamma = \beta_H c I_H$$
$$\text{and } \vartheta = \begin{pmatrix} \beta_H c \frac{I_H}{N_T} I_H + (\mu + d_H) I_H \\ \mu N_T + d_H I_H \end{pmatrix}.$$

By taking their partial derivatives with respect to the given variables, we obtained

$F = (\beta_H c)$ and $V = \mu + d_H$.

We also found the corresponding Jacobian matrix at the disease free equilibrium $E^0 = (N^0, I_H^0)$ as follows:

$$J(E^0) = \begin{pmatrix} -\mu & -d_H \\ 0 & \beta_H c - (\mu + d_H) \end{pmatrix}$$

.

Hence, the eigenvalues of the matrix are:

$\lambda_1 = -\mu$,

$\lambda_2 = \beta_H c - (\mu + d_H) = \beta_H c(1 - \frac{1}{R_H})$.

Thus, the first eigenvalue, λ_1 is always negative. The second eigenvalue, λ_2 is negative while $R_H < 1$.

Hence, the disease free equilibria in the system (3.2.1) is locally asymptotically stable if $R_H < 1$ while it is unstable if $R_H > 1$.

Thus , this completes the proof this theorem. Similarly, the endemic equilibrium theorem stated as follows. □

Theorem 3.2.3. *The endemic equilibrium of HIV in the system (3.2.1) is locally asymptotical stable if $R_H > 1$ and it is unstable whenever $R_H < 1$.*

Proof. : Here, we can denote the endemic equilibrium $E^1 = (N^1, I_H^1)$ and by solving (3.2.2), from the second equation we have $I_H^1 = (1 - \frac{1}{R_H})N^1$. By substituting this in the first equation of our system, we obtained
$E^1 = (\frac{\Lambda}{\mu + d_H(1-\frac{1}{R_H})}, \frac{\Lambda(1-\frac{1}{R_H})}{\mu + d_H(1-\frac{1}{R_H})})$ and its corresponding Jacobian matrices as

$$J(E^1) = \begin{pmatrix} -\mu & -d_H \\ c\beta_H(1-\frac{1}{R_H})^2 & -c\beta_H(1-\frac{1}{R_H}) \end{pmatrix}$$

.

The characteristic equation associated with the above matrix is given by

$$\lambda^2 + C_1\lambda + C_2 = 0.$$

Where,
$C_1 = \mu + \beta_H c(1 - \frac{1}{R_H})$,
$C_2 = \mu\beta_H c(1 - \frac{1}{R_H}) + \beta_H c d_H(1 - \frac{1}{R_H})^2$.

As we observed the coefficients C_1 and C_2 are both greater than zero if $R_H > 1$. And all the roots of the above characteristic equations are negatives or have negative real parts. Hence using these results and Routh

Hurwitz Criteria [84, 85, 86]:

- When $\lambda = -1$, $1 - C_1 + C_2 > 0$,
  $1 + C_2 > C_1$,
- When $\lambda = 1$, $1 + C_1 + C_2 > 0$,
- When $\lambda = 0$, $|C_2| < 1$.

Therefore, the epidemic equilibrium of the system (3.2.1) is locally asymptotical stable if $R_r > 1$, and it is unstable if $R_r < 1$. □

By combining the above HIV sub-model (3.2.1) and models (2.2.1) in chapter 2, we formulate the HIV-TB co-infection model in the following section.

3.3 Formulation of HIV-TB co-infection model

In this model, we divide the total population into five sub-populations of SIS epidemiological classes, Susceptible $S(t)$, TB only infectious (i.e infectious with drug sensitive strain $I_s(t)$ and infectious with drug resistant strain $I_r(t)$, HIV only infectious $I_H(t)$, and infectious with both HIV and TB, $I_{HTB}(t)$. It is assumed that susceptible population are recruited into the population at a constant rate Λ. They either acquire infection with TB following effective contact with infected population (at rates λ_s and λ_r) and move to the TB infectious class ($I_s(t)$ and $I_r(t)$) or acquire infection with HIV following effective contact with infected population (at a rate λ_H) and move to the HIV infectious class ($I_H(t)$). Infected individuals with TB only are either successfully

treated and move into susceptible class (at a rate $(1-r)\theta+\eta$) or acquire infection with HIV following effective contact with infected population(at rates $\sigma_s\lambda_H$ and $\sigma_r\lambda_H$) for drug sensitive and drug resistant respectively. The parameters $0<\sigma_s\leq 1$ and $0<\sigma_r\leq 1$ models the expected decrease in sexual activity (contact) by individuals with TB infection (because of ill health) [35, 51, 66] who move to the HIV-TB co-infectious class (I_{HTB}). They die from the disease (at rates d_s and d_r).

Infected individuals with HIV only either acquire infection with TB following effective contact with infected individuals (at rates $\gamma_s\lambda_s, \gamma_r\lambda_r$) and move to the HIV-TB co-infectious class (I_{HTB}) or die from HIV (at a rate d_H). Here $\gamma_s>1$ and $\gamma_r>1$ accounts for the assumed increase in susceptibility to TB infection (drug sensitive and resistant) as a result of HIV infection [45].

Co-infected individuals either recover with partial immunity and move into HIV only infectious class (at a rate υ) or die from TB (drug sensitive and drug resistant TB) (at rates $\kappa_s d_s$ and$\kappa_r d_r$). Here $\kappa_s>1$; $\kappa_r>1$ account for the increased mortality of the I_{HTB} individuals in comparison to individuals with TB infection but not infected with HIV [45] or from HIV (at a rate $\kappa_h d_H$, $\kappa_H>1$ accounts for the increased mortality of the I_{HTB} individuals in comparison to individuals with HIV infection but not infected with TB) [17, 25, 45]. The death due to natural causes occurs in all population classes at rate μ.

The flow diagram is expressed as shown below:

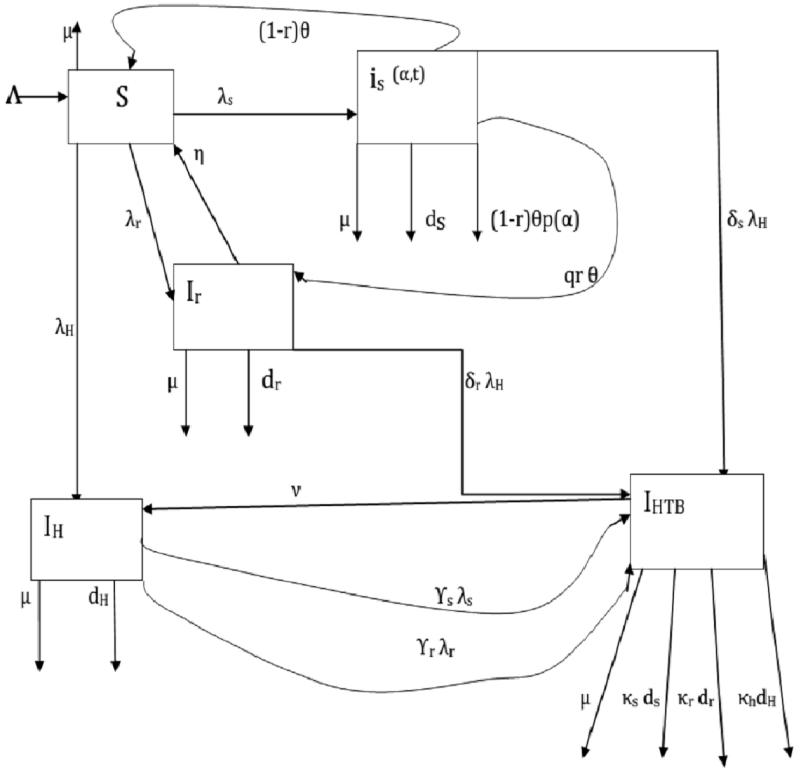


Figure 3.2: Flow diagram of HIV-TB co-infection with TB treatment.

Using the flow diagram for their interconnection, the above assumptions and notations, the HIV and TB co-infection with TB treatment model is written as follows:

$$
\begin{aligned}
&\frac{dS}{dt} = \Lambda - (\lambda_s + \lambda_r + \lambda_H)S - \mu S + \eta I_r + (1-r)\theta I_s^a \\
&(\frac{\partial}{\partial t} + \frac{\partial}{\partial \alpha})i_s(\alpha,t) = -[((1-r+qr)\theta + \sigma_s\lambda_H)p(\alpha) + \mu + d_s]i_s(\alpha,t) \\
&\frac{dI_r}{dt} = \lambda_r S - \sigma_r\lambda_H I_r - (d_r + \mu + \eta)I_r + qr\theta I_s^a \\
&\frac{dI_H}{dt} = \lambda_H S + \upsilon I_{HTB} - (\gamma_s\lambda_s + \gamma_r\lambda_r)I_H - (d_H + \mu)I_H \\
&\frac{dI_{HTB}}{dt} = \sigma_s\lambda_H I_s^a + \sigma_r\lambda_H I_r + (\gamma_s\lambda_s + \gamma_r\lambda_r)I_H - \omega I_{HTB}
\end{aligned}
\tag{3.3.1}
$$

where, $i_s(0,t) = \beta_s c S\frac{I_s^a}{N}$,

$I_s^a(t) = \oint_0^\infty p(\alpha)i_s(\alpha,t)d\alpha$, total number of active TB of drug-sensitive strain,

$I_s(t) = \oint_0^\infty i_s(\alpha, t)d\alpha$, total number of infected individuals with TB of drug-sensitive TB(both latent and active TB are included),
$\omega = \mu + \nu + \kappa_s d_s + \kappa_r d_r + \kappa_H d_H$.

3.4 Analysis of the HIV-TB co-infection model

In this section, we discuss some of the concepts of mathematical analysis of the HIV-TB co-infection model given in the system of equations (3.3.1). The aim is to obtain the basic reproduction number(s), to show the stability of equilibria of the system according to the basic reproduction number.

3.4.1 Well-posed problem

The definition of well-posed problem and its properties considered in chapter 2 are also true here too. Therefore, in the next sections we consider the stability, equilibria properties and numerical simulations of the model.

3.4.2 Basic reproduction number

By integrating the second equation with respect to α that runs between 0 and ∞ and expressing

$$\frac{dN}{dt} = \frac{dS}{dt} + \frac{dI_s}{dt} + \frac{dI_r}{dt} + \frac{dI_H}{dt} + \frac{dI_{HTB}}{dt} \tag{3.4.1}$$

We can also express S in terms of other variables as
$S = N - I_s - I_r - I_H - I_{HTB}$.
Hence the system of equation in (3.3.1) can be rewritten as

$$
\begin{aligned}
&\tfrac{dN}{dt} = \Lambda - \mu N - d_s p_1 m - d_r I_r - d_H I_H - d I_{HTB} \\
&\tfrac{dm}{dt} = \beta_s c(1 - p_1 \tfrac{m}{N} - \tfrac{I_r}{N} - \tfrac{I_H}{N} - \tfrac{I_{HTB}}{N}) p_2 m - m \\
&\tfrac{dI_r}{dt} = \beta_r c(1 - p_1 \tfrac{m}{N} - \tfrac{I_r}{N} - \tfrac{I_H}{N} - \tfrac{I_{HTB}}{N}) I_r - \\
&(\sigma_r \lambda_H + \mu + d_r + \eta) I_r + qr\theta p_2 m \\
&\tfrac{dI_H}{dt} = \beta_H c(1 - p_1 \tfrac{m}{N} - \tfrac{I_r}{N} - \tfrac{I_H}{N} - \tfrac{I_{HTB}}{N}) I_H + \upsilon I_{HTB} - \\
&(\gamma_s \lambda_s + \gamma_r \lambda_r) I_H - (d_H + \mu) I_H \\
&\tfrac{dI_{HTB}}{dt} = \sigma_s \lambda_H p_2 m + \sigma_r \lambda_H I_r + (\gamma_s \lambda_s + \gamma_r \lambda_r) I_H - \omega I_{HTB}
\end{aligned}
\tag{3.4.2}
$$

where, $i_s(0,t) = \beta_s c S \frac{I_s^a}{N}$,

$I_s^a(t) = \oint_0^\infty p(\alpha) i_s(\alpha, t) d\alpha$, total number of active TB of drug-sensitive strain,

$I_s(t) = \oint_0^\infty i_s(\alpha, t) d\alpha$, total number of infected individuals with TB of drug-sensitive TB (both latent and active TB are included)

Since the system of equations in (3.3.1) is non-linear, we take the linearized one for our purpose as follows:

$d = \kappa_s d_s + \kappa_r d_r + \kappa_h d_H$,

$\omega = \mu + \upsilon + d$,

p_2 is the same as computed in chapter 2 and given as

$p_1 = \oint_0^t e^{-(\mu + d_s)\alpha - \oint_0^\alpha \delta(s) ds} d\alpha$; which implies

$p_2 = \oint_0^t p(\alpha) e^{-(\mu + d_s)\alpha - \oint_0^\alpha \delta(s) ds} d\alpha$.

Using the generating matrix approaches as [82] and from the above system (3.4.2), we have:

$$
F = \begin{pmatrix}
\beta_s c p_2 m \\
\beta_r c I_r + qr\theta p_2 m \\
\beta_H c I_H + \nu I_{HTB} \\
(\sigma_s \beta_H c p_2 + \sigma_r \beta_H c + (\gamma_s \lambda_s + \gamma_r \lambda_r)) I_H \\
0
\end{pmatrix}
$$

$$\vartheta = \begin{pmatrix} m \\ (\sigma_r\lambda_H + \mu + \eta + d_r)I_r \\ (\mu + d_H)I_H \\ (\mu + d_H)I_{HTB} \\ \mu N + d_s p_1 m + d_r I_r + d_H I_H + (\omega - \mu - \nu)I_{HTB} \end{pmatrix}$$

Hence, the matrices F and V for the new infection and the remaining transfer terms are respectively given below:

$$F = \frac{\partial F_i}{x_j} = \begin{pmatrix} \beta_s c p_2 & 0 & 0 & 0 & 0 \\ qr\theta p_2 & \beta_r c & 0 & 0 & 0 \\ 0 & 0 & \beta_H c & \nu & 0 \\ 0 & 0 & 0 & \sigma_s\beta_H c p_2 + \sigma_r\beta_H c & 0 \\ 0 & 0 & 0 & 0 & 0 \end{pmatrix}$$

$$V = \frac{\partial \vartheta_i}{x_j} = \begin{pmatrix} 1 & 0 & 0 & 0 & 0 \\ 0 & \mu + \eta + d_r & 0 & 0 & 0 \\ 0 & 0 & \mu + d_H & 0 & 0 \\ 0 & 0 & 0 & \omega & 0 \\ \mu & d_s p_1 & d_r & d_H & d \end{pmatrix}$$

From this we obtained the determinant of V and its inverse as follows:

$\det(V) = \omega d(\mu + d_H)(\mu + \eta + d_r)$,

$$V^{-1} = \begin{pmatrix} 1 & 0 & 0 & 0 & 0 \\ 0 & \frac{1}{\mu+\eta+d_r} & 0 & 0 & 0 \\ 0 & 0 & \frac{1}{\mu+d_H} & 0 & 0 \\ 0 & 0 & 0 & \frac{1}{\omega} & 0 \\ \frac{\mu}{\omega-\mu-\nu} & \frac{d_s p_1}{d} & \frac{d_r}{d} & \frac{d_H}{d} & \frac{1}{d} \end{pmatrix}.$$

From the above, we have:

$$FV^{-1} = \begin{pmatrix} \beta_s c p_2 & 0 & 0 & 0 & 0 \\ qr\theta p_2 & \frac{\beta_r c}{\mu+\eta+d_r} & 0 & 0 & 0 \\ 0 & 0 & \frac{\beta_H c}{\mu+d_H} & \frac{\nu}{\omega} & 0 \\ 0 & 0 & 0 & \frac{d}{\omega} & 0 \\ 0 & 0 & 0 & 0 & 0 \end{pmatrix}$$

$$= \begin{pmatrix} R_s & 0 & 0 & 0 & 0 \\ qr\theta p_2 & R_r & 0 & 0 & 0 \\ 0 & 0 & R_H & \frac{\nu}{\omega} & 0 \\ 0 & 0 & 0 & \frac{d}{\omega} & 0 \\ 0 & 0 & 0 & 0 & 0 \end{pmatrix}.$$

Therefore, the eigenvalues of this is

$$\det \begin{pmatrix} (R_s-\lambda) & 0 & 0 & 0 & 0 \\ qr\theta p_2 & (R_r-\lambda) & 0 & 0 & 0 \\ 0 & 0 & (R_H-\lambda) & \frac{\nu}{\omega} & 0 \\ 0 & 0 & 0 & (\frac{d}{\omega}-\lambda) & 0 \\ 0 & 0 & 0 & 0 & -\lambda \end{pmatrix}$$

$$= (R_s-\lambda)(R_r-\lambda)(R_H-\lambda)(\tfrac{d}{\omega}-\lambda)(-\lambda) = 0.$$

The dominant eigenvalues are the basic reproduction of TB, $R_{TB} = \max(R_s, R_r)$ as we did in chapter 2 for the system (2.2.1), basic reproduction of HIV, R_H that is obtained the HIV sub-model in the system (3.2.2). Thus, the basic reproduction of the system (3.3.1) denoted by R is given by$R = \max(R_H, R_{TB})$ which are the spectral radius of the operator FV^{-1}.

3.4.3 Positivity of solution

As we did in the previous chapter, the model system (3.3.1) above describes the dynamics of a human population. Therefore; it is important to prove that the state variables susceptible $S(t)$, TB only infectious (i.e infectious with drug sensitive strain $I_s(t)$ and infectious with drug resistant strain $I_r(t)$, HIV only infectious $I_H(t)$, and infectious with both HIV and TB, $I_{HTB}(t)$ infected individuals are non-negative for all time $t \geq 0$. For this model analysis, we state and prove the next theorem.

Theorem 3.4.1. *The feasible region in the set* $D = \{(S, i_s, I_r, I_H, I_{HTB})\epsilon R^5 / N \leq \frac{\Lambda}{\mu}\}$ *is positivity-invariant for system (3.3.1)*

Proof. The rate of change of the total population computed from equation of model (3.3.1) computed in the system of equations (3.3.2) is given by
$\frac{dN}{dt} = \Lambda - \mu N - d_r I_r - d_H I_H - dI_{HTB} - d_s \oint_0^t m(t-\alpha) e^{-(\mu+d_s)\alpha - \oint_0^\alpha \delta(s)ds} d\alpha \leq$
$\Lambda - \mu N$
which implies the feasible region $D = \{(S(t), i_s(\alpha, t), I_r(t), I_H(t), I_{HTB)(t)}\epsilon R^5 / (S(t) +$
$\oint_0^\infty i_s(\alpha, t)d\alpha + I_r(t) + I_H + I_{HTB} = N \leq \frac{\Lambda}{\mu}\}$ and from equation(3.4.1) we observed that $\limsup_{t\to\infty} N \leq \frac{\Lambda}{\mu}$. It is clear that $\frac{dN}{dt} \leq \frac{\Lambda}{\mu}$, since $N(0) \leq \frac{\Lambda}{\mu}$.
And also from equation(3.3.1), we find that
$\frac{dS}{dt} = \Lambda - (\lambda_s + \lambda_r + \lambda_H)S - \mu S + (1 - r + \eta qr)\theta I_s^a \geq (\lambda_s + \lambda_r + \lambda_H)S$, which implies that $S(t) \geq S(0)e^{-(\lambda_s+\lambda_r+\lambda_H+\mu)t}$, for all $t \geq 0$,
Similarly ;$I_s(t) \geq I_s(0)e^{-(\mu+d_s)t}$ for all $t \geq 0$,
$I_r(t) \geq I_r(0)e^{-(\mu+d_r+\eta+\sigma_r\lambda_H)t}$ for all $t \geq 0$,
$I_H(t) \geq I_H(0)e^{-(\gamma_s\lambda_s+\gamma_r\lambda_r+(d_H+\mu)t}$,
$I_{HTB}(t) \geq I_{HTB}(0)e^{-\omega t}$ for all $t \geq 0$.
Thus, all the above shows that the solution of the system(3.3.1) is greater or

equal zero for all $t \geq 0$.

Therefore, the limits of the system in (3.3.1) with initial conditions remained in D and all the variables and parameters of it are non-negative for all $t \geq 0$ in its interval of existence feasible region D.

Hence, D is positivity invariant and attracting. Thus the mathematical model in(3.3.1) in the region D is epidemiologically well-posed. □

In the next section, we study the equilibria and stability properties of our model in (3.3.1).

3.4.4 Equilibria and stability properties of the model

In this section, we try to find the equilibria and determine the stability properties of the model in (3.3.1).

The disease free equilibria of the system in (3.3.1) is given by $E^0 = (\frac{\Lambda}{\mu}, 0, 0, 0, 0)$. is asymptotically stable if $R < 1$ and unstable if $R > 1$,

where $R = \max(R_{TB}, R_H)$. Therefore, all the following diseases free and epidemic equilibria satisfies the above.

Theorem 3.4.2. *The disease free equilibrium of the model (3.3.1) is locally asymptotically stable (both HIV and TB diseases will die out) if $R < 1$ otherwise it is unstable if $R > 1$.*

Proof. By substituting the diseases free equilibrium point to the system of equations in (3.4.2) which is the reduced form of (3.3.1), and using **theorem 2.4.3**, we obtained the corresponding Jacobian matrix as shown below:

$$J(E^0) = \begin{pmatrix} -\mu & -d_s p_1 & -d_r & -d_H & -d \\ 0 & R_s - 1 & 0 & 0 & 0 \\ 0 & qr\theta p_2 & \beta_r c(1 - \frac{1}{R_r}) & 0 & 0 \\ 0 & 0 & 0 & \beta_H c(1 - \frac{1}{R_H}) & \nu \\ 0 & 0 & 0 & 0 & -\omega \end{pmatrix}$$

Here, the eigenvalues of this matrix are

$\lambda_1 = -\mu$,

$\lambda_2 = -\omega$,

$\lambda_3 = R_s - 1$,

$\lambda_4 = \beta_r c(1 - \frac{1}{R_r})$,

$\lambda_5 = \beta_H c(1 - \frac{1}{R_H})$.

Hence, the first,λ_1 and the second, λ_2 eigenvalues are always negative. The third, λ_3, fourth, λ_4 and fifth, λ_5 eigenvalues are negative if all R_s, R_r and R_H are less than unity, respectively. That means when both basic reproduction numbers of TB and HIV are less than one ($R = \max(R_{TB}, R_{TB}) < 1$). Therefore, the disease free equilibrium of the model (3.3.1) is locally asymptotically stable if $R < 1$ and it is locally asymptotically unstable if $R > 1$. □

Similarly the endemic equilibria of the system (3.3.1) are shown in the theorem 3.4.3 below.

Theorem 3.4.3. *The endemic equilibrium of the model (3.3.1) is locally asymptotically stable if $R > 1$ otherwise it is unstable if $R < 1$.*

Proof. The endemic equilibria are obtained by equating the system (3.4.2) which is the reduced form of (3.3.1) equals to zero.

$$\Lambda - \mu N - d_s p_1 m - d_r I_r - d_H I_H - d I_{HTB} = 0$$
$$\beta_s c(1 - p_1\tfrac{m}{N} - \tfrac{I_r}{N} - \tfrac{I_H}{N} - \tfrac{I_{HTB}}{N})p_2 m - m = 0$$
$$\beta_r c(1 - p_1\tfrac{m}{N} - \tfrac{I_r}{N} - \tfrac{I_H}{N} - \tfrac{I_{HTB}}{N})I_r - (\sigma_r\lambda_H + \mu + d_r + \eta)I_r + qr\theta p_2 m = 0$$
$$\beta_H c(1 - p_1\tfrac{m}{N} - \tfrac{I_r}{N} - \tfrac{I_H}{N} - \tfrac{I_{HTB}}{N})I_H + \upsilon I_{HTB} - (\gamma_s\lambda_s + \gamma_r\lambda_r)I_H - (d_H + \mu)I_H = 0$$
$$\sigma_s\lambda_H p_2 m + \sigma_r\lambda_H I_r + (\gamma_s\lambda_s + \gamma_r\lambda_r)I_H - \omega I_{HTB} = 0.$$

From the second, and third equations of the system (3.4.2) respectively, we obtained

$$(1 - \tfrac{1}{R_s})N = p_1 m + I_r + I_H + I_{HTB}.$$

$$m = \tfrac{\mu+\eta+d_r}{qr\theta p_2}(1 - \tfrac{R_r}{R_s} + \tfrac{\sigma_r\lambda_H}{\mu+\eta+d_r})I_r.$$

Again after solving the fourth, and fifth equations of the above system, we found

$$I_{HTB} = \tfrac{\mu+d_H}{\nu}(1 - \tfrac{R_H}{R_s} + \tfrac{\gamma_s\lambda_s+\gamma_r\lambda_r}{\mu+d_H})I_H,$$

$$(\sigma_s\lambda_H p_2 m + \sigma_r\lambda_H I_r + (\gamma_s\lambda_s + \gamma_r\lambda_r)I_H = \omega I_{HTB}.$$

By substituting m as we expressed in terms of I_r above, which gives us
$(\sigma_r\lambda_H + \gamma_s\lambda_H p_2 x)I_r = (\omega y - (\gamma_s\lambda_s + \gamma_r\lambda_r))I_H,$
which is equivalent to
$I_H = \tfrac{(\sigma_r\lambda_H+\gamma_s\lambda_H p_2 x)}{(\omega y-(\gamma_s\lambda_s+\gamma_r\lambda_r))}I_r.$

Where,
$x = \tfrac{\mu+\eta+d_r}{qr\theta p_2}(1 - \tfrac{R_r}{R_s} + \sigma_r\lambda_H),$
$y = \tfrac{\mu+d_H}{\nu}(1 - \tfrac{R_H}{R_s} + \tfrac{\gamma_s\lambda_s+\gamma_r\lambda_r}{\mu+d_H}),$
$x' = \tfrac{\sigma_r\lambda_H+\gamma_s\lambda_H p_2 x}{\omega y-(\gamma_s\lambda_s+\gamma_r\lambda_r)},$
$m = xI_r,$

$I_H = x^{'} I_r,$

$I_{HTB} = x^{'} y I_r = y I_H.$

Here by substituting these values into the simplified form of the second equation of the system above, we found

$$(1 - \tfrac{1}{R_s})N = p_1 x I_r + I_r + x^{'} I_r + y x^{'} I_r,$$
$$(p_1 x + 1 + x^{'} + y x^{'}) I_r = (1 - \tfrac{1}{R_s})N,$$
$$I_r = \tfrac{(1-\frac{1}{R_s})}{(p_1 x + 1 + x^{'} + y x^{'})} N = x^{''} N,$$

Where, $x^{''} = \frac{(1-\frac{1}{R_s})}{(p_1 x + 1 + x^{'} + y x^{'})}$.

Finally we substituted all the values that we obtained in terms of N above into the first equations of our system (3.4.2) and obtained the endemic equilibrium denoted by $E^{'} = (N^{'}, m^{'}, I_r^{'}, I_H^{'}, I_{HTB}^{'})$ is given as follows:

$N^{'} = \frac{\Lambda}{\mu + x^{''}(d_s p_1 x + d_r + x^{'}(d_H + dx))},$

$I_r^{'} = x^{''} N,$

$m^{'} = x x^{''} N,$

$I_H^{'} = x^{'} x^{''} N,$

$I_{HTB}^{'} = y x^{'} x^{''} N.$

As we observed the system, according to the nature of equations, it is difficult to solve the endemic equilibrium analytically as we did the disease free equilibrium. Therefore we solve it numerically as shown in the following tables using the parameters values used in tables (2.2.1) and (3.2.1).

□

$p(\alpha)$	$N^{'}$	$m^{'}$	$I_{r}^{'}$	$I_{H}^{'}$	$I_{HTB}^{'}$
0.01	9884	1783.6	126.6	0	0
0.02	9912	1765.9	188.0	0	0
0.03	9939	1748.6	248.2	0	0
0.04	99656	1731.7	307.2	0	0
0.05	9991	1715.0	365.1	0	0
0.06	10017	1698.7	421.9	0	0
0.08	10042	1682.7	447.6	0	0
0.09	10066	1667.0	532.3	0	0
0.1	10090	1651.5	585.9	0	0
0.2	10308	1511.7	1072.6	0	0
0.3	10493	1393.7	1483.4	0	0
0.4	10650	1292.7	1834.6	0	0
0.5	10786	1205.5	2138.4	0	0
0.6	10905	1129.2	2403.7	0	0
0.7	11010	1062.0	2637.5	0	0
0.8	11103	1002.4	2845.0	0	0
1	11261	901.2	3197.2	0	0

Table 3.2: The solution of the endemic equilibrium when $\gamma_s = \gamma_r = 1.5$ with initial solution $(N^{'}, m^{'}, I_{r}^{'}, I_{H}^{'}, I_{HTB}^{'}) = (9856, 1801.6, 63.9, 0, 0)$ for $R_{TB} > 1, R_H < 1$.

R_H	$N^{'}$	$m^{'}$	$I_r^{'}$	$I_H^{'}$	$I_{HTB}^{'}$
2.2	506.7	0		276.4	0
3	416.9	0	0	277.9	0
5	348.8	0	0	279.1	0
7	326	0	0	279.5	0
9	314.6	0	0	279.8	0
11	307.7	0	0	279.8	0
12	305.2	0	0	279.8	0
13	303.2	0	0	279.9	0
25	291.7	0	0	280.0	0
30	289.7	0	0	280.1	0

Table 3.3: The solution of the endemic equilibrium with initial solution $(N^{'}, m^{'}, I_r^{'}, I_H^{'}, I_{HTB}^{'}) = (1551.7, 0, 0, 258.6, 0)$ for $R_{TB} < 1, R_H > 1$.

$\gamma_s = \gamma_r$	$N^{'}$	$m^{'}$	$I_r^{'}$	$I_H^{'}$	$I_{HTB}^{'}$
2	11241	478.9	239.4	62.3	78.8
3	12351	486.6	243.3	42.2	80.1
4	13010	478.8	239.4	31.2	78.8
5	13473	463.5	231.7	24.1	76.3
7	14085	428.2	214.1	15.9	70.4
8	14297	411.7	205.9	13.4	67.8
9	14470	396.5	198.2	11.5	65.2
10	14626	380.3	190.1	9.9	62.5
13	14963	341.1	170.6	6.8	56.1
16	15207	307.2	153.6	5	50.5
18	15333	288.3	144.1	4.2	47.4
19	15386	280.0	140.0	3.8	46.1
20	15437	271.7	135.9	3.5	44.7

Table 3.4: The solution of the endemic equilibrium when $\gamma_s = \gamma_r = 1.5$ with initial solution $(N^{'}, m^{'}, I_r^{'}, I_H^{'}, I_{HTB}^{'}) = (9465.3, 435.4, 217.7, 98, 93.1)$ for $R_{TB} > 1, R_H > 1$.

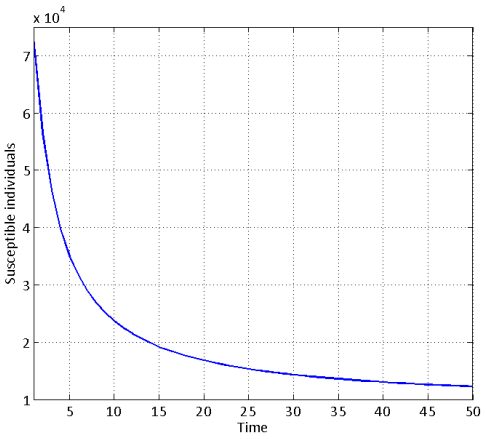
The above tables showed the endemic equilibrium of the system (3.3.1) and (3.4.2) a result of the following three alternative cases.

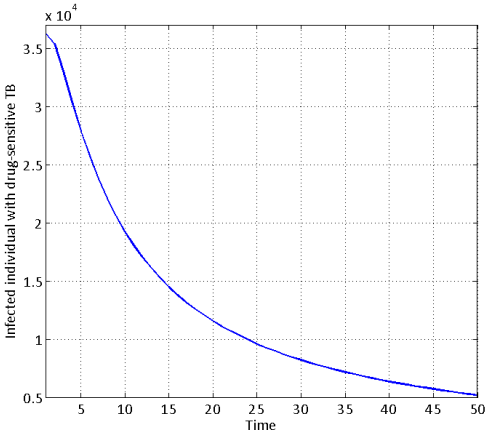
- Table (3.2) showed the endemic equilibrium of TB with the basic reproduction of TB is greater than one while the basic reproduction of HIV is less than one.

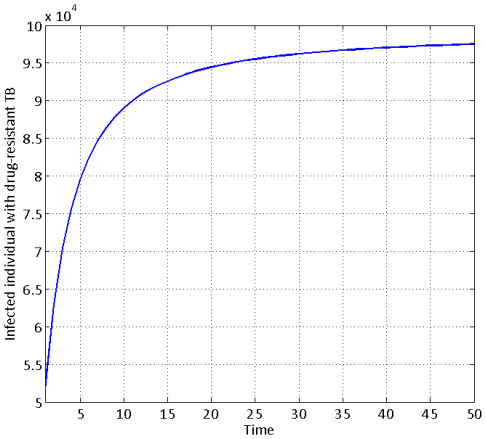
- Table (3.3) showed the endemic equilibrium of HIV with the basic reproduction of HIV is greater than one while the basic reproduction of TB is less than one.

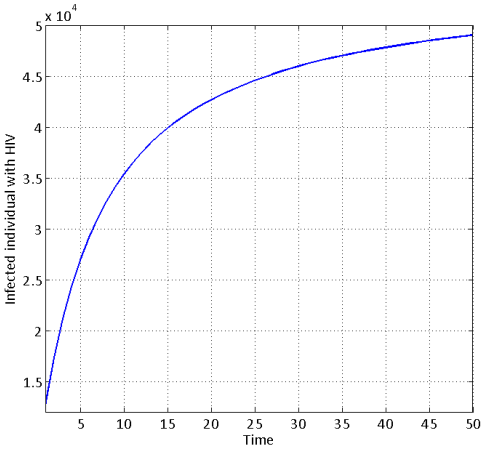
- Table (3.4) showed the endemic equilibrium of the system since both basic reproductions of TB and HIV are greater than one.
  Generally, all these cases implied the endemic equilibrium of HIV-TB co-infection model (3.3.1) and (3.4.2), since basic reproduction number of the system is $R = \max(R_{TB}, R_H) > 1$. Therefore, the endemic equilibrium of the model in (3.3.1) judged and depended on the values of the basic reproduction numbers of either TB disease in both drug-sensitive and resistant strains or the basic reproduction of HIV or the basic reproduction of both HIV and TB.

The following figures also showed the graph of the system (3.4.1) above at the endemic equilibrium with different initial solutions or values of the compartments:


x 10^4
Susceptible individuals
Time


x 10^4
Infected individual with drug-sensitive TB
Time


x 10^4
Infected individual with drug-resistant TB
Time


x 10^4
Infected individual with HIV
Time

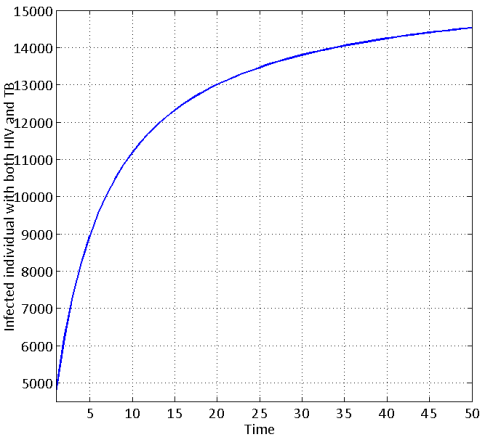
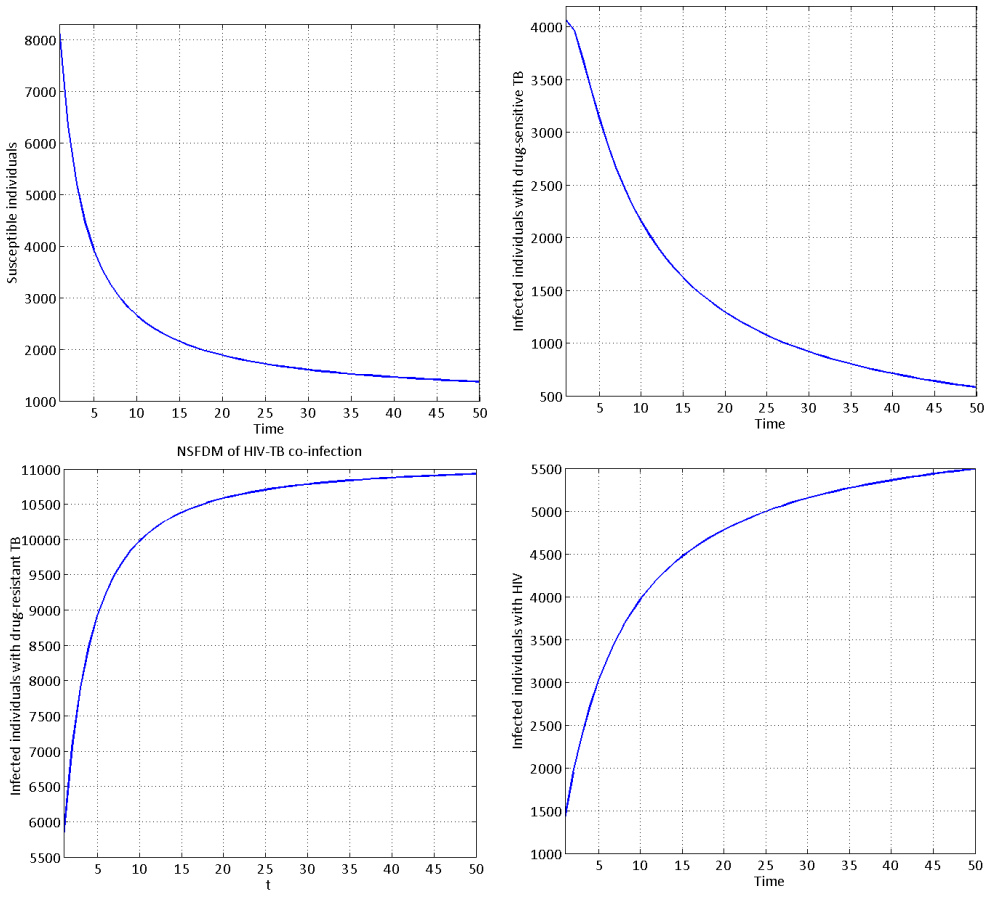

Infected individual with both HIV and TB
Time

Figure 3.3: The first two figures in the above showed, solution of susceptible to either TB or HIV on the left side and infected individual with drug-sensitive TB on the right side. The second two figures showed the solution of infected with drug-resistant TB on the left and HIV on the right sides, respectively. The last one showed the solution of infected with both HIV and TB (i.e infected with their co-infection). All of the solutions are with initial value $(S(0), i_s(0,0), I_r(0), I_H(0), I_{HTB}(0)) = (73171, 36277, 51640, 12623, 4734)$ and step sizes $h = 0.01$.



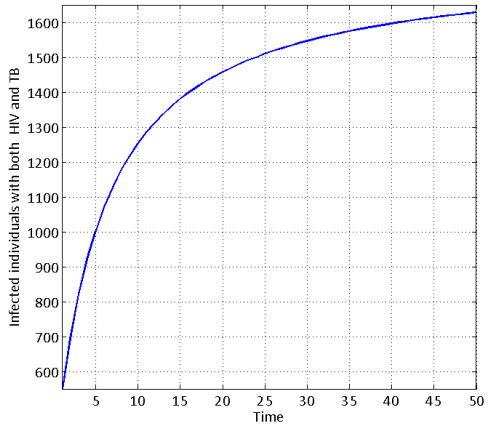
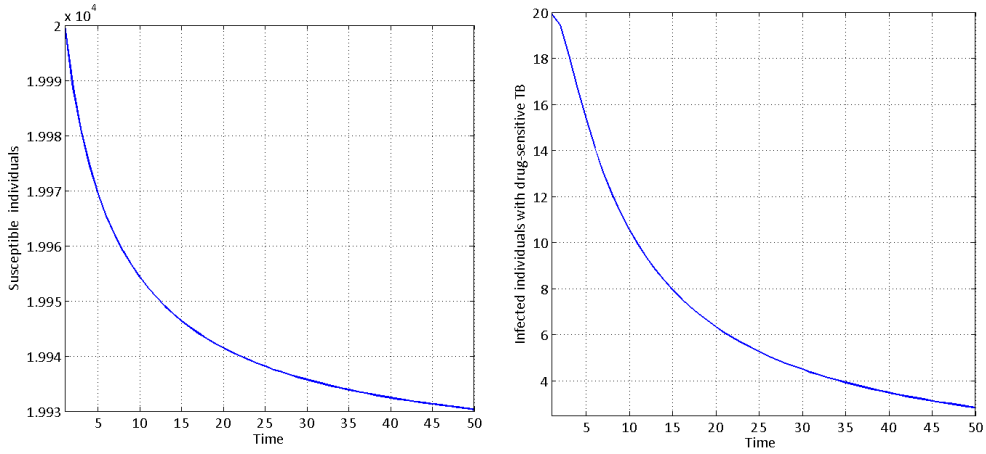


Figure 3.4: The first two figures in the above showed, solution of susceptible to either TB or HIV on the left side and infected individual with drug-sensitive TB on the right side. The second two figures show the solution of infected with drug-resistant TB on the left and HIV on the right sides, respectively. And the last one shows the solution of infected with both HIV and TB (i.e infected with their co-infection) with initial solutions $(S(0), i_s(0,0), I_r(0), I_H(0), I_{HTB}(0)) = ((8201, 4065, 5788, 1415, 531))$ and step sizes $h = 0.5$.



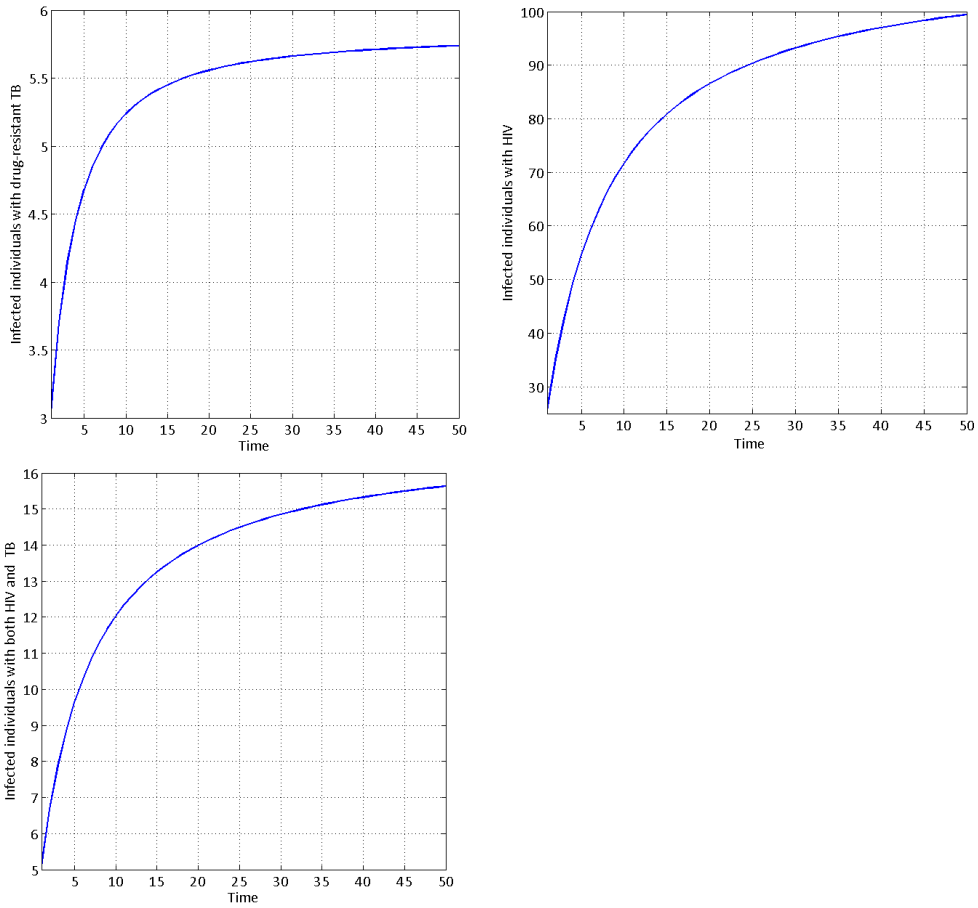
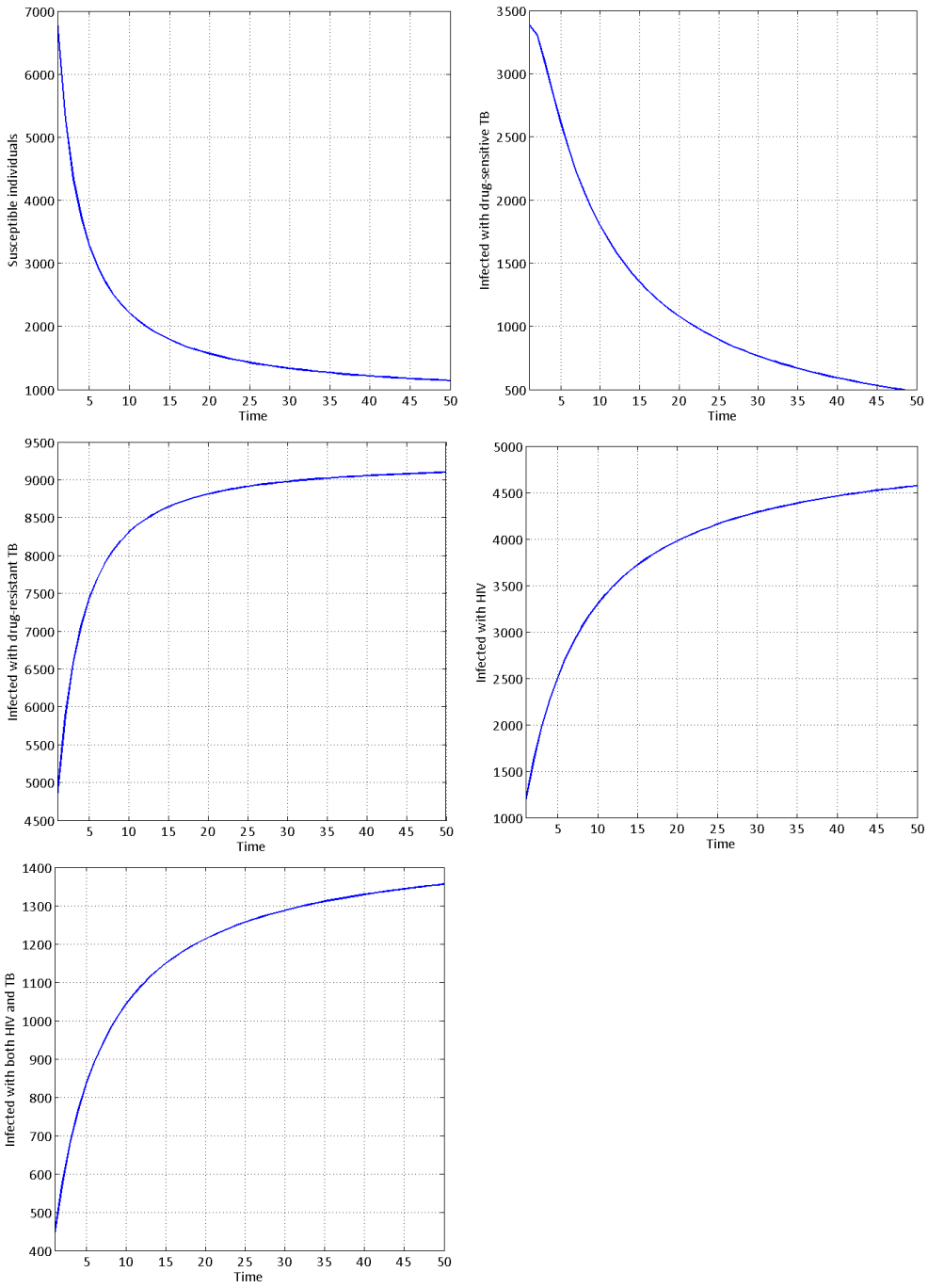


Figure 3.5: The first two figures in the above showed, solution of susceptible to either TB or HIV on the left side and infected individual with drug-sensitive TB on the right side. The second two figures show the solution of infected with drug-resistant TB on the left and HIV and the right sides, respectively. The last one shows the solution of infected with both HIV and TB (i.e infected with their co-infection) with initial solutions $(S(0), i_s(0,0), I_r(0), I_H(0), I_{HTB}(0)) = (20000, 20, 3, 25, 5)$ and step sizes $h = 2.5$ for $R > 1$.



Generally, all the figures we observed in chapter 2 and chapter 3 showed the convergence of the initial solution of the compartments with the tolerance of susceptible, infected with drug-sensitive TB, infected with drug-resistant

Figure 3.6: The first two figures in the above showed, solution of susceptible to either TB or HIV on the left side and infected individual with drug-sensitive TB on the right side. The second two figures that are in between the first two and the last one show the solution of infected with drug-resistant TB and HIV on the left and the right sides, respectively. And the last one shows the solution of infected with HIV and TB (i.e infected with their co-infection). All of the solutions are with initial value $(S(0), i_s(0,0), I_r(0), I_H(0), I_{HTB}(0)) = (6827, 3385, 4818, 1178, 442)$ and step sizes $h = 0.05$.

TB, infected with HIV only, and infected with both HIV and TB (their co-infection) individuals are 40%,25%, 20%, 30% and 25%, respectively.

Chapter 4

Formulation and analysis of nonstandard finite difference methods for HIV and TB co-infection models

In this chapter, we construct the NSFDMs and this is done in two separate sections. In the first section we construct the NSFDM for the sub-models (HIV only sub-model and TB-only sub-models) while the numerical method of the HIV-TB co-infections model is constructed in the second section of this chapter. The positivity of the solutions considered in the previous chapters are also shown in this method. In addition to these, comparison of other literatures approach are also reviewed in this chapter.

4.1 Introduction

In this chapter, the full model (3.3.1) of HIV and TB co-infection that accounts for TB treatment will be formulated and analyzed, by considering sub models (the TB and HIV only sub models) with their qualitative properties. To come up with this, first we analyze and construct the NSFD numerical methods for the sub models. The TB only sub model (2.2.1) accounts for TB treatment that shows treatment impacts on TB with the age of infection done in chapter 2 and (3.2.1) of HIV-only sub-models in chapter 3. Secondly we check whether these numerical methods converge to the theoretical equilibria of the full model, by checking the convergence of numerical methods for the sub models.

These methods were explored by many researchers to solve problems in the biological science and other fields. A few of them are mentioned as follows: In 2005 [48], Ronald E. Mickens introduced the concept of elementary stability, the property which brings correspondence between the local stability at equilibria of the differential equation and the numerical method. In [33], the NSFD methodology was used to constructed numerical method that is dynamically consistent for a large class of dynamical systems used in epidemiology. The method was elementary stable and preserved some properties including positivity solution, dissipative and globally asymptotic stability of the disease free equilibrium. Villanueva et al. [56] developed NSFD schemes to solve the numerical solution of a mathematical model of infant obesity with constant population size. Their model consists of a system of coupled nonlinear ordinary differential equations. The numerical results showed that their methods have better convergence properties as compared to the classical Euler or the fourth-order Runge-Kutta methods and the Matlab routines in the sense that these routines give negative values for some of the

state variables. Construction and Analysis of Efficient Numerical Methods to Solve Mathematical Models of TB and HIV Co-infection was conducted by Obaid Ahmed [32]. In their study competitive unconditionally stable NSFDMs were proposed for solving a TB-only sub-model and a full HIV-TB co-infection model represented by a nonlinear system of ordinary differential equations. Numerical results presented, confirmed the applicability of the proposed NSFDMs for the biological systems. These methods preserved the positivity of solutions and converging to stability properties of the equilibria for arbitrary step-sizes while the solutions obtained by other numerical methods experience difficulties in either preserving the positivity of the solutions or in converging to the correct equilibria. As we observed from the literature review in chapter 1 of this paper, several NSFDMs have been constructed for specific ODEs and PDEs [32, 48, 49, 66, 68, 72, 92].

To summarize all the above, in this chapter, we develop and investigate the applicability of the NSFDMs for numerical solution of systems of differential equations in biology, and improve the order of convergence of these methods both for ODE and PDE models expressed in (2.2.1), (3.2.1) and (3.3.1).

4.2 Formulation of nonstandard finite difference methods (NSFDMs)

To construct the NSFDMs for HIV-TB co-infections model and other sub-models mentioned in the previous chapters, we begin with time domain [0,T] which is partitioned as $0 = t_0 < t_1 < t_2 < ... < t_{n-1} < t_n = T$ (i.e. $t_n = nh$, where $h > 0$ is the time step-size).

In general, solving the systems of differential equations (2.2.1), (3.2.1) and (3.3.1) by a finite difference method consists of the following four steps:

- Discretizing the domain:

  The time domain [0, T] is represented by a mesh: a finite number of n+1 points. $0 = t_0 < t_1 < t_2 < ... < t_{n-1} < t_n = T$.

- Fulfilling the systems of equation at discrete time points:

  The differential equations being valid for t" $\in$ "$[0, T]$ at mesh points only.

- Replacing derivatives by finite differences:

  Here, it is time for the finite difference approximation of derivatives.

- Formulating a recursive algorithm:

  We seek the solution of our problem at the mesh points using the initial value at one of the mesh point, then we get the computational formula which is called recursive algorithm.

4.3 Formulation and analysis of NSFDMs for HIV -only sub-model

In this section, we construct the NSFDMs for HIV-only sub-model (3.2.1).
The derivative is replaced by the finite difference as
$\frac{dS}{dt} = \frac{S(t+h)-S(t)}{\phi(h)} + O(\phi(h))$ as $h \to 0$.
Where $\phi(h)$ is a denominator function [32] which is a real valued function and satisfies $\phi(h) = h + O(h^2)$, for all $h > 0$.
We denote $S(nh)$ by S^n, where
$n = 0, 1, 2, ...$, then the NSFDMs applied to the model (3.2.1) reads as:

$$\begin{aligned} \frac{S^{n+1}-S^n}{\phi_1(h)} &= \Lambda - \lambda_H S^{n+1} - \mu S^{n+1} \\ \frac{I_H^{n+1}-I_H^n}{\phi_2(h)} &= \lambda_H S^{n+1} - (\mu + d_H) I_H^{n+1} \end{aligned} \tag{4.3.1}$$

where,

$\phi_1(h) = \frac{e^{\mu h}-1}{\mu}$,

$\phi_2(h) = \frac{e^{(\mu+d_H)h}-1}{\mu+d_H}$.

After simplifying the equations in (4.3.1), we obtained

$$\begin{aligned} S^{n+1} &= \frac{S^n+\Lambda\phi_1(h)}{1+\phi_1(h)(\mu+c\beta_H \frac{I_H^n}{S^n+I_H^n})} \\ I_H^{n+1} &= \frac{I_H^n(1+\phi_2(h)c\beta_H S^{n+1}\frac{S^n}{S^n+I_H^n})}{1+\phi_2(d_H+\mu)} \end{aligned} \tag{4.3.2}$$

Remark 4.1: If the values of $\phi_1(h)$=h= $\phi_2(h)$, then the numerical method is called NSFDM-I [48, 72]. However, the numerical method is called NSFDM-II when the values of $\phi_1(h)$ and $\phi_2(h)$ are different from h as shown in (4.3.1) above.

We recall that the disease free equilibrium of the system (4.3.1) is given by $E^0 = (\frac{\Lambda}{\mu}, 0)$ that was proved to be locally asymptotically stable if $R_H < 1$ and unstable if $R_H > 1$.

In the following subsections, we see the disease free and the endemic equilibria of system (4.3.2) which is the simplified form of (4.3.1).

4.3.1 The numerical results and stability properties of HIV at the disease free equilibria

In this subsection, we see the properties of the disease free equilibrium using the following theorem.

Theorem 4.3.1. *The disease free equilibrium of HIV in (4.3.1) is locally asymptotically stable if the basic reproduction of HIV, $R_H < 1$ while it is unstable if $R_H > 1$ for real valued denominator functions $\phi_i(h) = h+O(h^2), i = 1, 2$ and for all $h > 0$.*

Proof. Here, we found the the partial derivatives of these functions of the system (4.3.1) with respect to the given variables (S^n, I_H^n) at the disease free equilibrium $E^* = (S^*, I_H^*) = (\frac{\Lambda}{\mu}, 0)$ and the matrix entries as follows:

$$\text{Let, } J(X) = \begin{pmatrix} \frac{S^n+\Lambda\phi_1(h)}{1+\phi_1(h)(\mu+c\beta_H\frac{I_H^n}{S^n+I_H^n})} \\ \frac{I_H^n(1+\phi_2(h)c\beta_H S^{n+1}\frac{S^n}{S^n+I_H^n})}{1+\phi_2(d_H+\mu)} \end{pmatrix},$$

where, $X = (S^n, I_H^n)$.

Then,

$$\frac{\partial J}{\partial X_{11}} = \frac{1+\phi_1(h)(\mu+c\beta_H\frac{I_H^n}{S^n+I_H^n})+(S^n+\Lambda\phi_1(h))(\frac{I_H^n}{(S^n+I_H^n)^2})}{(1+\phi_1(h)(\mu+c\beta_H\frac{I_H^n}{S^n+I_H^n}))^2}$$
$$= \frac{1+\phi_1(h)\mu}{(1+\phi_1(h)\mu)^2}$$
$$= \frac{1}{1+\phi_1(h)\mu},$$

$$\frac{\partial J}{\partial X_{12}} = \frac{-(S^n+\Lambda\phi_1(h))(\phi_1(h)c\beta_H(\frac{I_H^n+S^n-I_H^n}{(S^n+I_H^n)^2}))}{(1+\phi_1(h)(\mu+c\beta_H\frac{I_H^n}{S^n+I_H^n}))^2}$$
$$= \frac{-\phi_1(h)c\beta_H(S^n)^2-(\phi_1(h))^2c\beta_H\Lambda S^n}{(S^n)^2(1+\phi_1(h)\mu)^2}$$
$$= \frac{-\phi_1(h)c\beta_H(1+\phi_1(h)\mu)}{(1+\phi_1(h)\mu)^2}$$
$$= \frac{-\phi_1(h)c\beta_H}{1+\phi_1(h)\mu},$$

$$\frac{\partial J}{\partial X_{21}} = \frac{\phi_2(h)c\beta_H}{1+\phi_2(\mu+d_H)}(\frac{I_H^n((1+\phi_1\mu)(S^n+I_H^n)+c\beta_H I_H^n)-(1+\phi_1\mu)I_H^n(S^n+I_H^n)}{((1+\phi_1\mu)(S^n+I_H^n)+c\beta_H I_H^n)^2}$$
$$= 0(\frac{\phi_2(h)c\beta_H}{1+\phi_2(\mu+d_H)})$$
$$= 0,$$

$\frac{\partial J}{\partial X_{22}} = \frac{1+\phi_2(h)c\beta_H(\frac{(S^n+\phi_1(h)\Lambda)((1+\phi_1\mu)(S^n+I_H^n)+c\beta_H I_H^n)-I_H^n(S^n+I_H^n)(1+\phi_1\mu+\phi_1 c\beta_H)}{((1+\phi_1\mu)(S^n+I_H^n)+c\beta_H I_H^n)^2})}{1+\phi_2(\mu+d_H)}$
$= \frac{1+\phi_2(h)c\beta_H(\frac{S^n+\phi_1\Lambda}{(1+\phi_1\mu)S^n})}{1+\phi_2(\mu+d_H)}$
$= \frac{1+\phi_2(h)c\beta_H}{1+\phi_2(\mu+d_H)}.$

(i. e, $\frac{\partial J}{\partial X_{ij}} = \begin{pmatrix} \frac{1}{1+\phi_1(h)\mu} & \frac{-\phi_1(h)c\beta_H}{1+\phi_1(h)\mu} \\ 0 & \frac{1+\phi_2(h)c\beta_H}{1+\phi_2(\mu+d_H)} \end{pmatrix}), i = 1,2$ and $j = 1,2$ for S^n and I_H^n, respectively.

Therefore, the Jacobian matrix of the system (4.3.1) at the disease free equilibrium is

$$J(E^0) = \begin{pmatrix} \frac{1}{1+\phi_1(h)\mu} & \frac{-\phi_1(h)c\beta_H}{1+\phi_1(h)\mu} \\ 0 & \frac{1+\phi_2(h)c\beta_H}{1+\phi_2(\mu+d_H)} \end{pmatrix}$$

Therefore, the eigenvalues of this matrix are obtained by solving

$$\det \begin{pmatrix} \frac{1}{1+\phi_1(h)\mu} - \lambda & \frac{-\phi_1(h)c\beta_H}{1+\phi_1(h)\mu} \\ 0 & \frac{1+\phi_2(h)c\beta_H}{1+\phi_2(\mu+d_H)} - \lambda \end{pmatrix} = 0$$

$(\frac{1}{1+\phi_1(h)\mu} - \lambda)(\frac{1+\phi_2(h)c\beta_H}{1+\phi_2(\mu+d_H)} - \lambda) = 0$
implies that

$\lambda_1 = \frac{1}{1+\phi_1(\mu+c\beta_H)}$,
$\lambda_2 = \frac{1+\phi_2 c\beta_H}{1+\phi_2(\mu+d_H)}$.
As observed from these eigenvalues the first one is less than while the second is also less than one(unity) if and only if $c\beta_H < \mu + d_H$, which is $R_H < 1$. □

The following figures show the solutions of susceptible, $S(t)$ for HIV on the left sides and the infected individuals,$I_H(t)$ with HIV on the right sides with initial values $(S(0), I_H(0)) = (178445, 0)$ at different step sizes h indicated with the individual figure.

Remark 4.2 : Time(t) in all cases are measured in years.

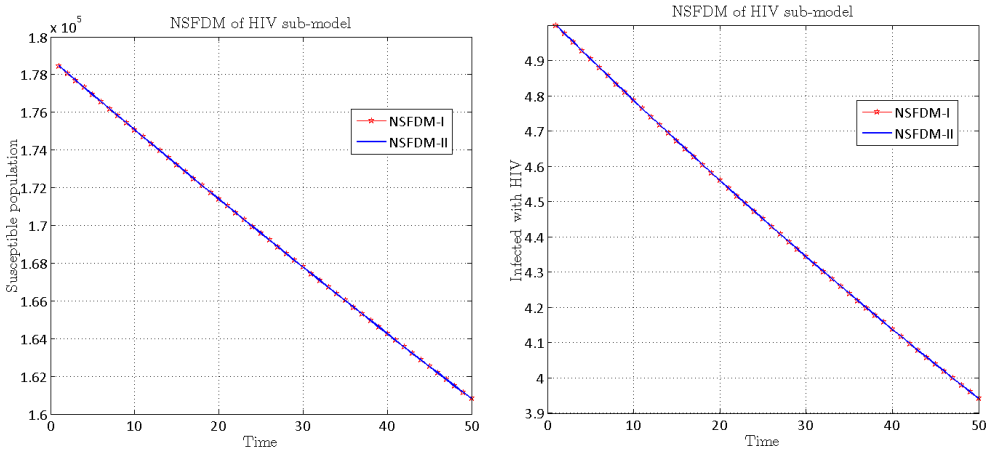


Figure 4.1: This shows the solution of HIV with initial solution $(S(0), I_H(0)) = (178440, 5)$ and step-size $h = 0.125$.

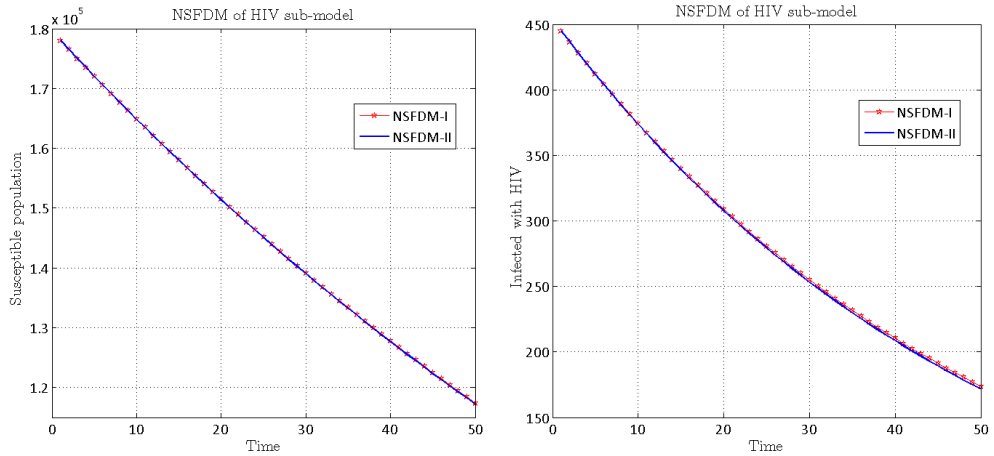


Figure 4.2: This figure shows the solution of HIV with initial solution $(S(0), I_H(0)) = (178000, 445)$ and step-size $h = 0.5$.

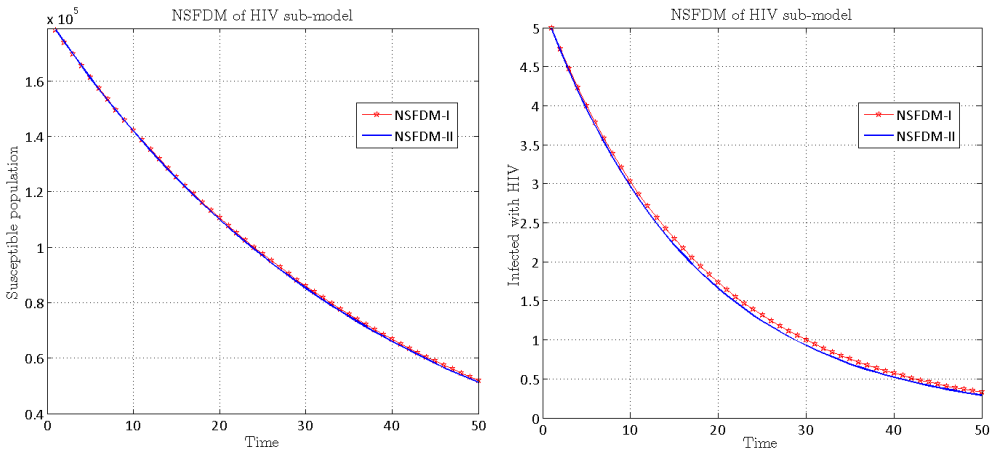


Figure 4.3: This shows the solution of HIV with initial solution $(S(0), I_H(0)) = (178440, 5)$ and step size $h = 1.5$.

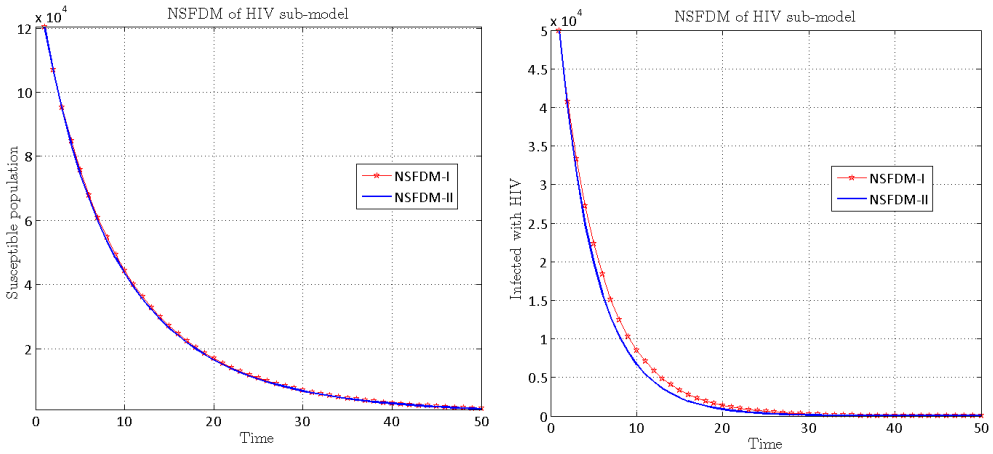


Figure 4.4: This shows the solution of HIV with initial solution $(S(0), I_H(0)) = (120445, 50000)$ with step size $h = 5$.

As we observed in the above figures, when the values of h approaches to zero, the solution of NSFDM of HIV in (4.2.1) approaches to the disease free

equilibrium for different initial solution at different step sizes h as $R_H < 1$). Therefore, the system in (3.2.1) is locally asymptotically stable at the endemic equilibrium when $R_H < 1$.

4.3.2 The numerical results and stability properties of HIV at the endemic equilibria

In this subsection, we check the stability properties of our system above when the equilibrium is endemic. Before we are going to prove the stability of the endemic equilibrium of HIV model (4.3.1) equivalent to (4.3.2), we first see the lemma's of [87] as shown below.

Lemma 4.3.2. *The quadratic equation $f(\lambda) = \lambda^2 - \alpha\lambda + \beta = 0$ has two roots that satisfy $|\lambda_i| < 1, i = 1, 2$, if and only if the following conditions are satisfied:*

1. $f(0) = \beta < 1$,

2. $f(-1) = 1 + \alpha + \beta > 0$,

3. $f(1) = 1 - \alpha + \beta > 0$.

Theorem 4.3.3. *The epidemic equilibrium of HIV in (4.3.1) is locally asymptotically stable if $R_H > 1$ while it is unstable if $R_H < 1$ for real valued denominator function $\phi_i(h) = h + O(h^2), i = 1, 2$ and for all $h > 0$.*

Proof. Here, we found the the partial derivatives of these functions of the system (4.3.1) with respect to the given variables (S^n, I_H^n) for

$$J(X_{ij}) = \begin{pmatrix} \frac{S^n+\Lambda\phi_1(h)}{1+\phi_1(h)(\mu+c\beta_H\frac{I_H^n}{S^n+I_H^n})} \\ \frac{I_H^n(1+\phi_2(h)c\beta_H\frac{S^n+\Lambda\phi_1(h)}{(1+\phi_1(h)\mu)(S^n+I_H^n)+\phi_1(h)c\beta_H I_H^n})}{1+\phi_2(h)(d_H+\mu)} \end{pmatrix},$$

where, $X_{ij} = (S^n, I_H^n)$,

are,

$$\frac{\partial J}{\partial X_{11}} = \frac{1+\phi_1(h)(\mu+d_H)(1-\frac{1}{R_H})}{1+\phi_1(h)\mu+\phi_1(h)c\beta_H(1-\frac{1}{R_H})},$$

$$\frac{\partial J}{\partial X_{12}} = \frac{-\phi_1(h)(\mu+d_H)}{(1+\phi_1(h)\mu)R_H+\phi_1(h)c\beta_H(R_H-1)},$$

$$\frac{\partial J}{\partial X_{21}} = \frac{\phi_2(h)c\beta_H(R_H-1)}{R_H^2(1+\phi_2(h)(\mu+d_H))}(\frac{R_H^2+\phi_1(h)\beta_H c(R_H-1)}{R_H(1+\phi_1(h)\mu)+\phi_1(h)\beta_H c(R_H-1)} - 1),$$

$$\frac{\partial J}{\partial X_{22}} = \frac{1+\frac{\phi_2(h)(\mu+d_H)(1+\phi_1\mu)}{(1+\phi_1(h)\mu)R_H+\phi_1(h)c\beta_H(R_H-1)}}{1+\phi_2(h)(\mu+d_H)}.$$

THus at the epidemic equilibrium $E^1 = (S^1, I_H^1) = (\frac{\Lambda}{\mu+c\beta_H(1-\frac{1}{R_H})}, \frac{\Lambda(R_H-1)}{\mu+c\beta_H(1-\frac{1}{R_H})})$, its jacobian matrix becomes:

$$J(E^1) =$$

$$\begin{pmatrix} \frac{1+\phi_1(h)(\mu+d_H)(1-\frac{1}{R_H})}{1+\phi_1(h)\mu+\phi_1(h)c\beta_H(1-\frac{1}{R_H})} & \frac{-\phi_1(h)(\mu+d_H)}{(1+\phi_1(h)\mu)R_H+\phi_1(h)c\beta_H(R_H-1)} \\ \frac{\phi_2(h)c\beta_H(R_H-1)}{R_H^2(1+\phi_2(h)(\mu+d_H))}(\frac{R_H^2+\phi_1(h)\beta_H c(R_H-1)}{R_H(1+\phi_1(h)\mu)+\phi_1(h)\beta_H c(R_H-1)} - 1) & \frac{1+\frac{\phi_2(h)(\mu+d_H)(1+\phi_1\mu)}{(1+\phi_1(h)\mu)R_H+\phi_1(h)c\beta_H(R_H-1)}}{1+\phi_2(h)(\mu+d_H)} \end{pmatrix}$$

Therefore, the eigenvalues of this matrix are obtained by solving the characteristics as shown below.

$$\det \begin{pmatrix} x^{'} - \lambda & x^{''} \\ x^{'''} & x^{''''} - \lambda \end{pmatrix} = 0,$$

$f(\lambda) = \lambda^2 - \alpha\lambda + \beta = 0,$

where,

$x^{'} = \frac{1+\phi_1(h)(\mu+d_H)(1-\frac{1}{R_H})}{1+\phi_1(h)\mu+\phi_1(h)c\beta_H(1-\frac{1}{R_H})},$

$x^{''} = \frac{-\phi_1(h)(\mu+d_H)}{(1+\phi_1(h)\mu)R_H+\phi_1(h)c\beta_H(R_H-1)},$

$x^{'''} = \frac{\phi_2(h)c\beta_H(R_H-1)}{R_H^2(1+\phi_2(h)(\mu+d_H))}(\frac{R_H^2+\phi_1(h)\beta_H c(R_H-1)}{R_H(1+\phi_1(h)\mu)+\phi_1(h)\beta_H c(R_H-1)} - 1),$

$x^{''''} = \frac{1+\frac{\phi_2(h)(\mu+d_H)(1+\phi_1\mu)}{(1+\phi_1(h)\mu)R_H+\phi_1(h)c\beta_H(R_H-1)}}{1+\phi_2(h)(\mu+d_H)},$

$\alpha = x^{'} + x^{''''},$
$\beta = x^{'}x^{''''} + x^{''}x^{'''}.$

From these Jacobian entries above, we observed the following for any step-size h:

$|x^{'}| < 1$, since $d_H < c\beta_H$ for $R_H > 1$ and $|x^{''''}| < 1$, immediate for $R_H > 1$.

where as $-x^{''}$ and $x^{'''}$ are both greater than zero for $R_H > 1$.

As a result of these,

$x^{'} + x^{''''} = \alpha > 0,$

$x^{'}x^{''''} - x^{''}x^{'''} = \beta > 0$, since $x^{'}, -x^{''}, x^{'''}$ and $x^{''''}$ are all greater than zero (0).

Therefore, according to lemma 4.2.2 above, we have:

$f(0) = \beta = x^{'}x^{''''} - x^{''}x^{'''} < 1,$

$f(-1) = 1 + \alpha + \beta > 0,$

$f(1) = 1 - \alpha + \beta > 0.$ This completes the proof of the theorem. □

In the following table, we can see the corresponding values of the susceptible and infected individuals at the time step-sizes, h.

h	S^*	I_H^*	λ_1	λ_2
0.5	117664	21010	0.992	1.064
3	107808	25919	0.957	1.352
5	83941	32154	0.921	1.551
8	52276	36494	0.876	1.804
10	25425	33731	0.848	1.946
15	7985	20905	0.781	2.230

Table 4.1: The following figures show the solutions of susceptible for HIV on the left sides and the infected individuals with HIV on the right sides with different initial solutions at different step sizes h indicated with the individual figure.

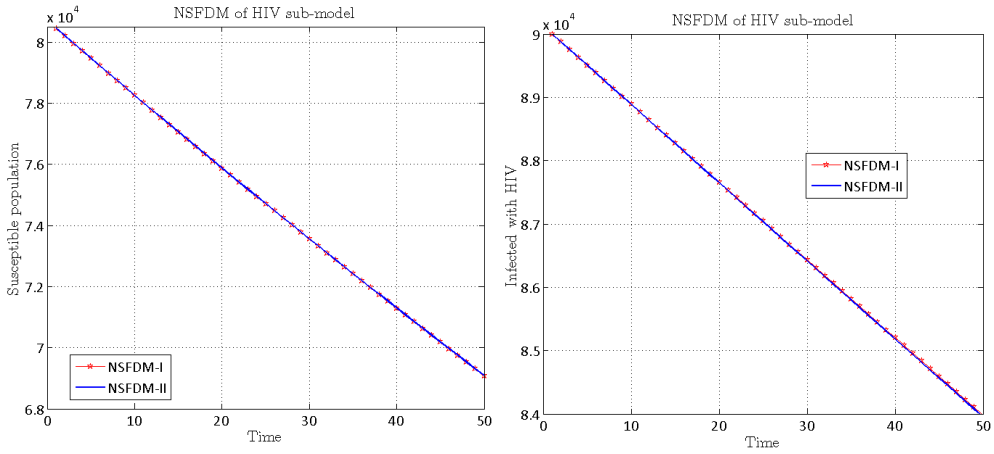


Figure 4.5: Solution of HIV with initial solutions with $(S(0), I_H(0)) = (80445, 900000)$ and step size $h = 0.05$.

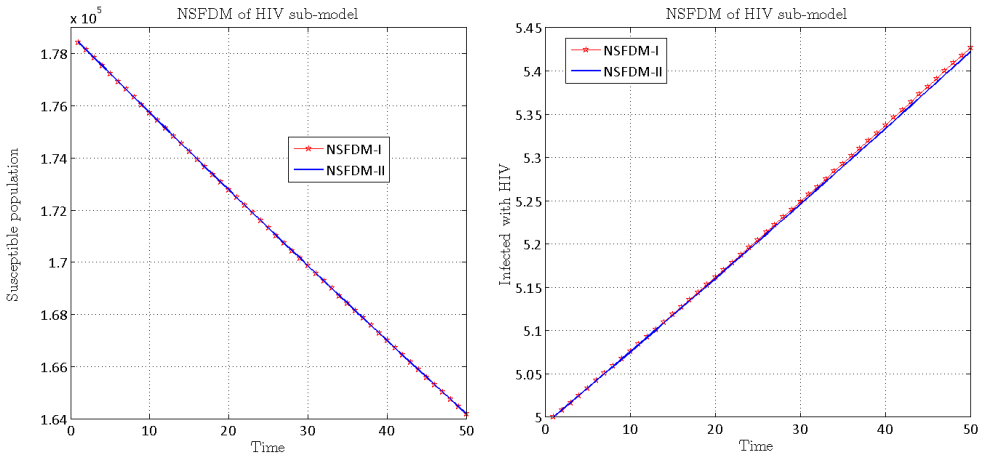


Figure 4.6: Solution of HIV with initial solutions with $(S(0), I_H(0)) = (178440, 5)$ and step size $h = 0.1$.

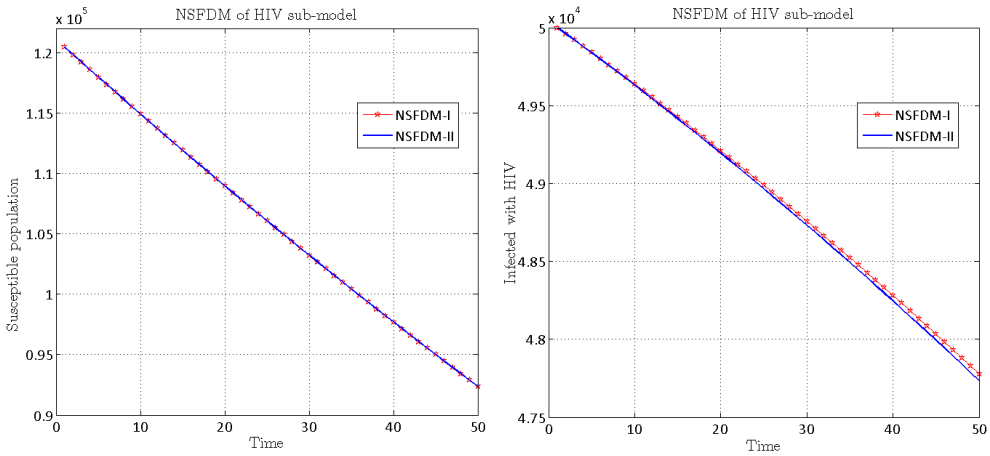


Figure 4.7: This is the solution with of HIV with initial solution $(S(0), I_H(0)) = (120445, 50000)$ and step size $h = 0.1$.

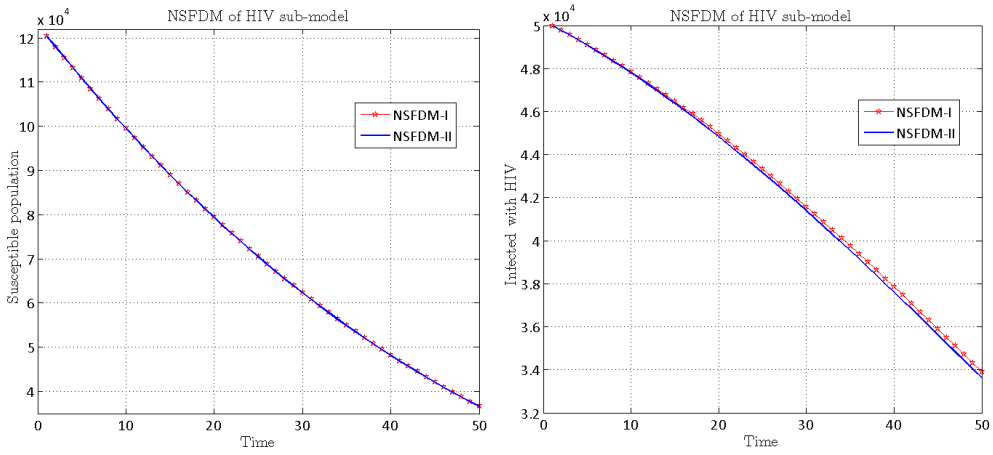


Figure 4.8: This shows the solution of HIV with initial solution $(S(0), I_H(0)) = (120445, 50000)$ and step size $h = 0.5$.

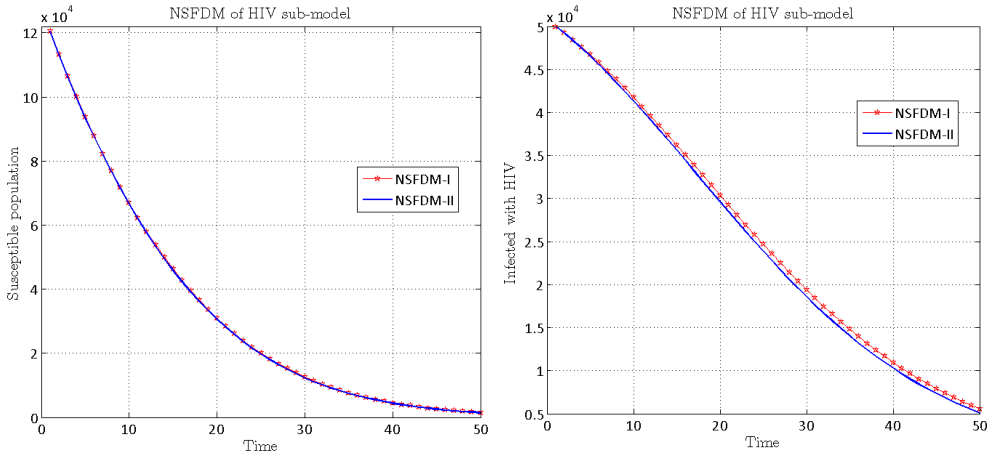


Figure 4.9: Solution of HIV with initial solution $(S(0), I_H(0)) = (120445, 50000)$ and step size $h = 1.5$.

Remark 4.3: As the values of h approaches to zero, the solution of NSFDM of HIV in (4.3.1) as we observed in the above figures approaches to the endemic equilibrium (i.e $R_H > 1$).

Therefore, the system in (3.2.1) is locally asymptotically stable at the endemic equilibrium when $R_H > 1$.

4.4 Formulation and analysis of NSFDMs for TB -only sub-model

In this section, we construct NSFDMs for the TB-sub-model in (2.2.1). Following the same notations and approach as in the previous sections, the NSFDMs of the model is written as follows:

$$\begin{aligned}
&\tfrac{S^{n+1}-S^n}{\phi_1(h)} = \Lambda - (\lambda_s + \lambda_r + \mu)S^{n+1} + \eta I_r^n + (1-r)\theta i_s^{(n,j)} \\
&\tfrac{(i_s^{(n+1,j)}-i_s^{(n,j)})}{\phi_2(h)} + \tfrac{(i_s^{(n,j+1)}-i_s^{(n,j)})}{\phi_3(h)} = -z^{'} i_s^{(n,j)} \\
&\tfrac{(I_r^{n+1}-I_r^n)}{\phi_4(h)} = \lambda_r S^{n+1} - (\mu + d_r + \eta)I_r^{n+1} + qr\theta i_s^{(n,j)}
\end{aligned} \tag{4.4.1}$$

The simplified form of (4.2.2.1) becomes

$$\begin{aligned}
S^{n+1} &= \tfrac{S^n + \phi_1(h)(\Lambda + \eta I_r^n + (1-r)\theta i_s^{(n,j)})}{1+\phi_1(h)(\mu+\lambda_r+\lambda_s)} \\
i_s^{(n+1,j)} &= (1 + z - \phi_2(h)z^{'})i_s^{(n,j)} - z i_s^{(n,j+1)} \\
I_r^{n+1} &= \tfrac{I_r^n + \phi_4(h)(\lambda_r S^{n+1} + qr\theta i_s^{(n,j)})}{1+\phi_4(h)(\mu+d_r+\eta)}
\end{aligned} \tag{4.4.2}$$

Where,

$z = \frac{\phi_2(h)}{\phi_3(h)}$,

$z^{'} = (1 - r + qr)\theta p(\alpha) + \mu + d_s$,

$\phi_1(h) = \frac{e^{\mu h}-1}{\mu}$,

$\phi_2(h) = \frac{e^{(\mu+d_s)h}-1}{\mu+d_s}$,

$\phi_3(h) = \frac{e^{(\mu+d_s\rho(\alpha))h}-1}{\mu+d_s\rho(\alpha)}$,

$\phi_4(h) = \frac{e^{(\mu+d_r+\eta)h}-1}{\mu+d_r+\eta}$.

In the following subsection we see the numerical results and the stability properties of TB at diseases free and endemic equilibria.

4.4.1 The numerical results and stability properties of TB at the disease free equilibria

This section shows the numerical results and stability properties of (4.4.1) above. We obtained the Jacobian matrix of TB sub-model at the disease free equilibrium by taking the partial derivatives of the model (4.4.1) as follows:

Theorem 4.4.1. *The disease free equilibrium of TB in (4.4.1) is locally asymptotically stable if* $R_{TB} < 1$ *while it is unstable if* $R_{TB} > 1$ *for real valued denominator functions* $\phi_i(h) = h + O(h^2), i = 1, 2, 3, 4$ *and for all* $h > 0$.

Proof. To find the jacobian matrix of the system in (4.4.2) which is the simplified form of (4.4.1) first we obtained the partial derivatives of the system at the disease free equilibrium $E^* = (S^*(0), i_s^*(0,0), I_r^*(0)) = (\frac{\Lambda}{\mu}, 0, 0)$ as follows:

Let

$G(X) =$

$$(\tfrac{S^n+\phi_1(h)(\Lambda+\eta I_r^n+(1-r)\theta i_s^{(n,j)})}{1+\phi_1(h)(\mu+\lambda_r+\lambda_s)}, (1+z-\phi_2(h)z')i_s^{(n,j)}-zi_s^{(n,j+1)}, \tfrac{I_r^n+\phi_4(h)(\lambda_r S^{n+1}+qr\theta i_s^{(n,j)})}{1+\phi_4(h)(\mu+d_r+\eta)}),$$

where,

$X = (S^n, i_s^{nj}, I_r^n).$

$\frac{\partial G}{\partial X_{11}} = \frac{1}{1+\mu\phi_1(h)},$

$\frac{\partial G}{\partial X_{12}} = \frac{\phi_1(h)((1-r)\theta-\frac{R_s}{p_2})}{1+\mu\phi_1(h)},$

$\frac{\partial G}{\partial X_{13}} = \frac{\phi_1(h)(\eta-\beta_r c)}{1+\mu\phi_1(h)},$

$\frac{\partial G}{\partial X_{21}} = 0,$

$\frac{\partial G}{\partial X_{22}} = 1 + z(1-p(\alpha)) - z'\phi_2(h),$

$\frac{\partial G}{\partial X_{23}} = 0,$

$\frac{\partial G}{\partial X_{31}} = 0,$
$\frac{\partial G}{\partial X_{32}} = \frac{qr\theta\phi_4(h)}{1+(\mu+\eta+d_r)\phi_4(h)},$
$\frac{\partial G}{\partial X_{32}} = \frac{1+\beta_r c\phi_4(h)}{1+(\mu+\eta+d_r)\phi_4(h)}.$
And its jacobian matrix is

$$J(E^*) = \begin{pmatrix} \frac{1}{1+\mu\phi_1(h)} & \frac{\phi_1(h)((1-r)\theta-\frac{R_s}{p_2})}{1+\mu\phi_1(h)} & \frac{\phi_1(h)(\eta-\beta_r c)}{1+\mu\phi_1(h)} \\ 0 & 1+z(1-p(\alpha))-z^{'}\phi_2(h) & 0 \\ 0 & \frac{qr\theta\phi_4(h)}{1+(\mu+\eta+d_r)\phi_4(h)} & \frac{1+\beta_r c\phi_4(h)}{1+(\mu+\eta+d_r)\phi_4(h)} \end{pmatrix}$$

The characteristic of this matrix becomes

$$\det \begin{pmatrix} \frac{1}{1+\mu\phi_1(h)}-\lambda & \frac{\phi_1(h)((1-r)\theta-\frac{R_s}{p_2})}{1+\mu\phi_1(h)} & \frac{\phi_1(h)(\eta-\beta_r c)}{1+\mu\phi_1(h)} \\ 0 & 1+z(1-p(\alpha))-z^{'}\phi_2(h)-\lambda & 0 \\ 0 & \frac{qr\theta\phi_4(h)}{1+(\mu+\eta+d_r)\phi_4(h)} & \frac{1+\beta_r c\phi_4(h)}{1+(\mu+\eta+d_r)\phi_4(h)}-\lambda \end{pmatrix}$$

$= (\frac{1}{1+\mu\phi_1(h)}-\lambda)(1+z(1-p(\alpha))-z^{'}\phi_2(h)-\lambda)(\frac{1+\beta_r c\phi_4(h)}{1+(\mu+\eta+d_r)\phi_4(h)}-\lambda)$

$= 0.$

Hence,
$\lambda_1 = \frac{1}{1+\mu\phi_1(h)},$
$\lambda_2 = 1+z(1-p(\alpha))-z^{'}\phi_2(h),$
$\lambda_3 = \frac{1+\beta_r c\phi_4(h)}{1+(\mu+\eta+d_r)\phi_4(h)},$
and
$|\lambda_i| < 1$, for $i = 1,2,3$ when $R_r < 1$ and $1 < p(\alpha)+z^{'}\phi_3(h)$.
Therefore, the disease free equilibrium of the system (4.4.1) is locally asymptotically stable if $R_{TB} < 1$ while it is unstable if $R_{TB} > 1$. □

The following figures showed the solution of the system (4.4.1) at the disease free equilibrium when $R_{TB} < 1$.

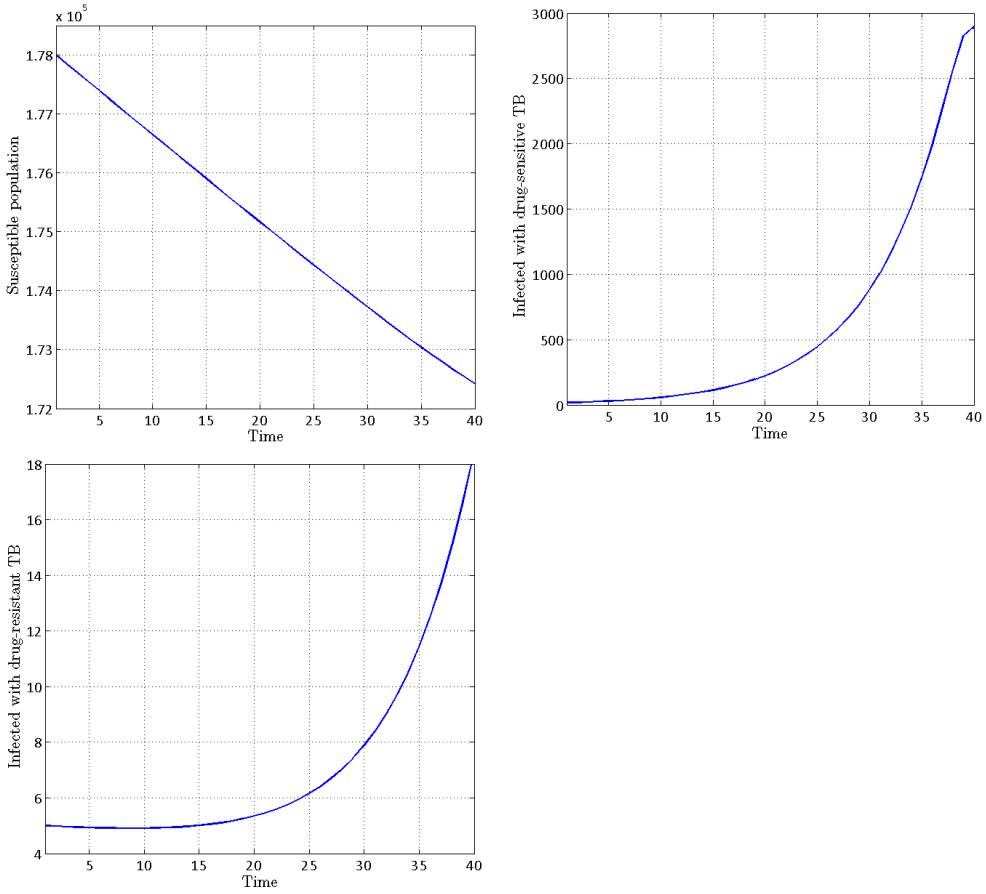


Figure 4.10: The first on the left side shows the susceptible population for TB and right on the infected individuals with drug-sensitive TB. The last one shows the infected one with dug-resistant TB. The solution of NSFDM of TB with initial solution $(S(0), i_s(0,0), I_r(0)) = (178400, 40, 5)$ and step size $h = 0.05$.

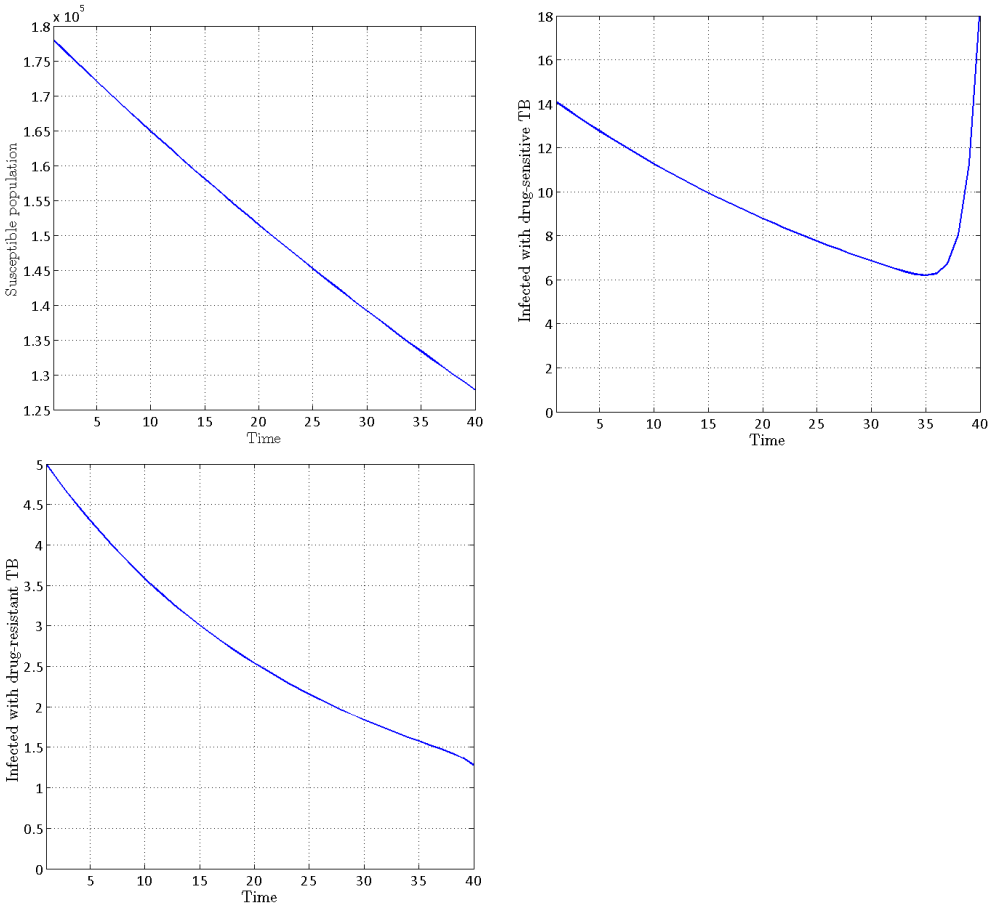


Figure 4.11: The first on the left side shows the susceptible population for TB and right on the infected individuals with drug-sensitive TB. The last one shows the infected one with dug-resistant TB. That is, this shows the solution of the disease free equilibrium of TB with initial value $(S(0), i_s(0,0), I_r(0)) = (178400, 40, 5)$ and step size $h = 0.5$ for n.

In general, the solution of NSFDM of TB sub-model in (4.4.1) (the solution of the susceptible, infected with drug-sensitive TB, infected with drug-resistant TB individuals), in the above figures converge to the solution at disease free equilibrium for different initial solutions with different step-size h; particularly when h approaches to zero and $R_{TB} < 1$.

Therefore, the system in (2.2.1) of chapter 2 and (4.4.1) in the above is locally asymptotically stable at the disease free equilibrium when $R_{TB} < 1$.

4.4.2 The numerical results and stability properties of TB at the endemic equilibria

To find the Jacobian matrix of our system in (4.4.1) at the endemic equilibrium, we used the endemic equilibrium $E^* = (S^*, m^*, I_r^*)$ of TB model (2.2.1) of chapter two which is given as

$S^* = (\frac{\Lambda}{\mu+d_s\chi+\frac{d_r(1-\frac{1}{R_s})}{1+\chi}})(1-(1-\frac{1}{R_s})(\frac{\chi+p_1}{(\chi+1)p_1}))$,

$m^* = \frac{\Lambda\chi(1-\frac{1}{R_s})}{\mu+d_s\chi+\frac{d_r(1-\frac{1}{R_s})}{1+\chi}}$,

$I_r^* = \frac{\Lambda(1-\frac{1}{R_s})}{(\mu+d_s\chi+\frac{d_r(1-\frac{1}{R_s})}{1+\chi})(1+\chi)}$,

where,

$\chi = \frac{p_1(\mu+\eta+d_r)(1-\frac{R_r}{R_s})}{qr\theta p_2}$,

$m^* = \lambda_s S^*$. Therefore, the partial derivatives of the system (4.4.2) at the this endemic equilibrium are:

$X = (S^n, m^n, I_r^n)$.

$\frac{\partial G}{\partial X_{11}} = \frac{1}{1+\phi_1(h)(\mu+\lambda_s+\lambda_r)} + \phi_1(h)(\lambda_s+\lambda_r)(1+\mu\phi_1(h)+\chi d_s\phi_1(h)+\frac{1-\frac{1}{R_s}}{1+\chi}(d_r+\eta+\frac{(1-r)\theta\chi}{p_1}-\frac{\chi+p_1}{(1+\chi)p_1}))$,

$\frac{\partial G}{\partial X_{12}} = \frac{\phi_1(h)(1-r)\theta}{1+\phi_1(h)(\mu+\lambda_s+\lambda_r)} + \frac{\phi_1(h)}{(1+\phi_1(h)(\mu+\lambda_s+\lambda_r))^2}(\frac{(1-\frac{1}{R_s})}{1+\chi}(\chi\beta_s c+\beta_r c-\beta_s c)(1+\mu\phi_1(h)+\phi_1(h)d_s\chi+\frac{(1-\frac{1}{R_s})}{1+\chi}(\eta+d_r+\frac{(1-r)\theta\chi}{p_1}-\frac{\chi}{p_1}-1))$,

$\frac{\partial G}{\partial X_{13}} = \frac{\phi_1(h)\eta}{1+\phi_1(h)(\mu+\lambda_s+\lambda_r)} + \frac{\lambda_s+\lambda_r+\frac{\mu}{N}-\beta_r c}{(1+\phi_1(h)(\mu+\lambda_s+\lambda_r))^2}(1+\mu\phi_1(h)+\phi_1(h)d_s\chi+\phi_1(h)\frac{(1-\frac{1}{R_s})}{1+\chi}(\eta+d_r+\frac{(1-r)\theta\chi}{p_1}-\frac{\chi}{p_1}-1))$,

$\frac{\partial G}{\partial X_{21}} = 0$,

$\frac{\partial G}{\partial X_{22}} = 1 + z(1 - p(\alpha)) - z^{'}\phi_2(h),$
$\frac{\partial G}{\partial X_{23}} = 0,$
$\frac{\partial G}{\partial X_{31}} = \frac{\phi_4(h)\lambda_r(\frac{\partial G}{\partial X_{11}} - \frac{1}{N})}{1+\phi_4(h)(\mu+\eta+d_r)},$

$\frac{\partial G}{\partial X_{32}} = \frac{\phi_4(h)(qr\theta+\lambda_r(\frac{\partial G}{\partial X_{12}} - \frac{S^{n+1}}{N}))}{1+\phi_4(h)(\mu+\eta+d_r)},$

$\frac{\partial G}{\partial X_{33}} = \frac{1+\phi_4(h)\lambda_r(\frac{\partial G}{\partial X_{13}} + \frac{S^{n+1}(S^n+m_s^n)}{N})}{1+\phi_4(h)(\mu+\eta+d_r)}.$

Therefore, the jacobian matrix of the NSFDMs (4.4.1) of TB model at the endemic equilibrium becomes

$J(E^1) = (\frac{\partial G}{\partial X_{ij}})_{i,j=1}^{3}$

$$= \begin{pmatrix} \frac{\partial G}{\partial X_{11}} & \frac{\partial G}{\partial X_{12}} & \frac{\partial G}{\partial X_{13}} \\ 0 & 1 + z(1 - p(\alpha)) - z^{'}\phi_2(h) & 0 \\ \frac{\partial G}{\partial X_{31}} & \frac{\partial G}{\partial X_{32}} & \frac{\partial G}{\partial X_{33}} \end{pmatrix}$$

The characteristic of this matrix is

$$\det \begin{pmatrix} \frac{\partial G}{\partial X_{11}} - \lambda & \frac{\partial G}{\partial X_{12}} & \frac{\partial G}{\partial X_{13}} \\ 0 & 1 + z(1 - p(\alpha)) - z^{'}\phi_2(h) - \lambda & 0 \\ \frac{\partial G}{\partial X_{31}} & \frac{\partial G}{\partial X_{32}} & \frac{\partial G}{\partial X_{33}} - \lambda \end{pmatrix} = 0$$

$(1+z(1-p(\alpha))-z^{'}\phi_2(h)-\lambda)(\lambda^2-(\frac{\partial G}{\partial X_{11}}+\frac{\partial G}{\partial X_{33}})\lambda+\frac{\partial G}{\partial X_{11}}\frac{\partial G}{\partial X_{33}}-\frac{\partial G}{\partial X_{13}}\frac{\partial G}{\partial X_{31}}) = 0$

, which implies that

$1 + z(1 - p(\alpha)) - z^{'}\phi_2(h) - \lambda = 0$ or

$\lambda^2 - (\frac{\partial G}{\partial X_{11}} + \frac{\partial G}{\partial X_{33}})\lambda + \frac{\partial G}{\partial X_{11}}\frac{\partial G}{\partial X_{33}} - \frac{\partial G}{\partial X_{13}}\frac{\partial G}{\partial X_{31}}) = 0$

Thus, we have the following:

- $\lambda = 1 + z(1 - p(\alpha)) - z^{'}\phi_2(h),$

- $\lambda^2 - (\frac{\partial G}{\partial X_{11}} + \frac{\partial G}{\partial X_{33}})\lambda + \frac{\partial G}{\partial X_{11}}\frac{\partial G}{\partial X_{33}} - \frac{\partial G}{\partial X_{13}}\frac{\partial G}{\partial X_{31}} = 0$

By rearranging the second equation above we obtained the simplified one as

$$\frac{\partial G}{\partial X_{11}}\frac{\partial G}{\partial X_{33}} - \frac{\partial G}{\partial X_{13}}\frac{\partial G}{\partial X_{31}} = \frac{\frac{\partial G}{\partial X_{11}} + \frac{\phi_1(h)\lambda_r}{N^n}\frac{\partial G}{\partial X_{13}} + \phi_4(h)\lambda_r S^{n+1}\frac{\partial G}{\partial X_{11}}(\frac{1}{I_r^n} - \frac{1}{N^n}) + \frac{\partial G}{\partial X_{11}}\frac{\partial G}{\partial X_{13}}\lambda_r(\phi_4(h) - \phi_1(h))}{1+\phi_4(h)(\mu+\eta+d_r)}.$$

Using **lemma 4.3.2**, we have

$f(\lambda) = \lambda^2 - (\frac{\partial G}{\partial X_{11}} + \frac{\partial G}{\partial X_{33}})\lambda + \frac{\partial G}{\partial X_{11}}\frac{\partial G}{\partial X_{33}} - \frac{\partial G}{\partial X_{13}}\frac{\partial G}{\partial X_{31}} = 0,$

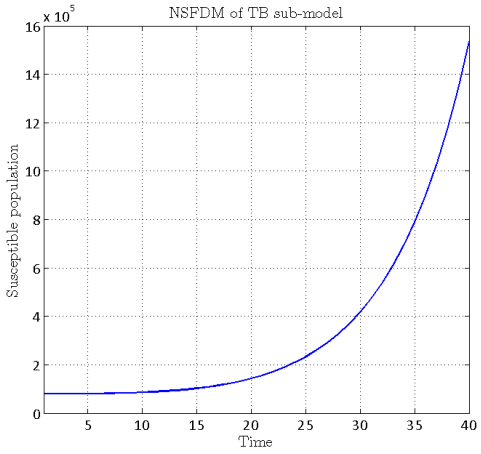
$f(0) = \frac{\frac{\partial G}{\partial X_{11}} + \frac{\phi_1(h)\lambda_r}{N^n}\frac{\partial G}{\partial X_{13}} + \phi_4(h)\lambda_r S^{n+1}\frac{\partial G}{\partial X_{11}}(\frac{1}{I_r^n} - \frac{1}{N^n}) + \frac{\partial G}{\partial X_{11}}\frac{\partial G}{\partial X_{13}}\lambda_r(\phi_4(h) - \phi_1(h))}{1+\phi_4(h)(\mu+\eta+d_r)} < 1$ for $\phi_4(h) > \phi_1(h),$

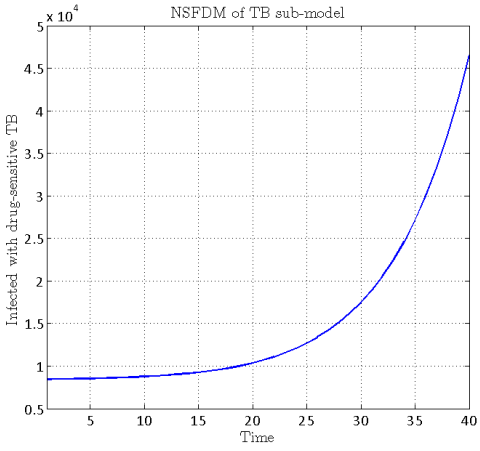
$f(-1) = 1 + \frac{\partial G}{\partial X_{11}} + \frac{\partial G}{\partial X_{33}} + \frac{\partial G}{\partial X_{11}}\frac{\partial G}{\partial X_{33}} - \frac{\partial G}{\partial X_{13}}\frac{\partial G}{\partial X_{31}} > 0,$

$f(1) = 1 - (\frac{\partial G}{\partial X_{11}} + \frac{\partial G}{\partial X_{33}}) + \frac{\partial G}{\partial X_{11}}\frac{\partial G}{\partial X_{33}} - \frac{\partial G}{\partial X_{13}}\frac{\partial G}{\partial X_{31}} > 0.$

Thus, this completes the proof of the theorem and it is true when $R_s > 1$ as shown in the first two partial derivatives. Therefore, the endemic equilibrium is locally asymptotically stable when $R_{TB} > 1$ otherwise it is unstable when $R_{TB} < 1$.

In the following, we see that figures show the solutions of susceptible, infected with drug-sensitive and drug-resistant TB at some points of different initial solutions for different step-sizes h.





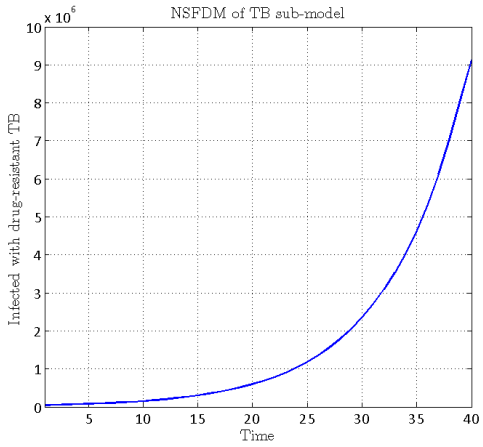
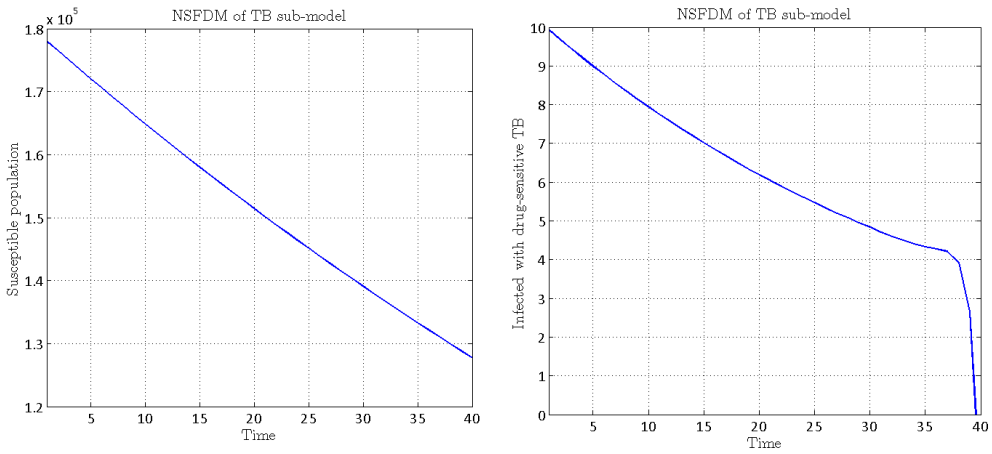


Figure 4.12: The first on the left side shows the susceptible individuals for TB and right on the infected individuals with drug-sensitive TB. The last one shows the infected one with dug-resistant TB initial solution $(S(0), i_s(0,0), I_r(0)) = (178000, 20, 5)$ and step size $h = 0.05$.



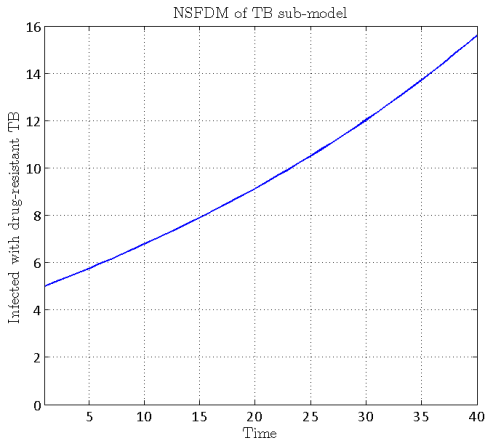
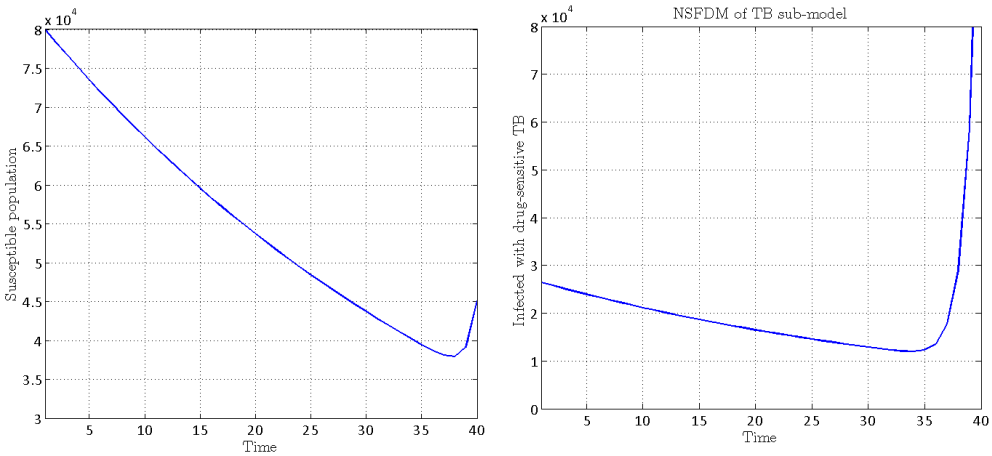


Figure 4.13: The first on the left side shows the solutions of susceptible individuals for TB and right one the infected individuals with drug-sensitive TB. The last one shows the infected one with dug-resistant TB with initial solution $(S(0), i_s(0,0), I_r(0)) = (178000, 20, 5)$ and step size $h = 0.5$.



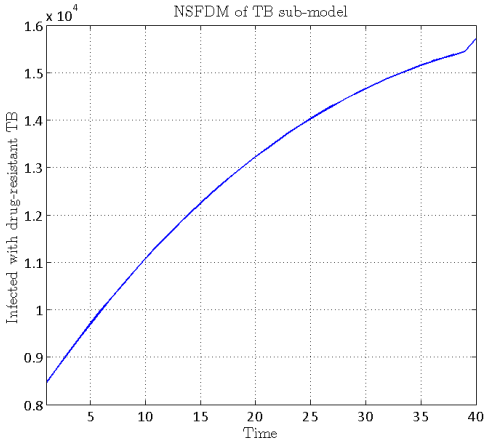
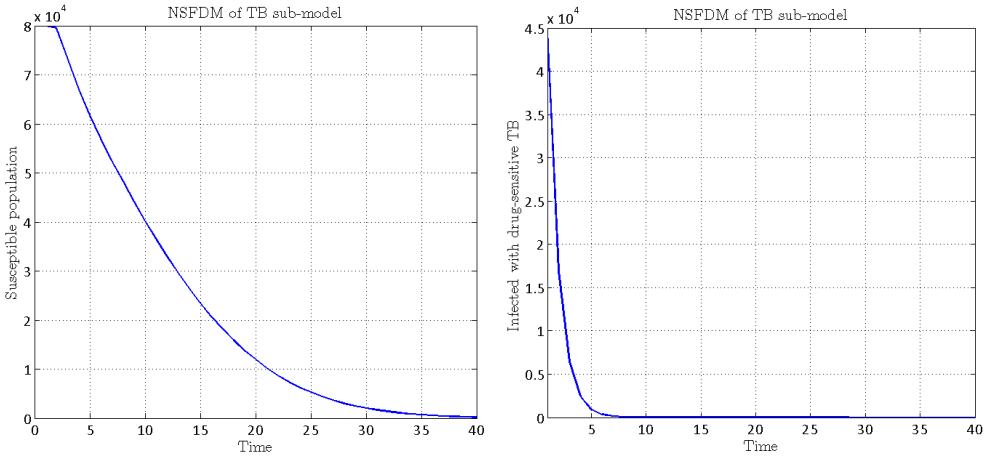


Figure 4.14: The first on the left side shows the susceptible individuals for TB and right on the infected individuals with drug-sensitive TB. The last one shows the infected one with dug-resistant TB. Generally, this shows the solution of endemic equilibrium of TB with initial value $(S(0), i_s(0,0), I_r(0)) = (80000, 90000, 8445)$ and step size $h = 0.5$.



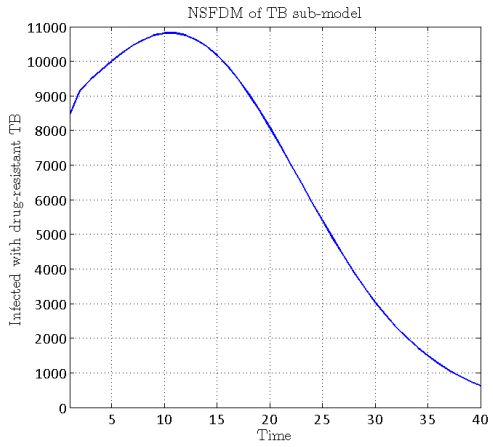


Figure 4.15: The first on the left side shows the susceptible individuals for TB and right on the infected individuals with drug-sensitive TB. The last one shows the infected one with dug-resistant TB with initial solution $(S(0), i_s(0,0), I_r(0)) = (80000, 90000, 8445)$ and step size $h = 2$.

In general, the solution of NSFDM for the TB sub-model in (4.4.1)(the solution of the susceptible, infected with drug-sensitive TB, infected with drug-resistant TB individuals), as shown in the above figures converge to the solution at the endemic equilibrium for different initial solutions with different step-size h, and for $R_{TB} > 1$.
Therefore, the system (2.2.1) in chapter 2 which is equivalent to the system (4.4.1) in chapter 4 is locally asymptotically stable at the endemic equilibrium when $R_{TB} > 1$.

4.5 Formulation and analysis of NSFDMs for HIV-TB co-infection full model

In this section, we construct NSFDMs for the co-infection model of HIV and TB as observed the individual sub-models in the previous sections. The

figures below show the NSFDMs of the co-infection of HIV and TB model (3.3.1) indicated above.

The NSFDMs of the model is written as follows:

$$\begin{aligned}
&\frac{S^{n+1}-S^n}{\phi_1(h)} = \Lambda - (\lambda_H + \lambda_r + \lambda_s)S^{n+1} - \mu S^{n+1} + (1 - r + \eta qr)\theta i_s^{(n,j)} \\
&\frac{(i_s^{(n+1,j)}-i_s^{(n,j)})}{\phi_2(h)} + \frac{(i_s^{(n,j+1)}-i_s^{(n,j)})}{\phi_3(h)} = -(((1 - r + qr)\theta + \delta_s\lambda_H)p(\alpha) + \mu + d_s)i_s^{(n,j)} \\
&\frac{(I_r^{n+1}-I_r^n)}{\phi_4(h)} = \lambda_r S^{n+1} - \delta_r\lambda_H I_r^{n+1} - (\mu + d_r)I^{n+1} + (1 - \eta)qr\theta i_s^{(n,j)} \\
&\frac{(I_H^{n+1}-I_H^n)}{\phi_5(h)} = \lambda_H S^{n+1} + \nu I_{HTB}^n - (\gamma_s\lambda_s + \gamma_r\lambda_r)I_H^{n+1} - (\mu + d_H)I_H^{n+1} \\
&\frac{(I_{HTB}^{n+1}-I_{HTB}^n)}{\phi_6(h)} = \delta_s\lambda_H i_s^{(n,j)} + \delta_r\lambda_H I_r^{n+1} - (\gamma_s\lambda_s + \gamma_r\lambda_r)I_H^{n+1} - \omega I_{HTB}^{n+1}
\end{aligned} \tag{4.5.1}$$

where

$\lambda_s = \frac{\beta_s i_s^{(n,j)}}{S^n + i_s^{(n,j)} + I_r^n + I_H^n + I_{HTB}^n}$,

$\lambda_r = \frac{\beta_r I_r^n}{S^n + i_s^{(n,j)} + I_r^n + I_H^n + I_{HTB}^n}$,

$\lambda_H = \frac{\beta_H I_H^n}{S^n + i_s^{(n,j)} + I_r^n + I_H^n + I_{HTB}^n}$,

$\phi_1(h) = \frac{e^{\mu h}-1}{\mu}$,

$\phi_2(h) = \frac{e^{(\mu+d_s)h}-1}{\mu+d_s}$,

$\phi_3(h) = \frac{e^{(\mu+d_s\rho(\alpha))h}-1}{\mu+d_s\rho(\alpha)}$

$\phi_4(h) = \frac{e^{(\mu+d_r)h}-1}{\mu+d_r}$,

$\phi_5(h) = \frac{e^{(\mu+d_H)h}-1}{\mu+d_H}$,

$\phi_6(h) = \frac{e^{(\mu+\omega)h}-1}{\mu+\omega}$,

$\omega = \nu + \kappa_s d_s + \kappa_r d_r + \kappa_H d_H$.

The above equations are simplified and written as:

$$
\begin{aligned}
S^{n+1} &= \tfrac{S^n+\phi_1(h)\Lambda+\phi_1(h)(1-r+\eta qr)\theta i_s^{(n,j)}}{1+\phi_1(h)(\mu+\lambda_H+\lambda_r+\lambda_s)} \\
i_s^{(n+1,j)} &= (1+\tfrac{\phi_2(h)}{\phi_3(h)} - \phi_2(h)(((1-r+qr)\theta+\delta_s\lambda_H)p(\alpha)+\mu+d_s)i_s^{(n,j)} \\
&-\tfrac{\phi_2(h)}{\phi_3(h)} i_s^{(n,j+1)} \\
I_r^{n+1} &= \tfrac{I_r^n+\phi_4(h)(\lambda_r S^{n+1}+(1-\eta)qr\theta i_s^{(n,j)})}{1+\phi_4(h)(\delta_r\lambda_H+\mu+d_r)} \\
I_H^{n+1} &= \tfrac{I_H^n+\phi_5(h)(\lambda_H S^{n+1}+\nu I_{HTB}^n)}{1+\phi_5(h)(\gamma_s\lambda_s+\gamma_r\lambda_r+\mu+d_H)} \\
I_{HTB}^{n+1} &= \tfrac{I_{HTB}^n+\phi_6(h)(\lambda_H(\delta_s i_s^{(n,j)}+\delta_r I_r^n)+(\gamma_s\lambda_s+\gamma_r\lambda_r)I_H^{n+1})}{1+\phi_6(h)(\mu+\omega)}
\end{aligned}
\tag{4.5.2}
$$

For $n = 0, 1, 2, ...$ and $j = 0, 1, 2, ...$

Here, we determine the numerical simulation and stability properties of the system (4.5.2) and the simplified form of (4.5.1) both at the disease free and endemic equilibrium in the following subsections.

4.5.1 The numerical results and stability properties of the full model at the disease free equilibria

From the Jacobian matrix of the system in (4.5.2) above, we obtained the following Jacobian matrix of it at the disease free equilibrium $E^0(S^0, i_s^0, I_r^0, I_H^0, I_{HTB}^0) = (\frac{\Lambda}{\mu}, 0, 0, 0, 0)$.

Let $G(X) =$

$$
\begin{pmatrix}
\frac{S^n+\phi_1(h)\Lambda+\phi_1(h)(1-r+\eta qr)\theta i_s^{(n,j)}}{1+\phi_1(h)(\mu+\lambda_H+\lambda_r+\lambda_s)} \\
(1+\frac{\phi_2(h)}{\phi_3(h)} - \phi_2(h)(((1-r+qr)\theta+\delta_s\lambda_H)p(\alpha)+\mu+d_s)i_s^{(n,j)} - \frac{\phi_2(h)}{\phi_3(h)} i_s^{(n,j+1)} \\
\frac{I_r^n+\phi_4(h)(\lambda_r S^{n+1}+(1-\eta)qr\theta i_s^{(n,j)})}{1+\phi_4(h)(\delta_r\lambda_H+\mu+d_r)} \\
\frac{I_H^n+\phi_5(h)(\lambda_H S^{n+1}+\nu I_{HTB}^n)}{1+\phi_5(h)(\gamma_s\lambda_s+\gamma_r\lambda_r+\mu+d_H)} \\
\frac{I_{HTB}^n+\phi_6(h)(\lambda_H(\delta_s i_s^{(n,j)}+\delta_r I_r^n)+(\gamma_s\lambda_s+\gamma_r\lambda_r)I_H^{n+1})}{1+\phi_6(h)(\mu+\omega)}
\end{pmatrix},
$$

where $X = (S^n, i_s^n, I_r^n, I_H^n, I_{HTB}^n)$.

From the system (4.5.2) which is the simplified form of (4.5.1) at the disease free equilibrium, first by deriving the partial derivatives of the matrix with respect to the component variables, we have:

$J(E^0) = (\frac{\partial G}{\partial X_{ij}})_{i,j=1}^{5} =$

$$\begin{pmatrix} \frac{\partial G}{\partial X_{11}} & \frac{\partial G}{\partial X_{12}} & \frac{\partial G}{\partial X_{13}} & \frac{\partial G}{\partial X_{14}} & \frac{\partial G}{\partial X_{15}} \\ \frac{\partial G}{\partial X_{21}} & \frac{\partial G}{\partial X_{22}} & \frac{\partial G}{\partial X_{23}} & \frac{\partial G}{\partial X_{24}} & \frac{\partial G}{\partial X_{25}} \\ \frac{\partial G}{\partial X_{31}} & \frac{\partial G}{\partial X_{32}} & \frac{\partial G}{\partial X_{33}} & \frac{\partial G}{\partial X_{34}} & \frac{\partial G}{\partial X_{35}} \\ \frac{\partial G}{\partial X_{41}} & \frac{\partial G}{\partial X_{42}} & \frac{\partial G}{\partial X_{43}} & \frac{\partial G}{\partial X_{44}} & \frac{\partial G}{\partial X_{45}} \\ \frac{\partial G}{\partial X_{51}} & \frac{\partial G}{\partial X_{52}} & \frac{\partial G}{\partial X_{53}} & \frac{\partial G}{\partial X_{54}} & \frac{\partial G}{\partial X_{55}} \end{pmatrix}$$

$=$

$$\begin{pmatrix} \frac{1}{1+\mu\phi_1(h)} & \frac{\phi_1(h)((1-r)\theta)-\beta_s c}{1+\mu\phi_1(h)} & \frac{\phi_1(h)(R_r+\frac{1-\eta}{\mu+\eta+d_r})}{1+\mu\phi_1(h)} & \frac{\phi_1(h)\beta_H c}{1+\mu\phi_1(h)} & 0 \\ 0 & a & 0 & 0 & 0 \\ 0 & \frac{\phi_4(h)qr\theta}{1+\phi_4(h)(\mu+\eta+d_r)} & \frac{1+\phi_4(h)(1+\mu\phi_1(h))\beta_r c}{\phi_4(h)(\mu+\eta+d_r)} & 0 & 0 \\ 0 & 0 & 0 & \frac{1+\phi_5(h)\beta_H c}{1+\phi_5(h)(\mu+d_H)} & \frac{\phi_5(h)}{1+\phi_5(h)(\mu+d_H)} \\ 0 & 0 & 0 & 0 & \frac{1}{1+\phi_6(h)\omega} \end{pmatrix}$$

$a = 1 + z(1 - p(\alpha)) - z^{'}\phi_2(h) - \lambda,$

$b = \frac{1+\phi_4(h)(1+\mu\phi_1(h))\beta_r c}{\phi_4(h)(\mu+\eta+d_r)},$

$d = \frac{\phi_1(h)(R_r+\frac{1-\eta}{\mu+\eta+d_r})}{1+\mu\phi_1(h)}$. Then the characteristic equation of this model is

$$\det \begin{pmatrix} \frac{1}{1+\mu\phi_1(h)} - \lambda & \frac{\phi_1(h)(\theta-r\theta-\beta_s c)}{1+\mu\phi_1(h)} & d & \frac{\phi_1(h)\beta_H c}{1+\mu\phi_1(h)} & 0 \\ 0 & a-\lambda & 0 & 0 & 0 \\ 0 & \frac{\phi_4(h)qr\theta}{1+\phi_4(h)(\mu+\eta+d_r)} & b-\lambda & 0 & 0 \\ 0 & 0 & 0 & \frac{1+\phi_5(h)\beta_H c}{1+\phi_5(h)(\mu+d_H)} - \lambda & \frac{\phi_5(h)}{1+\phi_5(h)(\mu+d_H)} \\ 0 & 0 & 0 & 0 & \frac{1}{1+\phi_6(h)\omega} - \lambda \end{pmatrix}$$

$= 0$

Hence, the eigenvalues of this matrix are:

$\lambda_1 = \frac{1}{1+\mu\phi_1(h)}$,

$\lambda_2 = 1 + z(1 - p(\alpha)) - z^{'}\phi_2(h)$,

$\lambda_3 = \frac{1+\phi_4(h)(1+\mu\phi_1(h))\beta_r c}{\phi_4(h)(\mu+\eta+d_r)}$,

$\lambda_4 = \frac{1+\phi_5(h)\beta_H c}{1+\phi_5(h)(\mu+d_H)}$,

$\lambda_5 = \frac{1}{1+\phi_6(h)\omega}$.

We observed that all the eigenvalues are less than unity ($|\lambda_i| < 1$ for $i = 1, 2, 3, 4, 5$) and when both $R_{TB} < 1$ and $R_H < 1$. Therefore, the system in (4.5.2) above is locally asymptotically stable at the disease free equilibrium if $R < 1$ since $R = \max(R_{TB}, R_H)$ and otherwise it is unstable.

4.5.2 The numerical results and stability properties of the model at the endemic equilibria

In this subsection, we check the stability and convergence of the NSFDM of the full-model (HIV-TB co-infection model) according to the value of the tolerance of each of the compartment and the figures as observed at the end of this section. At the nd of this section we generalize the convergency of the NSFDM compared to the convergency of the system we discussed in chapter 3 section at the endemic equilibrium.

Let recall the simplified system of nonstandard finite methods equation (4.5.2) and

$$G(X) = \begin{pmatrix} \frac{S^n+\phi_1(h)\Lambda+\phi_1(h)(1-r+\eta qr)\theta i_s^{(n,j)}}{1+\phi_1(h)(\mu+\lambda_H+\lambda_r+\lambda_s)} \\ (1+\frac{\phi_2(h)}{\phi_3(h)}-\phi_2(h)(((1-r+qr)\theta+\delta_s\lambda_H)p(\alpha)+\mu+d_s)i_s^{(n,j)}-\frac{\phi_2(h)}{\phi_3(h)}i_s^{(n,j+1)} \\ \frac{I_r^n+\phi_4(h)(\lambda_r S^{n+1}+(1-\eta)qr\theta i_s^{(n,j)})}{1+\phi_4(h)(\delta_r\lambda_H+\mu+d_r)} \\ \frac{I_H^n+\phi_5(h)(\lambda_H S^{n+1}+\nu I_{HTB}^n)}{1+\phi_5(h)(\gamma_s\lambda_s+\gamma_r\lambda_r+\mu+d_H)} \\ \frac{I_{HTB}^n+\phi_6(h)(\lambda_H(\delta_s i_s^{(n,j)}+\delta_r I_r^n)+(\gamma_s\lambda_s+\gamma_r\lambda_r)I_H^{n+1})}{1+\phi_6(h)(\mu+\omega)} \end{pmatrix},$$

By substituting the solution of model we obtained in theorem 3.4.3 at the endemic equilibrium, we obtained the following partial derivatives at the endemic in terms of N above of the system (3.4.2) and obtained the endemic equilibrium denoted by $E^{'} = (N^{'}, m^{'}, I_r^{'}, I_H^{'}, I_{HTB}^{'})$ is expressed in terms of $E^{'} = (S^{'}, i_s^{'}, I_r^{'}, I_H^{'}, I_{HTB}^{'})$ is given as follows:

$$\frac{\partial G}{\partial X_{11}} = \frac{1+\phi_1(\mu+\lambda_s+\lambda_r+\lambda_H)+(S^n+\phi_1(\Lambda+\eta I_r^n+(1-r)m^n))\frac{\phi_1(\lambda_s+\lambda_r+\lambda_H)}{N^n}}{(1+\phi_1(\mu+\lambda_s+\lambda_r+\lambda_H))^2},$$

$$\frac{\partial G}{\partial X_{12}} = \frac{\phi_1(1-r)(1+\phi_1(\mu+\lambda_s+\lambda_r+\lambda_H))+(S^n+\phi_1(\Lambda+\eta I_r^n+(1-r)m^n))\frac{\phi_1(\lambda_s+\lambda_r+\lambda_H-\beta_s c)}{N^n}}{(1+\phi_1(\mu+\lambda_s+\lambda_r+\lambda_H))^2},$$

$$\frac{\partial G}{\partial X_{13}} = \frac{\eta\phi_1(1+\phi_1(\mu+\lambda_s+\lambda_r+\lambda_H))+(S^n+\phi_1(\Lambda+\eta I_r^n+(1-r)m^n))\frac{\phi_1(\lambda_s+\lambda_r+\lambda_H-\beta_r c)}{N^n}}{(1+\phi_1(\mu+\lambda_s+\lambda_r+\lambda_H))^2},$$

$$\frac{\partial G}{\partial X_{14}} = \frac{(S^n+\phi_1(\Lambda+\eta I_r^n+(1-r)m^n))\frac{\phi_1(\lambda_s+\lambda_r+\lambda_H-\beta_H c)}{N^n}}{(1+\phi_1(\mu+\lambda_s+\lambda_r+\lambda_H))^2},$$
$$\frac{\partial G}{\partial X_{15}} = \frac{(S^n+\phi_1(\Lambda+\eta I_r^n+(1-r)m^n))\phi_1(\lambda_s+\lambda_r+\lambda_H)}{N^n(1+\phi_1(\mu+\lambda_s+\lambda_r+\lambda_H))^2},$$

$$\frac{\partial G}{\partial X_{21}} = \frac{\phi_2\sigma_s p_\alpha\lambda_H i_s^{n,j}}{N^n},$$
$$\frac{\partial G}{\partial X_{22}} = 1+\frac{\phi_2}{\phi_3}-\phi_2(((1-r+qr)\theta+\sigma_s\lambda_H)p(\alpha)+\mu+d_s)+\frac{\phi_2\sigma_s p_\alpha\lambda_H i_s^{n,j}}{N^n},$$
$$\frac{\partial G}{\partial X_{23}} = \frac{\phi_2\sigma_s p_\alpha\lambda_H i_s^{n,j}}{N^n},$$
$$\frac{\partial G}{\partial X_{24}} = \frac{\phi_2\sigma_s p_\alpha(\lambda_H-\beta_H c) i_s^{n,j}}{N^n},$$
$$\frac{\partial G}{\partial X_{25}} = \frac{\phi_2\sigma_s p_\alpha\lambda_H i_s^{n,j}}{N^n},$$

$$\frac{\partial G}{\partial X_{31}} = \frac{\phi_4\lambda_r(\frac{\partial G}{\partial X_{11}}-\frac{S^{n+1}}{N^n})}{1+\phi_4(\mu+\eta+d_r+\sigma_r\lambda_H} + \frac{\phi_4\sigma_r\lambda_H(I_r^n+\phi_4\lambda_r S^{n+1}+\phi_4 qr\theta i_s^{n,j})}{N^n(\mu+\eta+d_r+\sigma_r\lambda_H)^2},$$
$$\frac{\partial G}{\partial X_{32}} = \frac{\phi_4\lambda_r(\frac{\partial G}{\partial X_{12}}-\frac{S^{n+1}}{N^n})+qr\theta}{1+\phi_4(\mu+\eta+d_r+\sigma_r\lambda_H} + \frac{\phi_4\sigma_r\lambda_H(I_r^n+\phi_4\lambda_r S^{n+1}+\phi_4 qr\theta i_s^{n,j})}{N^n(\mu+\eta+d_r+\sigma_r\lambda_H)^2},$$
$$\frac{\partial G}{\partial X_{33}} = \frac{1+\phi_4\beta_r c\frac{(N-I_r^n)S^{n+1}}{(N^n)^2}+\phi_4\lambda_r\frac{\partial G}{\partial X_{13}}}{(\mu+\eta+d_r+\sigma_r\lambda_H)^2} + \frac{\phi_4\sigma_r\lambda_H(I_r^n+\phi_4\lambda_r S^{n+1}+\phi_4 qr\theta i_s^{n,j})}{N^n(\mu+\eta+d_r+\sigma_r\lambda_H)^2},$$
$$\frac{\partial G}{\partial X_{34}} = \frac{\phi_4\lambda_r(\frac{\partial G}{\partial X_{14}}-\frac{S^{n+1}}{N^n})}{1+\phi_4(\mu+\eta+d_r+\sigma_r\lambda_H} + \frac{\phi_4\sigma_r\lambda_H(I_r^n+\phi_4\lambda_r S^{n+1}+\phi_4 qr\theta i_s^{n,j})}{N^n(\mu+\eta+d_r+\sigma_r\lambda_H)^2},$$
$$\frac{\partial G}{\partial X_{35}} = \frac{\phi_4\lambda_r(\frac{\partial G}{\partial X_{15}}-\frac{S^{n+1}}{N^n})}{1+\phi_4(\mu+\eta+d_r+\sigma_r\lambda_H)} + \frac{\phi_4\sigma_r\lambda_H(I_r^n+\phi_4\lambda_r S^{n+1}+\phi_4 qr\theta i_s^{n,j})}{N^n(\mu+\eta+d_r+\sigma_r\lambda_H)^2},$$

$$\frac{\partial G}{\partial X_{41}} = \frac{\phi_5\lambda_H(\frac{\partial G}{\partial X_{11}}-\frac{S^{n+1}}{N^n})}{1+\phi_5(\mu+d_H+\lambda_s\lambda_s+\lambda_r\lambda_r)} + \frac{\phi_5(\lambda_s\lambda_s+\lambda_r\lambda_r)(I_H^n+\phi_5 I_{HTB}^n+\phi_5\lambda_H S^{n+1})}{N^n(1+\phi_5(\mu+d_H+\lambda_s\lambda_s+\lambda_r\lambda_r))^2},$$
$$\frac{\partial G}{\partial X_{42}} = \frac{\phi_5\lambda_H(\frac{\partial G}{\partial X_{12}}-\frac{S^{n+1}}{N^n})}{1+\phi_5(\mu+d_H+\lambda_s\lambda_s+\lambda_r\lambda_r)} + \frac{\phi_5(\lambda_s\lambda_s+\lambda_r\lambda_r)(I_H^n+\phi_5(I_{HTB}^n+\lambda_H S^{n+1}))}{N^n(1+\phi_5(\mu+d_H+\lambda_s\lambda_s+\lambda_r\lambda_r))^2},$$
$$\frac{\partial G}{\partial X_{43}} = \frac{\phi_5\lambda_H(\frac{\partial G}{\partial X_{13}}-\frac{S^{n+1}}{N^n})}{1+\phi_5(\mu+d_H+\lambda_s\lambda_s+\lambda_r\lambda_r)} + \frac{\phi_5(\frac{\gamma_s\lambda_s}{N^n}+\frac{\gamma_r\beta_s c(N^n-i_s^{n,j})}{(N^n)^2})(I_H^n+\phi_5(I_{HTB}^n+\lambda_H S^{n+1}))}{N^n(1+\phi_5(\mu+d_H+\gamma_s\lambda_s+\gamma_r\lambda_r))^2},$$
$$\frac{\partial G}{\partial X_{44}} = \frac{1+\phi_5\lambda_H(\frac{\partial G}{\partial X_{14}}+\frac{S^{n+1}}{N^n})}{1+\phi_5(\mu+d_H+\lambda_s\lambda_s+\lambda_r\lambda_r)} + \frac{\phi_5(\gamma_s\lambda_s+\gamma_r\lambda_r)(I_H^n+\phi_5(I_{HTB}^n+\lambda_H S^{n+1}))}{N^n(1+\phi_5(\mu+d_H+\gamma_s\lambda_s+\gamma_r\lambda_r))^2},$$
$$\frac{\partial G}{\partial X_{45}} = \frac{\phi_5(1+\lambda_H(\frac{\partial G}{\partial X_{15}}+\frac{S^{n+1}}{N^n}))}{1+\phi_5(\mu+d_H+\lambda_s\lambda_s+\lambda_r\lambda_r)} + \frac{\phi_5(\gamma_s\lambda_s+\gamma_r\lambda_r)(I_H^n+\phi_5(I_{HTB}^n+\lambda_H S^{n+1}))}{N^n(1+\phi_5(\mu+d_H+\gamma_s\lambda_s+\gamma_r\lambda_r))^2},$$

$$\frac{\partial G}{\partial X_{51}} = \frac{\phi_6((\gamma_s\lambda_s+\gamma_r\lambda_r)I_H^n-(\sigma_s i_s^{(n,j)}+\sigma_r I_r^n)\lambda_H)}{N^n(1+\phi_6\omega)},$$
$$\frac{\partial G}{\partial X_{52}} = \frac{\phi_6(\frac{\sigma_s\lambda_H i_s^{(n+1,j)}}{N^n}+\sigma_s\lambda_H\frac{\partial G}{\partial X_{22}}+\frac{\sigma_r\lambda_H I_r^{n+1}}{N^n}+\frac{(\gamma_s\lambda_s+\gamma_r\lambda_r-\beta_s c)I_H^{n+1}}{N^n})}{(1+\phi_6\omega)},$$
$$\frac{\partial G}{\partial X_{53}} = \frac{\phi_6(\frac{-(\sigma_s\lambda_H i_s^{(n+1,j)})+\sigma_r\lambda_H I_r^{n+1}}{N^n}+\sigma_r\lambda_H\frac{\partial G}{\partial X_{33}}+\frac{(\gamma_s\lambda_s+\gamma_r\lambda_r-\beta_r c)I_H^{n+1}}{N^n})}{(1+\phi_6\omega)},$$

$$\frac{\partial G}{\partial X_{54}} = \frac{\phi_6((\gamma_s\lambda_s+\gamma_r\lambda_r)(\frac{I_H^{n+1}}{N^n}-\frac{\partial G}{\partial X_{44}})+(\sigma_s i_s^{(n+1,j)}+\sigma_r I_r^{n+1})(\lambda_H-\beta_H c))}{N^n(1+\phi_6\omega)},$$
$$\frac{\partial G}{\partial X_{55}} = \frac{1+\phi_6((\gamma_s\lambda_s+\gamma_r\lambda_r)I_H^{n+1}-(\sigma_s i_s^{(n+1,j)}+\sigma_r I_r^{n+1})\lambda_H)}{N^n(1+\phi_6\omega)},$$

For,

$x = \frac{\mu+\eta+d_r}{qr\theta p_2}(1-\frac{R_r}{R_s}+\sigma_r\lambda_H),$

$y = \frac{\mu+d_H}{\nu}(1-\frac{R_H}{R_s}+\frac{\gamma_s\lambda_s+\gamma_r\lambda_r}{\mu+d_H}),$

$x^{'} = \frac{\sigma_r\lambda_H+\gamma_s\lambda_H p_2 x}{\omega y-(\gamma_s\lambda_s+\gamma_r\lambda_r)},$

$x^{''} = \frac{(1-\frac{1}{R_s})}{(p_1 x+1+x^{'}+yx^{'})}.$

$N^{'} = \frac{\Lambda}{\mu+x^{''}(d_s p_1 x+d_r+x^{'}(d_H+dx))},$

$S^n = N^{'}-x^{''}N-xx^{''}N-x^{'}x^{''}N-yx^{'}x^{''}N$

$= (1-x^{''}-xx^{''}-x^{'}x^{''}-yx^{'}x^{''})\frac{\Lambda}{\mu+x^{''}(d_s p_1 x+d_r+x^{'}(d_H+dx))},$

$m^{'} = xx^{''}N,$

$I_r^{'} = x^{''}N,$

$m^{'} = xx^{''}N,$

$I_H^{'} = x^{'}x^{''}N,$

$I_{HTB}^{'} = yx^{'}x^{''}N.$

Using the above information, we obtained the following Jacobian matrix at the endemic equilibrium $E^1(S^1, m^1, I_r^1, I_H^1, I_{HTB}^1) =$

$((1-x^{''}-xx^{''}-x^{'}x^{''}-yx^{'}x^{''})N, xx^{''}N, x^{''}N, x^{'}x^{''}N, yx^{'}x^{''}N)$

$J(E^1) = (\frac{\partial G}{\partial X_{ij}})_{i,j=1}^5 =$

$$\begin{pmatrix} \frac{\partial G}{\partial X_{11}} & \frac{\partial G}{\partial X_{12}} & \frac{\partial G}{\partial X_{13}} & \frac{\partial G}{\partial X_{14}} & \frac{\partial G}{\partial X_{15}} \\ \frac{\partial G}{\partial X_{21}} & \frac{\partial G}{\partial X_{22}} & \frac{\partial G}{\partial X_{23}} & \frac{\partial G}{\partial X_{24}} & \frac{\partial G}{\partial X_{25}} \\ \frac{\partial G}{\partial X_{31}} & \frac{\partial G}{\partial X_{32}} & \frac{\partial G}{\partial X_{33}} & \frac{\partial G}{\partial X_{34}} & \frac{\partial G}{\partial X_{35}} \\ \frac{\partial G}{\partial X_{41}} & \frac{\partial G}{\partial X_{42}} & \frac{\partial G}{\partial X_{43}} & \frac{\partial G}{\partial X_{44}} & \frac{\partial G}{\partial X_{45}} \\ \frac{\partial G}{\partial X_{51}} & \frac{\partial G}{\partial X_{52}} & \frac{\partial G}{\partial X_{53}} & \frac{\partial G}{\partial X_{54}} & \frac{\partial G}{\partial X_{55}} \end{pmatrix}$$

Then its characteristics becomes

$$\det \begin{pmatrix} \frac{\partial G}{\partial X_{11}} - \lambda & \frac{\partial G}{\partial X_{12}} & \frac{\partial G}{\partial X_{13}} & \frac{\partial G}{\partial X_{14}} & \frac{\partial G}{\partial X_{15}} \\ \frac{\partial G}{\partial X_{21}} & \frac{\partial G}{\partial X_{22}} - \lambda & \frac{\partial G}{\partial X_{23}} & \frac{\partial G}{\partial X_{24}} & \frac{\partial G}{\partial X_{25}} \\ \frac{\partial G}{\partial X_{31}} & \frac{\partial G}{\partial X_{32}} & \frac{\partial G}{\partial X_{33}} - \lambda & \frac{\partial G}{\partial X_{34}} & \frac{\partial G}{\partial X_{35}} \\ \frac{\partial G}{\partial X_{41}} & \frac{\partial G}{\partial X_{42}} & \frac{\partial G}{\partial X_{43}} & \frac{\partial G}{\partial X_{44}} - \lambda & \frac{\partial G}{\partial X_{45}} \\ \frac{\partial G}{\partial X_{51}} & \frac{\partial G}{\partial X_{52}} & \frac{\partial G}{\partial X_{53}} & \frac{\partial G}{\partial X_{54}} & \frac{\partial G}{\partial X_{55}} - \lambda \end{pmatrix}$$

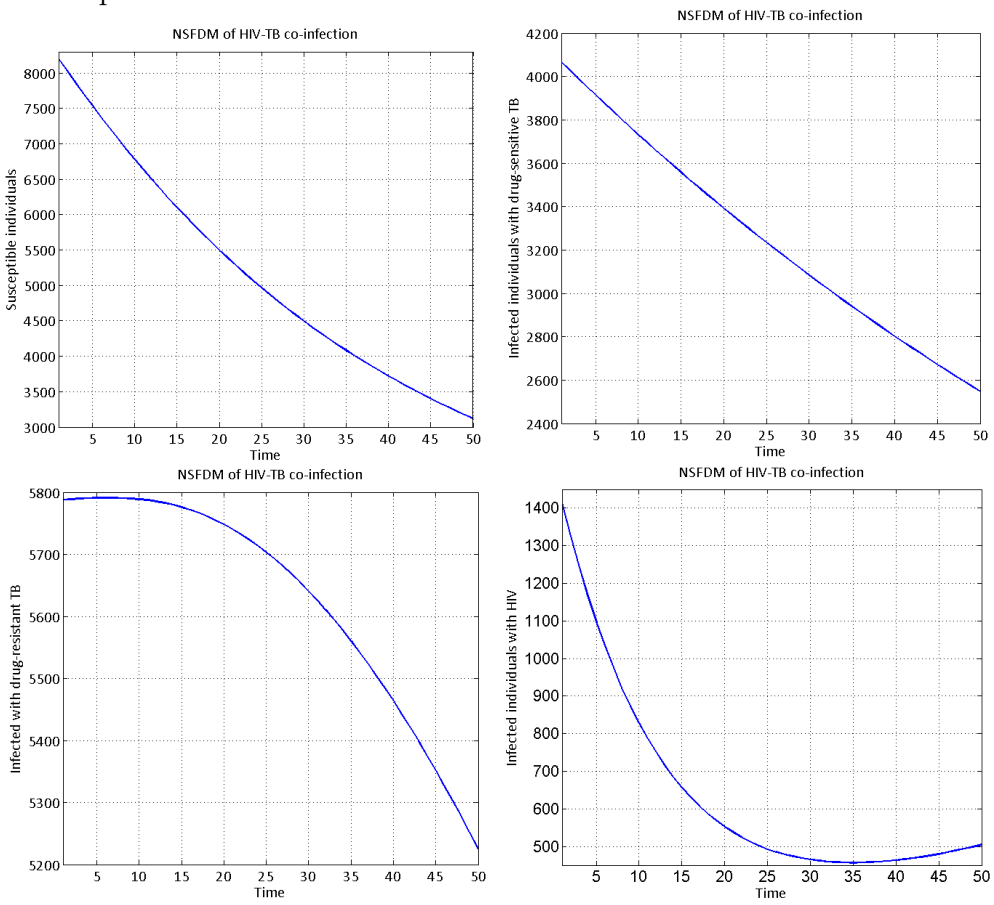
$= 0$

Here, since to find the eigenvalues of the Jacobian matrix in terms of the given variables is to large and somewhat difficult so that it better to find its eigenvalues by taking specific (fixed) values for the variables. Hence we obtained the following eigenvalues of the above characteristics at the endemic equilibrium for (i.e $R = \max(R_H, R_{TB}) > 1$ or $R_H > 1$ and $R_{TB} > 1$).

h	$S(0)$	$i_s(0,0)$	$I_r(0)$	$I_H(0)$	$I_{HTB}(0)$	λ_1	λ_2	λ_3	λ_4	λ_5
0.05	8201	4066	5788	1415	531	-4.4050	-0.0020	-0.1801	-0.9637	-2.2002
8	73171	36277	51640	12623	4734	-7.9196	-0.0204	-0.9153	-1.7013	-3.2034
15	2945	1941	686	158	41	-1.2934	-1.2934	-0.0020	-0.7820	-2.0002

Table 4.2: This table showed the negative eigenvalues of the above characteristics equation as we did in theorem 2.4.1 and corollary 2.4.2 with different initial solutions at the endemic equilibrium for $R_{TB} > 1, R_H > 1$.

The following figures (4.16, 4.17, 4.18, 4.19, 4.20 and 4.21) showed the solutions of susceptible to either TB or HIV, infected individuals with drug-sensitive and drug-resistant to TB, infected with HIV, and infected with both HIV and TB at the endemic equilibria with different initial solutions and step-sizes h.



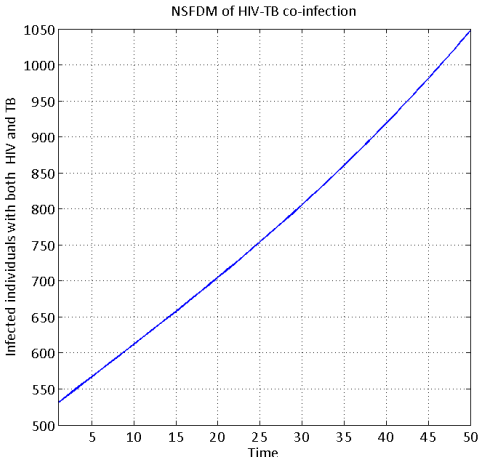
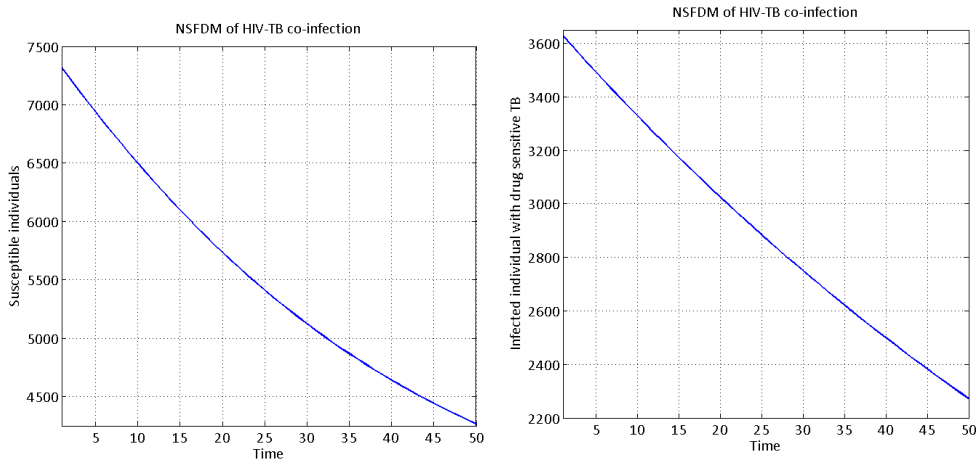


Figure 4.16: The first two figures in the above show, solutions of susceptible to either TB or HIV on the left side and infected individual with drug-sensitive TB on the right side. The second two figures that are in between the first two and the last one show the solutions of infected with drug-resistant TB and HIV on the left and the right sides, respectively. The last one shows the solution of infected with HIV and TB or infected with their co-infection with initial solutions $(S(0), i_s(0,0), I_r(0), I_H(0), I_{HTB}(0)) = ((8201, 4065, 5788, 1415, 531))$ and step sizes $h = 1.5$.



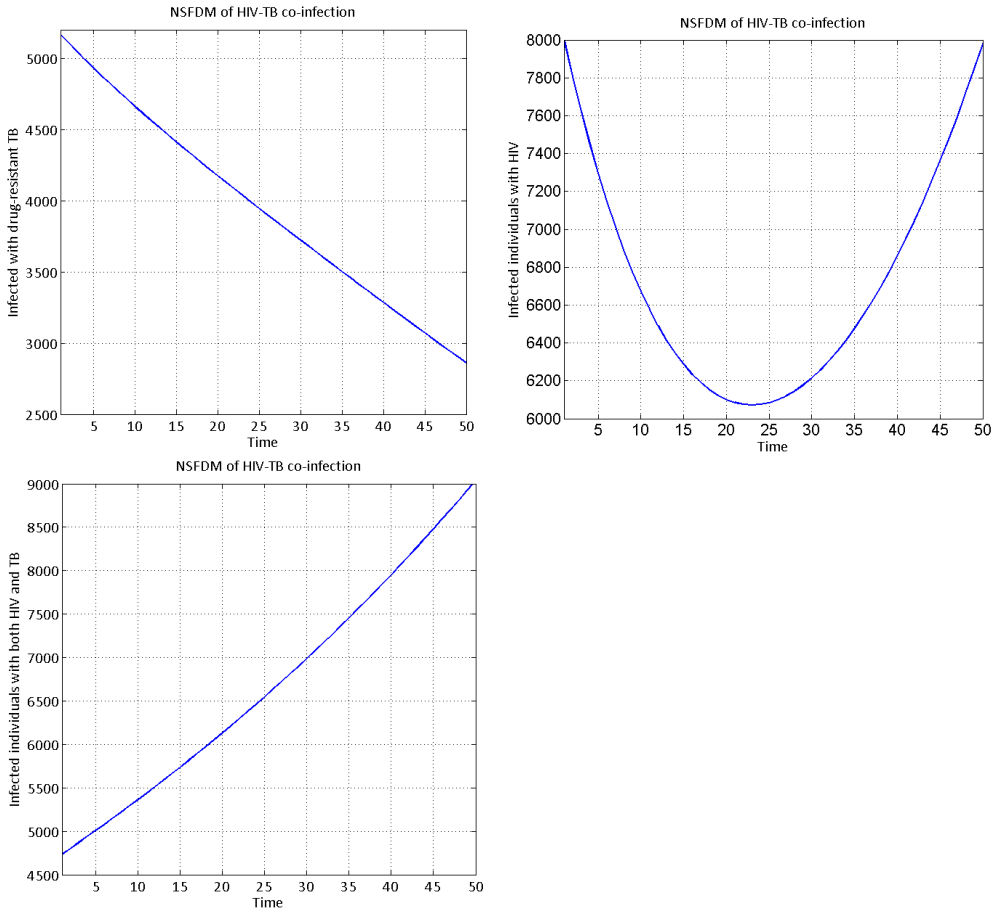
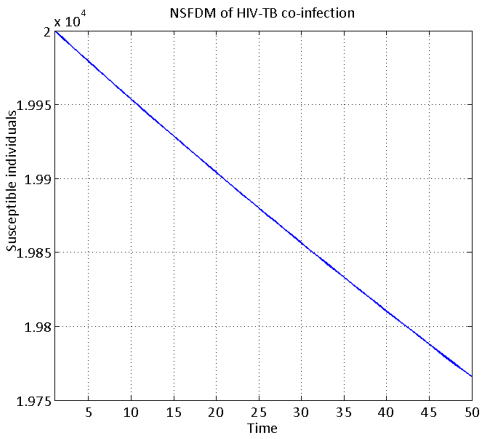
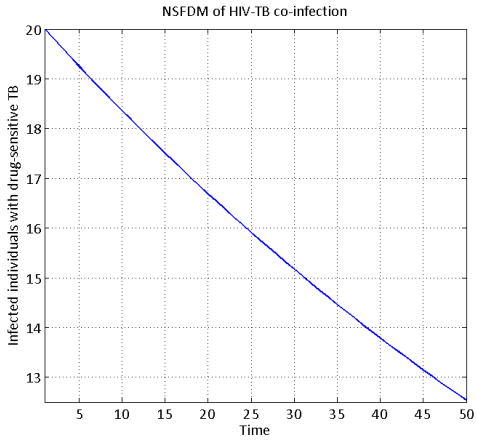
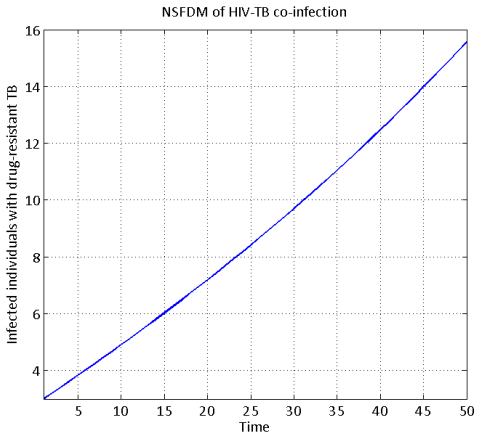
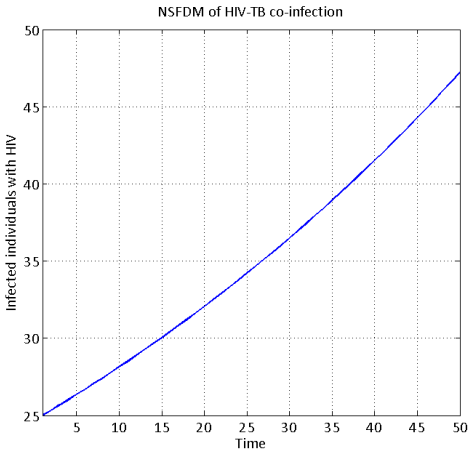


Figure 4.17: The first two figures in the above show, solutions of susceptible to either TB or HIV on the left side and infected individual with drug-sensitive TB on the right side. The second two figures that are in between the first two and the last one show the solutions of infected with drug-resistant TB and HIV on the left and the right sides, respectively. The last one shows the solution of infected with their co-infection) with initial solutions $(S(0), i_s(0,0), I_r(0), I_H(0), I_{HTB}(0)) = (7317, 3627, 30000, 8000, 4734)$ and at the step sizes $h = 0.8$.


NSFDM of HIV-TB co-infection
x 10^4
Susceptible individuals
Time


NSFDM of HIV-TB co-infection
Infected individuals with drug-sensitive TB
Time


NSFDM of HIV-TB co-infection
Infected individuals with drug-resistant TB
Time


NSFDM of HIV-TB co-infection
Infected individuals with HIV
Time

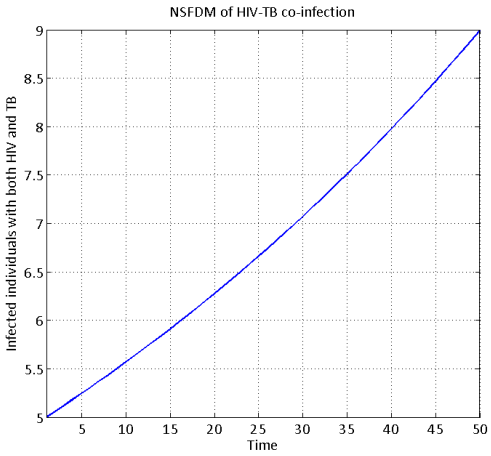
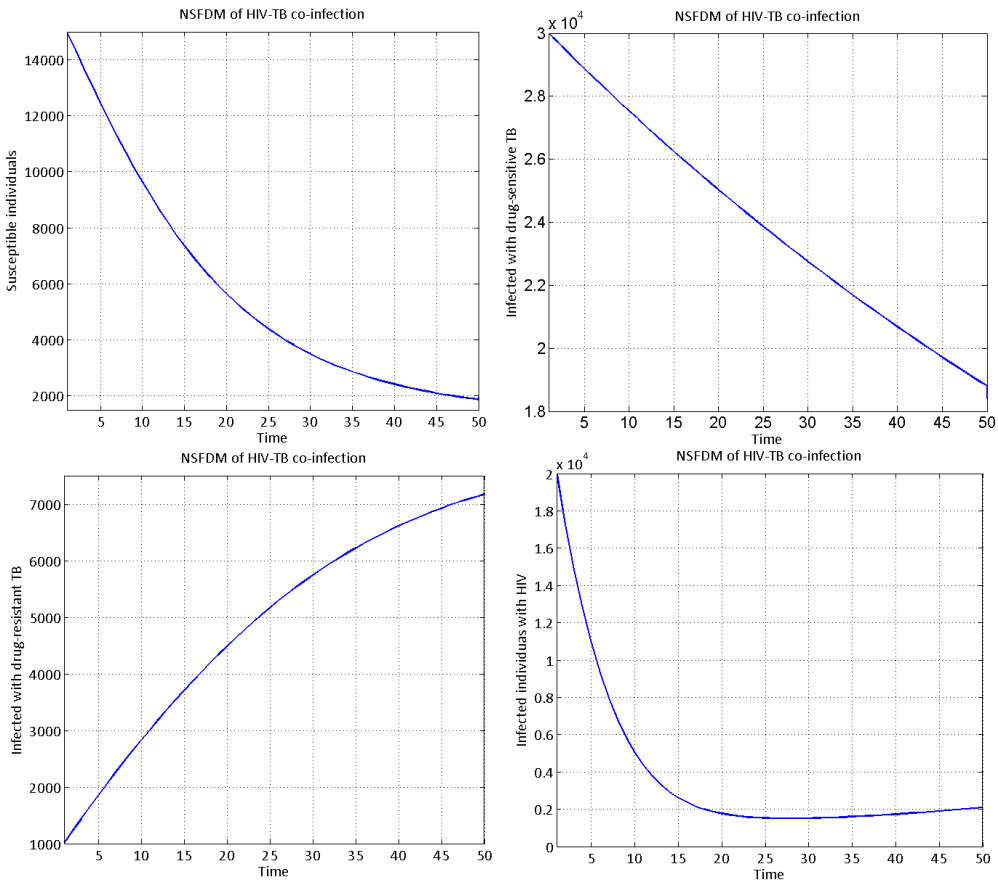

NSFDM of HIV-TB co-infection
Infected individuals with both HIV and TB
Time

Figure 4.18: The first two figures in the above showed, solution of susceptible to either TB or HIV on the left side and infected individual with drug-sensitive TB on the right side. The second two figures that are in between the first two and the last one show the solution of infected with drug-resistant TB and HIV on the left and the right sides, respectively. The last one shows the solution of infected with HIV and TB and with initial value $(S(0), i_s(0,0), I_r(0), I_H(0), I_{HTB}(0)) = (20000, 20, 3, 25, 5)$ and step sizes $h = 0.1$.



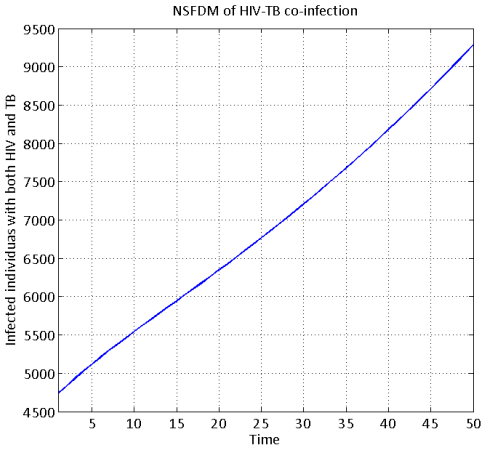
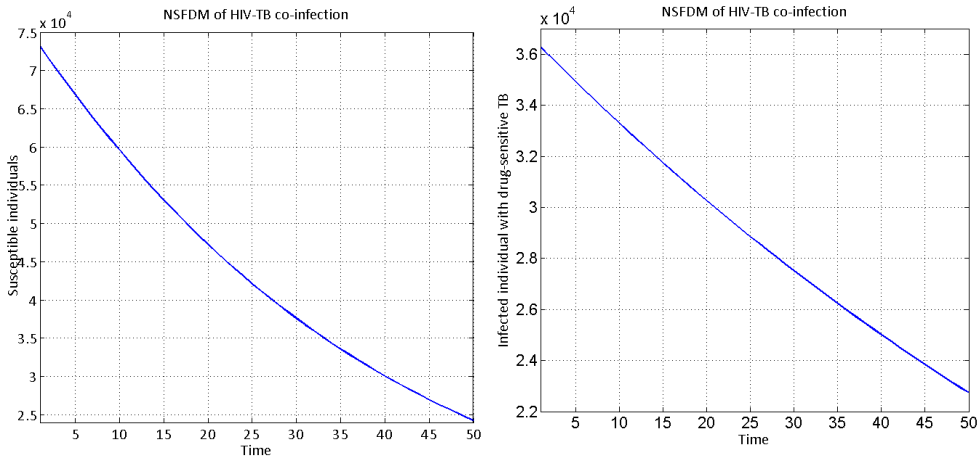


Figure 4.19: The first two figures in the above showed, solution of susceptible to either TB or HIV on the left side and infected individual with drug-sensitive TB on the right side. The second two figures that are in between the first two and the last one show the solution of infected with drug-resistant TB and HIV on the left and the right sides, respectively. But the last one shows the solution of infected with both HIV and TB. These are the solutions of the individuals with initial solution $(S(0), i_s(0,0), I_r(0), I_H(0), I_{HTB}(0)) = (1500, 30000, 1000, 20000, 4734)$ and step sizes $h = 8$.



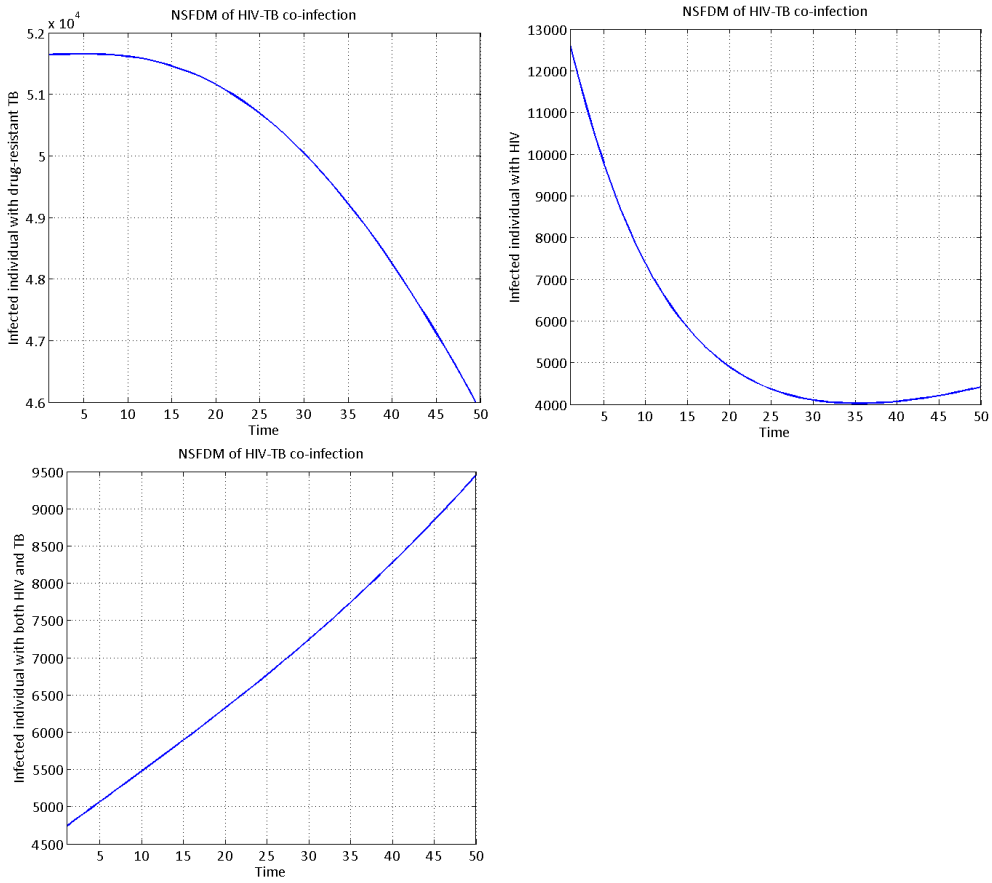
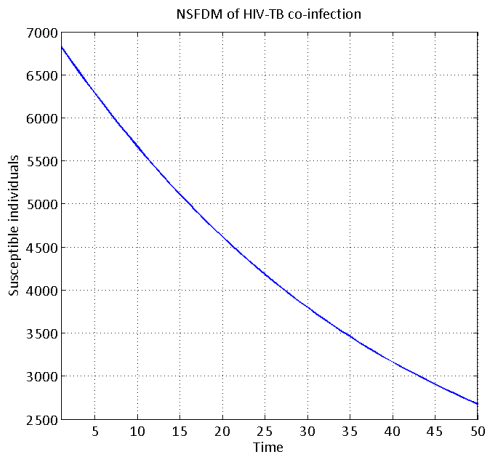
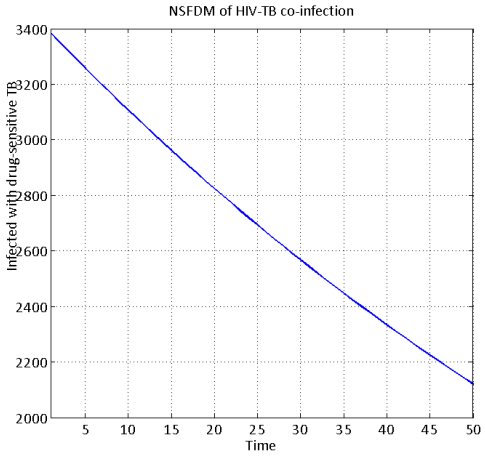
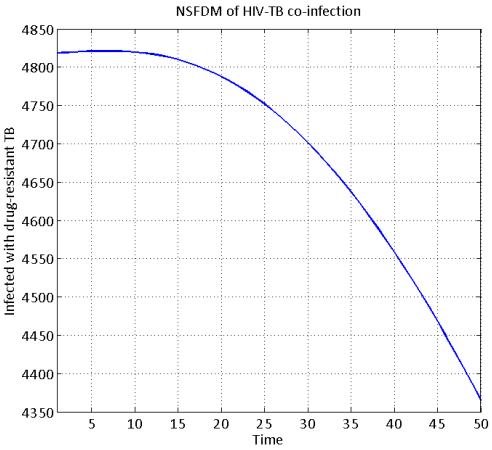
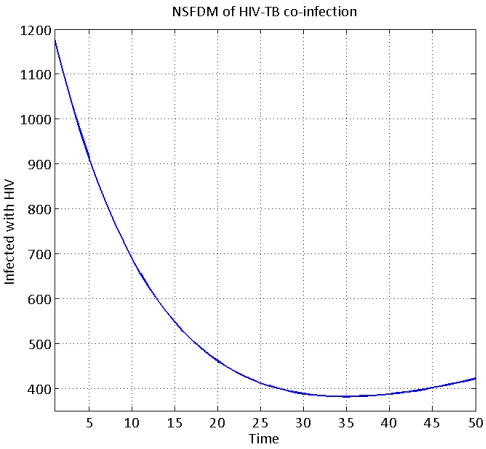


Figure 4.20: The first two figures in the above showed, solution of susceptible to either TB or HIV on the left side and infected individual with drug-sensitive TB on the right side. The second two figures that are in between the first two and the last one show the solution of infected with drug-resistant TB and HIV on the left and the right sides, respectively. The last one shows the solution of infected with HIV and TB. All of the solutions are with initial value $(S(0), i_s(0,0), I_r(0), I_H(0), I_{HTB}(0)) = (73171, 36277, 51640, 12623, 4734)$ and step sizes $h = 0.1$.


NSFDM of HIV-TB co-infection
Susceptible individuals
Time


NSFDM of HIV-TB co-infection
Infected with drug-sensitive TB
Time


NSFDM of HIV-TB co-infection
Infected with drug-resistant TB
Time


NSFDM of HIV-TB co-infection
Infected with HIV
Time

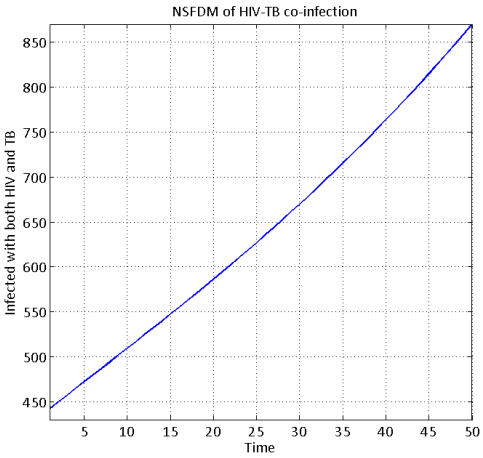

NSFDM of HIV-TB co-infection
Infected with both HIV and TB
Time

Figure 4.21: The first two figures in the above showed, solution of susceptible to either TB or HIV on the left side and infected individual with drug-sensitive TB on the right side. The second two figures that are in between the first two and the last one show the solution of infected with drug-resistant TB and HIV on the left and the right sides, respectively. The last one shows the solution of infected with HIV and TB (i.e infected with their co-infection). All of the solutions are with initial value $(S(0), i_s(0,0), I_r(0), I_H(0), I_{HTB}(0)) = (6827, 3385, 4818, 1178, 442)$ and step sizes $h = 0.05$.

Generally, we summarized the solutions of NSFDM for HIV only sub-model is locally asymptotically stable at the disease free equilibrium and unstable at the endemic equilibrium when $R_H < 1$. Otherwise it is vicev-ersa. It is equivalent to the stability and unstably of HIV model in (3.2.1). Similarly, the NSFDM formulated for TB only sub-model in this chapter has equivalent locally asymptotically stability property at the endemic equilibria and unstable at the disease free equilibrium when $R_{TB} > 1$, respectively as we computed for TB model in (2.2.1).

Lastly, the NSFDM of the full model of HIV-TB co-infection in (4.5.1) and (4.5.2) has the same stability and unstability property as we did in the HIV-TB co-infection model (3.3.1) in chapter 3. The solutions of the susceptible, infected with drug-sensitive and drug-resistant TB, infected with HIV, and infected with both HIV and TB individuals) in the above figures converge to the equilibria for different initial solutions at different step-size h. As we observed from the figures all above, particularly when h approaches to zero,the initial solutions more converges to their equilibria with the tolerance of susceptible, infected with drug-sensitive TB, infected with drug-resistant TB, infected with HIV and infected with both HIV and TB (their con-

fection) individuals are 2%, 1%,1%,7% and 2% respectively. Compared to the convergency of our model in chapter 2 and 3, the (NSFDM) numerical method developed in this thesis converges the solutions with less tolerance either to the disease free or the endemic equilibria as shown in all the figures throughout the chapters. In case of the positivity of its solution all the solutions were showing positive values. Therefore, the system in (3.3.1) and our NSFDM of the system (4.5.1) are locally asymptotically stable at the endemic equilibrium when $R > 1$. Otherwise it is unstable.

Chapter 5

Conclusion, recommendations and future work

In this thesis, we constructed and analyzed the nonstandard finite difference numerical method for HIV-TB co-infection with treatment model. Here first we studied the sub-models (HIV-only and TB-only) and then the full model HIV-TB co-infection.

In chapter 2, we developed and analyzed a mathematical model describing the dynamics of TB with age of infection. The model accounts for one-strain model at the age of infection with drug sensitive TB. By assuming the proportion of the sensitive strain, $p(\alpha)$ (which active at the infection age (α) that has of form $0 \leq p(\alpha) \leq 1$ which is neither negative nor increasing function. The drug resistant strain accounts active TB only. Drug-resistant and drug-sensitive strains are modeled, but only the age of the infection with drug-sensitive strain is considered. Since $i_s(\alpha, t)$ is a function of two independent continuous variables we have a PDE in the model which makes the model more complicated than the models based on ODE.

Chapter 3 investigated the above approach to study HIV sub-model and a co-

infection of HIV-TB model. In this chapter, the model developed in chapter 2 is combined with HIV model to formulate tuberculosis and a deterministic model of HIV and TB co-infection. In this section, we study the stability of the disease-free equilibrium, and the endemic equilibrium. To this end, the effects of TB treatment on the dynamics of HIV-TB co-infections were investigated.

In Chapter 4, at the first stage we constructed and analyzed robust numerical methods (NSFDMs) that solve TB sub-model with both strains in chapter 2 and HIV sub-model in chapter 3. At the second stage, we constructed the NSFDM that solve the HIV-TB co-infection model presented in chapter 3. The models we formulated the first two chapters were investigated using the NSFDM of numerical method developed in the chapter 4 in detail.

The solution of the HIV only sub-model, TB only sub-model and the full model of HIV-TB co-infection were transferred to the NSFDM in the fourth chapter, (the solutions of the susceptible, infected with drug-sensitive and drug-resistant TB, infected with HIV, and infected with both HIV and TB individuals) in the above figures converge to the equilibria for different initial solutions at different step-size h. In addition to this, the positivity of its solutions were also shown through the whole chapters which is coincide with epidemiological concepts of the positivity of human beings. The NSFDM more converges the initial solutions to their equilibria with tolerance of susceptible, infected with drug-sensitive TB, infected with drug-resistant TB, infected with HIV and infected with HIV-TB co-infection individuals are 2%, 1%,1%,7% and 2% respectively. Compared to the convergency of our model in chapters 2 and 3, the numerical method (NSFDM)developed in this thesis converges the solutions with less tolerance either to the disease free or the endemic equilibria as shown in all the figures considered.

Moreover, we computed the basic reproduction numbers for TB, R_{TB} and HIV, R_H and the overall reproduction number for the system $R = \max(R_H, R_{TB})$. After the computation was over according to the values of the overall basic reproduction number if $R < 1$ then the disease-free equilibrium is locally asymptotically stable and the endemic equilibria is asymptotically unstable respectively. Otherwise it is viceversa. The TB-only endemic equilibrium is locally asymptotically stable if $R_{TB} > 1$, and $R_H < 1$. However, the symmetric condition, $R_{TB} < 1$ and $R_H > 1$, does not necessarily guarantee the stability of the HIV-only equilibrium, but it is possible that TB can coexist with HIV when $R_H > 1$, due to the inactive (latent) existence of TB in the human beings, particularly the HIV-TB co-infection with TB treatment in Ethiopia.

Furthermore, the asymptotically stable and unstable properties of the models of TB only sub-model (2.2.1), HIV only sub-model (3.2.1) and the full model of HIV-TB co-infection (3.3.1) were equivalent to the NSFDM of TB only sub-model (4.4.1), the HIV only sub-model (4.3.1) and the NSFDM of the full model of HIV-TB co-infection (4.5.1), respectively.

The method developed in this thesis works for first order mixed ODE and PDE as we observed in our model. Hence some of the scope our future research become the order of convergence of the method, the applicability of the method for second and above order ODE and PDE of epidemiological models.

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