Deterministic Mathematical Modelling of Tuberculosis and HIV Diseases

A Thesis

Submitted in Fulfillment of the Requirements

for the Award of the Degree of

DOCTOR OF PHILOSOPHY

in

MATHEMATICS

by

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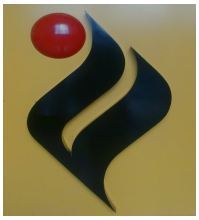

SCHOOL OF MATHEMATICS AND COMPUTER APPLICATIONS

THAPAR UNIVERSITY

PATIALA-147004, PUNJAB, INDIA

OCTOBER, 2014

CERTIFICATE

This is to certify that the thesis entitled **" Deterministic Mathematical Modelling of Tuberculosis and HIV Diseases"**, submitted by Ms. Navjot Kaur, in fulfillment of the requirements for the award of the degree of Doctor of Philosophy in the School of Mathematics and Computer Applications, Thapar University, Patiala, is a record of candidate's own research work carried out by her under our supervision and guidance. The matter presented in this thesis has not been submitted in part or full to any other University or Institute for the award of any degree.

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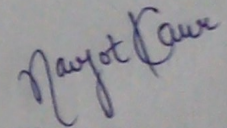
DECLARATION

I hereby declare that this thesis entitled, "Deterministic Mathematical Modelling of Tuberculosis and HIV Diseases", is an original work done by me for the award of the degree of Doctor of Philosophy in Mathematics. I also declare that this thesis or any part of it has not been submitted by me for the award of any degree, diploma, title or recognition and that the references cited herein have been duly acknowledged.



(**Navjot Kaur**)

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Dedicated

To

My Parents

To my supervisors ...

Gur bin ghor andhar guru bin samajh na avai
Gur bin surat na sidh guru bin mukat na pavai.

Acknowledgments

Bow the Almighty; who is the cause and end!

I would like to thank Almighty for all the blessings that he has shower on me, including the opportunity to start and complete this phase and making my life more bountiful.

I express sincere gratitude to my supervisor Dr. Mini Ghosh, Associate Professor, School of Advanced Sciences, VIT University, Chennai, who introduced me to the field of mathematical modeling. She closely monitored my progress, provided me with prompt and insightful feedback, and gently pushed me towards meeting self-imposed deadlines. I express my deep sense of gratitude to my supervisor and Dr. Rajiv Sharma, for their generous support, hospitality, care and guidance during my visits and stay at Chennai.

I feel privileged to express deepest gratitude to my supervisor Dr. S.S. Bhatia, Professor and Former Head, School of Mathematics and Computer Applications, Thapar University, Patiala who has been a constant source of knowledge and inspiration. I am extremely indebted to him for providing time to listen and give his valuable comments and suggestions.

I extend my thanks to Prof. Prakash Gopalan, Director, Thapar University for providing necessary infrastructure and resources to accomplish my research work. My gratitude is extended to Dr. P.K. Bajpai, Dean of Research and Sponsored Projects for his support and needful help during the various stages of my research work.

I express my sincere thanks to Dr. Rajesh Kumar (Head of School of Mathematics

and Computer Applications, Thapar University, Patiala), Dr. A. K. Lal, Dr. Maninder Kaur, Dr. Jatindeerdeep Kaur and Dr. Kulvir Singh (School of Physics and Materials Science) for their unequivocal support and suggestions. I thank all the staff members of School of Mathematics and Computer Applications, Thapar University for their support and cooperation.

I am grateful to the Doctoral committee comprising Dr. Rajesh Kumar Gupta and Dr. Manoj Kumar Sharma (School of Physics and Materials Science) for monitoring the progress and providing valuable suggestions for improvement of this work.

I owe my thanks to Dr. Gurdarshan Singh, Professor (Retd.), Khalsa College, Patiala whose encouraging and stimulating words have always inspired me to 'aspire and excel'.

My sincere thanks to Dr. Deepti Gupta, Professor, Department of English and Cultural Studies, Panjab University, Chandigarh for carefully reading my thesis and giving insightful comments.

I express heartily thanks to my friends Priya Shahi, Rashmi Sachdeva, Karamjeet Kaur and other research fellows of my department for helping me in various matters. I also convey my thanks to Mr. Pardeep Kumar Singla, Mr. Abhikash, Mr. Magdoom and Mr. Harish for their cooperation during this period.

Words are inadequate in paying regards to my dear father and mother for their blessings, continuous encouragement and patience. I am thankful to them for introducing me to the wonderful world of research. Their endless efforts have made a great contribution to all my successful endeavors in life. I express my deep gratitude to my sister Manjot and brother Jaideep, whose love, care and support have been an invaluable source of encouragement to me.

Navjot Kaur

October, 2014.

Abstract

The main objective of mathematical modelling of infectious diseases is to identify and study the factors that influence the spread of disease and to predict the future dynamics of a particular disease or combination of diseases. Among all the prevailing infectious diseases in the world, the Acquired Immunodeficiency Syndrome (AIDS) is the most serious life threatening condition caused by infection with the Human Immunodeficiency Virus (HIV) for which there is no cure available at present. Tuberculosis (TB) is a common, and in many cases fatal, infectious disease caused by various strains of myco-bacteria, usually Mycobacterium Tuberculosis. This thesis focuses on the use of deterministic mathematical models and their analysis to gain qualitatively as well as quantitatively meaningful insight into the transmission dynamics of HIV, TB and HIV-TB co-infection. The thesis is divided into seven chapters.

Chapter 1 starts with a brief history of the spread of infectious diseases in the human population. Then, an overview of the epidemiological mathematical models and their role in the study of transmission dynamics of epidemics is given. After that a brief account of related mathematical models of HIV, TB and HIV-TB co-infection by various authors from the recent literature is reported. Later, some basic epidemiological and mathematical preliminaries and methodologies required in the analysis of the mathematical models discussed in subsequent chapters have been reported.

Chapter 2 examines the role of awareness and screening of infective individuals in the transmission of the HIV/AIDS infection. A deterministic nonlinear model for the HIV/AIDS is formulated and investigated by considering only the sexually-active population. The basic reproduction number (R_0) and different equilibria of the model are computed and stability of these equilibria are discussed in detail. Primarily, the study emphasizes the need of mass awareness programs and screening centers to provide better counseling to the infectives who continue to participate in the transmission of the virus.

Chapter 3, presents a nonlinear model for HIV/AIDS by incorporating the role of female sex-workers in the transmission of HIV/AIDS. It has been observed that the female sex-workers is a core group responsible for the transmission of HIV/AIDS epidemic among sex-workers, their clients and partners. Further, it has been shown that the global dynamics of the model are completely determined by the basic reproduction number R_0. The presented analysis supports the need for preventive and curative services to guide and empower female sex workers so that they adopt healthier sex behavior which can reduce their risk of HIV infection.

Chapter 4 investigates a stage-structured HIV/AIDS model. The whole population under consideration is subdivided into eight compartments incorporating three different stages: children, adult and old population. The presented model exhibits two equilibria: disease- free equilibrium (DFE) and endemic equilibrium (EE). The stability of these equilibria is discussed and numerical simulation is performed to investigate the role of awareness in reducing the infection prevalence of HIV/AIDS in the population.

Chapter 5 deals with the role of screening and treatment in the transmission of TB disease. The equilibria and threshold of the model are obtained. The stability of different equilibria is also discussed. We observe that this model shows backward bifurcation, i.e. in this case $R_0 < 1$ is not sufficient to eliminate the disease from the population. One needs to lower R_0 much below one to make the disease free equilibrium to be stable.

Chapter 6, presents a HIV/AIDS-TB co-infection model with treatment and screening of HIV infectives by considering simple mass action type incidence. It is observed that the system always tends either to TB-only equilibrium point or to HIV-only equilibrium point provided the corresponding reproduction number is greater than one. The co-infection equilibrium point is always unstable whenever it exists. From the analysis we observe that a strong co-ordination, between the national TB and the AIDS control programs is required for effective management of HIV-TB patients and to further lower the count of dual infections.

Chapter 7 deals with a non-linear mathematical model to study the transmission dynamics of the HIV-TB co-infection by considering standard incidence. Here too, the roles of screening and treatment are taken into account. The non-negative equilibria of the model are computed and the stability of these equilibria is discussed in detail. Our results reported in this chapter clearly indicate that a proper screening and counseling can check the spread of HIV and TB diseases and effective control strategies need to be formulated around screening with proper counseling.

Towards the end, the future directions in this research area are outlined. The relevant references are listed in Bibliography.

Research Publications

Published/Accepted Papers in Referred Journals

1. Navjot Kaur, Mini Ghosh and S. S. Bhatia, "Modeling the Spread of HIV in a Stage Structured Population: Effect of Awareness", **International Journal of Biomathematics**, 5(5) 2012. **(SCI) Impact Factor: 0.633.**

2. Navjot Kaur, Mini Ghosh and S. S. Bhatia, "Mathematical Analysis of the Transmission Dynamics of HIV/AIDS: Role of Female Sex Workers", **Applied Mathematics & Information Sciences**, 8(5) 2014, 2491–2501. **(SCI) Impact Factor: 0.731.**

3. Navjot Kaur, Mini Ghosh and S. S. Bhatia, "The Role of Screening and Treatment in the Transmission Dynamics of HIV/AIDS and Tuberculosis Co-infection: A Mathematical Study", **Journal of Biological Physics**, 40(2) (2014), 139–166. **(SCI) Impact Factor: 1.152.**

4. Navjot Kaur, Mini Ghosh and S. S. Bhatia, "HIV-TB Co-infection: A Simple Mathematical Model", **Journal of Advanced Research in Dynamical and Control Systems** (Accepted).

Communicated Papers

1. Navjot Kaur, Mini Ghosh and S. S. Bhatia, "Analysis of a Simple TB Model with Exogenous Reinfection and Case Detection", **Model Assisted Statistics and Applications** (Under Minor Revision).

2. Navjot Kaur, Mini Ghosh and S. S. Bhatia, "Role of Awareness and Screening of Infectives in the Transmission Dynamics of HIV: A Simple Mathematical Model", submitted to **Differential Equations and Dynamical System**.

3. Navjot Kaur, Mini Ghosh and S. S. Bhatia, "Mathematical Modelling of HIV/AIDS and Tuberculosis Co-infection: Effect of Screening and Treatment", submitted to **Journal of Biological Systems**. **(SCI)**

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Nomenclature

1.	HIV	Human Immunodeficiency Virus
2.	AIDS	Acquired Immune Deficiency Syndrome
3.	MTB	Mycobacterium Tuberculosis
4.	DOTS	Directly Observed Treatment, Short-course
5.	HAART	Highly Active Antiretroviral Therapy
6.	ARV	Antiretroviral
7.	MCTC	Mother to Child Transmission
8.	STD	Sexually Transmitted Disease
9.	STI	Sexually Transmitted Infection
10.	WHO	World health organization
11.	CDC	Centers for Disease Control and Prevention
12.	NIH	National Institutes of Health
13.	NTP	National Tuberculosis Control Programme
14.	UNAIDS	Joint United Nations Programme on HIV/AIDS

Chapter 1

Introduction

1.1 General introduction

The spread and control of infectious diseases such as swine flu, dengue, Human Immunodeficiency Virus (HIV), Tuberculosis (TB), childhood infections, influenza, and vector borne diseases in the human population is an issue of serious concern. Despite many advances made in scientific and medical practice, the figure associated with the mortality rate of the human population due to infectious diseases is significantly large. This is leading to the financial downturn and affecting the demographic dividend of most developing nations. When we look back at history (430-428 BC), the plague of Athens is considered the first major epidemic of recorded history. After that the Black Death devastated Europe four-times and between 1346-1350, millions of people died due to Bubonic Plague (Black Death). The Black Death virus widened its grip on the population after the end of the epidemic outbreak and re-appeared in Britain (Plague of London) in 1665 [22].

In the sixteenth century, another serious epidemic of smallpox plague attacked the Aztecs and killed around 35 million people. An influenza pandemic occurred after the First World War and caused the death of around 20 million people. The twenty-first century has witnessed great outbreaks of epidemics: 1905-1906 the Bombay plague, 2003, Severe Acute Respiratory Syndrome (SARS) in China, Tiawan and Singapore, etc.

In broader terms, infectious diseases can be classified into two categories: micro-parasitic diseases (those caused by virus and bacteria) and macro-parasitic diseases (those caused by worms) [22; 64]. The present work focuses on two micro-parasitic diseases: HIV and TB. HIV is a viral infection whereas TB is bacterial. The main aim of this thesis is to understand and analyze the transmission dynamics of these two diseases using mathematical models.

1.1.1 Mathematical modelling

Mathematical modeling is the translation of real world physical problem into mathematical problem(s) using abstract symbols, parameters and expressions, then solving and analyzing the mathematical problems and interpreting these solutions as per real world situations, data and language. Mathematical models are extensively used for planning, implementing, evaluating, comparing and further optimizing various findings and control strategies.

As per Kapur [99], the power of the mathematical model lies in the fact that with the mathematical model "we soar high into the mathematical atmosphere along with the problem, fly high into the mathematical atmosphere along with the problem, fly there for some time and come down to the earth with possible solution". In this context, the mathematics for modeling is motivated by the real world problems around us. Generally, the mathematical models can be classified as linear or non-linear, static or dynamic, deterministic or stochastic and discrete or continuous and these classifications are determined by the nature of the problem. In the formulation of a model, compatibility between the feasibility and reality of the problem is essential and another important part is to identify the state variables and to specify the relationships amongst them. An efficient and appropriate model includes well-defined agreement between predictions and observations for arriving at a valid conclusion. A wisely formulated and analyzed model tries to give

a relationship between the assumed mechanism at the individual level and the resulting phenomenon at the population level.

In the modern scientific and technical world, mathematical models are extensively used across physical, biological and social sciences with applications in ecology and epidemiology to examine population fluctuations, spread of pollutants, water catchments, erosion, spread and effect of epidemics and a lot more. In formulating a model, different modeling approaches can be used, such as empirical models, stochastic models, simulation models, deterministic and statistical models depending on the nature of the problem. Moreover, in some problems a combination of different approaches is used to better understand the problem and it can lead to more significant outcomes.

1.1.2 Epidemiological preliminaries

Epidemic : An epidemic is an unusually large widespread outbreak of the disease.

Agent : Pathogens that is a microparasite which causes disease e.g. a virus, bacterium.

Vector: An organism capable of transferring the infectious agent from one host to another.

Contact rate: The rate at which individuals in a population interact in a way that can potentially transmit an infection.

Asymptomatic: The individual who does not show symptoms of the disease.

Susceptible: Those individuals who can incur the disease but are not yet infective. The class of susceptible individuals is usually denoted by 'S'.

Exposed: A member of the host population is classified as exposed if it has been infected, but is not yet infectious. The exposed class is the collection of such individuals and is usually denoted by 'E'.

Infected: A member of the host population is classified as infected if it carries the disease and is infectious that means it transmits the disease to others. The class containing

infective individuals is usually denoted by 'I'.

Recovered or Removed: A member of the host population is classified as removed if it is unable to take part in the transmission of infection, either it is no longer infectious and has become temporarily immune, or it has been isolated or is dead. The class of recovered individuals is usually denoted by 'R'.

Latent period: The latent period is the time in which an individual is infected but is not yet infectious, e.g. for Chickenpox 15 days, Measles 10 days, Influenza 2 days.

Incubation period: The time between the infection and appearance of symptoms of a disease is called the incubation period.

Infectious period: The time period during which infectives are able to transmit an infection to any susceptible host or vector they contact.

Basic reproduction number: In epidemiology, the basic reproduction number (sometimes called reproduction number or basic reproductive rate) of an infection is the mean number of secondary cases that an infected individual will generate in the population with no immunity to the disease in the absence of interventions to control the infection [61]. It is oftenly denoted by 'R_0'. This metric is very useful as it helps to determine whether an infectious disease will spread through a population or not. In general if $R_0 < 1$, then on an average an infected individual produces less than one new infection over the course of its infectious period, and the infection cannot grow. On the other hand, if $R_0 > 1$, then each infected individual produces, on an average, more than one new infection and the disease can invade the population.

Deterministic model: A model is said to be deterministic if its entire future course and its entire past are uniquely determined by its state at present instant of time.

Stochastic model: A model in which random events are explicitly accounted for.

Epidemic models: Hethcote [82], has introduced three basic types of deterministic epidemiological models for infectious diseases. Mainly, there are eight possible compartment models SI, SIS, SEI, SEIS, SIR, SIRS, SEIR and SEIRS that are widely used to describe the dynamics of infectious diseases. Apart from these, there are a number of

possibilities in choosing a compartment structure. Additionally, there are many possible forms of the incidence, waiting times in the compartments, demographic structures and epidemiological-demographic interactions. Now, SIS, SIR and SIRS epidemic models are briefly defined.

SIS model:

In an SIS epidemiological model, the total population under consideration is divided into only two disjoint classes: Susceptible (S) and infectives (I). This model is for the diseases for which infection does not confer immunity. It is called the SIS model since in this case individuals from susceptible class move to the infected class and then back to susceptible class upon recovery e.g. influenza, and malaria, etc.

SIR model:

In an SIR epidemiological model, the total population under consideration is divided into three disjoint classes: Susceptible (S), infectives (I) and recovered (R). This epidemic model is useful for the representation of diseases which give permanent immunity. In this case individuals from the susceptible class move to the infected class and then from the infected class they move to the recovered class upon recovery. This model is useful for many infectious diseases including measles, mumps, and rubella.

SIRS model:

This epidemic model is used to describe the dynamics of diseases which give temporary immunity. Here, the total population is divided into three disjoint classes: Susceptible (S), infectives (I) and recovered (R). In this case, individuals move from susceptible to infected, then infected class to recovered class and then again from recovered class to susceptible class after losing their immunity (for more details see [60; 99; 111] and [122]).

1.1.3 Parameters that influence epidemic spread

In order to compare the relative usefulness of modelling approaches, a set of standard criteria is examined. The criteria is based on the following factors that affect epidemic

spread:

- Susceptible population size
- Mode of transmission
- Homogeneity of population density
- Infection transmissibility
- Immunity levels of individuals
- Movement of individuals
- Infection incubation time
- Environmental/demographic factors
- Geographic and economic factors
- Infectious period

1.2 Epidemiology and dynamics of infectious diseases

The mathematical epidemiology has contributed immensely to understanding the behavior of infectious diseases, their impact and possible future prediction about their spread and control. The dynamics of infectious diseases in humans represents one of the oldest and richest domains of mathematical biology. From the classical work of Hamer [79] and Ross [148] to the series of more modern developments associated with Anderson and May [17], Dietz [62], Hethcote [80; 83], Castillo-Chavez [52] and others, the subject has grown exponentially both in volume and in significance. The epidemiology is a study of cause, distribution, determinants of health-related conditions in the population, with the

objective to trace factors that are responsible for their occurrence and the application of this study to the control and prevention of health problems, [107].

Possibly, the first known epidemiological model (for smallpox) was published by Bernoulli [34] in the year 1760. Later in 1906, Hamer [79] formulated a discrete-time deterministic epidemic model by using the mass-action principle for the spread of measles and hence, the modern mathematical biology was initiated by degrees and step by step with the works of Bernoulli [34] and Hamer [79]. In 1911, Ross [148] used a differential equation based epidemic model to describe the transmission dynamics of malaria between human beings and mosquitoes. Through his work, he determined that there exists a threshold of the size of mosquitoes below which malaria transmission can be controlled. At that time, it was an outstanding contribution in the research of transmission dynamics of malaria and for his other contributions along with this, he was awarded the Noble Prize (1902) in medicine.

Kermack and McKendrick [100] formulated a well recognized 'Susceptible Infective-Recovered (SIR)' compartmental model to study the outbreak of Black Death in London and of plague in Mumbai in 1906. Later, in 1932 they formulated a 'Susceptible Infective-Susceptible (SIS)' model and on the basis of investigations through this model, they introduced the concept of thresholds that determines whether the disease will persist or will be eradicated from the population. These findings established the fundamentals of the theory of epidemics. Intensive studies on epidemics, in the middle of the twentieth century, have resulted in useful outcomes. In the literature on infectious diseases, a remarkable publication is the book by Bailey (see [28]).

A detailed account of the modeling and analysis of epidemic diseases can be found in literature in the form of lecture notes, monograph and research papers, etc. ([30; 80; 84; 172]). The research on the study of infectious diseases using deterministic mathematical models was pioneered in the twentieth century. Since then, a number of mathematical models have been formulated and studied for diseases such as smallpox, malaria, AIDS,

SARS, measles, rubella, cholera, whooping cough, diphtheria, gonorrhea, syphilis, and tuberculosis. The population biology of infectious diseases has been investigated by Anderson and May [23]. The widespread occurrence and increasing incidence of various infectious diseases have become a major public health problem in most tropical nations and elsewhere ([28; 29; 30]). In general, the spread of such diseases in the human population depends upon various factors such as the number of infectives, susceptibles, modes of transmission (carriers, vectors), social, cultural and economic factors, environmental, ecological and geographical conditions [72].

An account of the modeling and study of epidemic diseases can be found in Waltman [172]. The effect of demography, social factors, environmental factors as well as migration from one region to another also play an important role in the transmission of an infectious disease and some of these factors have been incorporated by Ghosh in [71]. Many infectious diseases are spread through the environment and are transmitted to the human population by carriers, insects or other vectors. Some of the infectious diseases are transmitted both ways, i.e. directly as well as indirectly. In direct transmission, the susceptibles get contaminated with bacteria by infectives through meeting or mixing, on the other hand, in indirect transmission bacteria enters the environment and gets into contact with susceptibles; (for more details see [74; 80]). At present, several mathematical models [46; 63; 150; 157; 176; 178] are available to study the dynamic nature of epidemics and although these models have deterministic characteristics, still they have been widely used by incorporating various factors like migration, vaccination and its gradual loss, chemotherapy, quarantine, passive immunity, genetic heterogeneity and non-uniform distribution of population, etc.

1.3 Epidemiology of Human Immunodeficiency Virus (HIV)

1.3.1 History

HIV is one of the leading infectious diseases in the world, claiming more than 60 million infections and more than 25 million lives over the past three decades. The history of HIV is very complex. The 'Acquired Immunodeficiency Syndrome (AIDS)' was first documented on June 5, 1981, in the 'Morbidity and Mortality Weekly Report (MMWR)', published by the 'Centers for Disease Control and Prevention (CDC)', when they described the 'Pneumocysis carinii (now named as P. jiroveci)' pneumonia in 5 homosexual men in Los Angeles, California, USA. Then in 1984, the American biomedical scientist Robert Charles Gallo co-invented HIV as the cause of AIDS. The HIV virus acts as the causative agent of AIDS and it was discovered by the French scientists Francoise Barr-Sinoussi and Luc Montagnier in year 1983 for which they received the Nobel Prize for Medicine in 2008 [58].

In 1985, a serologic test for HIV became commercially available but the availability of a diagnostic test was the closing feature of these early years. The most critical feature of HIV is that once an individual gets infected with this virus he/she remains infected with it for the entire lifetime. It has been reported that the prolonged period between the HIV infection and symptomatic AIDS (approximately 11 years in case of adults), was the reason of widespread transmission of HIV transmission before the recognition of this disease and any preventive efforts to reduce its spread, [58]. By the end of the year 1986, 85 countries had reported 38,401 cases of AIDS to the World Health Organization (WHO). In terms of region these figures were : Africa - 2,323; Americas - 31,741; Asia-84; Europe - 3,858; and Oceania - 395. There were approximately 34 [31.4-35.9] million people living with HIV in 2011. The African and American continents make nearly half

of new HIV infections every year and approximately 60% of people living with HIV are in the sub-Saharan Africa. According to the WHO fact sheet 2011, among 34 million HIV infectives nearly half are women. It is observed that most of the cases have occurred among sexually active persons aged between 20-49 years. Children under 15 make up less than 3% of the reported cases. In 2012, UNAIDS [2] reports in a global summary of the AIDS epidemic estimated that 35.3 million [32.2 million -38.8 million] people are living with HIV. Among which, 32.1 million [29.1 million - 35.3 million] are adults and 17.7 million [16.4 million - 19.3 million] are women. The AIDS epidemic has had a discrete impact on women, which has been exacerbated by their role within society and their biological vulnerability to HIV infection. Biologically, women are twice more likely to become infected with HIV through unprotected heterosexual intercourse than men.

India has a population of one billion plus and still growing and around half of this population is adult in the sexually active age group. In 1986 the first AIDS case was detected in India and since then, HIV infections have been reported in all the Indian states. The concentration of the HIV/AIDS problem is highest in Maharastra with the rate above two percent, followed by Tamil Nadu, Andhra Pradesh, Karnataka and Manipur where it ranges between one to two percent.

1.3.2 Consequences

HIV targets the immune system and weakens people's surveillance and defense system against importunate/portunate infections and some types of cancer. As the virus destroys and weakens the function of immune cells, infected individuals gradually become immune-deficient. This immunodeficiency results in increased susceptibility to a wide range of infections and diseases that people with healthy immune systems can fight off in a normal manner. The most advanced stage of HIV infection is AIDS which can take 10-15 years to develop. This stage of HIV infection is defined by the development of certain cancers,

infections or other severe clinical manifestations [1].

HIV/AIDS pandemic plays a crucial role in the resurgence of TB and has become a treat to human population, worldwide. It increases the vulnerability of the infected individuals to a number of infectious agents like mycobacterium, the causative agent responsible for TB [102; 155]. The infection states of HIV are described based upon the corresponding $CD4^+$ cell. The HIV infected individual are assumed to progress through various stages: acute infection stage (asymptomatic) if $CD4^+$ count is greater than 500 cells/mm^3; clinical latency stage (symptomatic) if $CD4^+$ count ranges between 200-499 cells/mm^3 and AIDS indicator condition if $CD4^+$ count is less than 200 cells/mm^3. An HIV infected patient can become aware of his/her HIV status at each infection state through testing and that can be linked to care.

1.3.3 Transmission

HIV usually has a high degree of variability because the virus mutates rapidly. The HIV infection can be diagnosed through blood tests that detect the presence or absence of antibodies and antigens. HIV can be transmitted via unprotected sex and close contact with a variety of body fluids of infected individuals, such as blood, breast milk, semen and vaginal secretion. Individuals cannot become infected through ordinary day-to-day contact such as kissing, hugging, shaking hands or sharing personal objects, meal. Hence, HIV is mainly transmitted through:

(i) Unprotected anal or vaginal sex with an HIV- infected partner;

(ii) Mother-to-child transmission during pregnancy, childbirth, or breastfeeding;

(iii) Transfusion with HIV-infected blood products;

(iv) Sharing of contaminated injection equipment, tattooing, skin-piercing tools and surgical equipment.

1.3.4 Treatment

At present, no cure has been found for the HIV infection but with effective treatment with 'Anti-retroviral (ARV)' drugs, patients can control the virus. HIV growth can be suppressed by 'Anti-Retroviral Therapy (ART)' consisting of the combination of three or more ARV drugs. These drugs can not kill the virus, i.e. ART cannot cure HIV infection but only controls its growth by slowing down viral replication within a person's body and thus allows an individual's immune system to strengthen and regain the power to fight off infection and other health related issues. With proper ART, people living with HIV can live relatively healthier and productive lives as compared to the HIV positive individuals without any treatment. Currently, around thirty-two medications have been approved by the U.S. government to fight HIV and AIDS, with many more in the developmental phase. The HIV/AIDS medications fall into several groups or 'classes'. A treatment regimen consists of drugs from different classes to maximize the effectiveness against HIV. Each class attacks HIV in a slightly different manner and has diverse risks and advantages. In 2011, more than 8 million people living with HIV were receiving antiretroviral therapy in low and middle-income countries, but another 7 million people need to be enrolled in treatment to meet the target of providing ART to 15 million people by 2015. As per the WHO report, more than 9.7 million people living with HIV received antiretroviral therapy (ART) in low- and middle-income countries in 2012, [4].

Since currently no cure exists for the HIV disease, only prevention is effective in controlling its spread amongst the population. The detection of HIV infection and subsequent counseling can be treated as a control measure. Various practices and initiatives have been conducted by health organizations such as World Health Organization (WHO), the Joint United Nations Programme on HIV/AIDS (UNAIDS), the U.S. National Institutes of Health (NIH) to disseminate awareness regarding the available prevention and control measures. In India, HIV counseling and testing services were started in 1997. Currently, there are a number of centres : 'Integrated Counseling and Testing Center

(ICTCs)'/'Prevention of Parent to Child Transmission (PPTCTs)', 'Surveillance Centres under NACO (National AIDS Control Organization)' that are actively working in screening and providing counseling to HIV infectives. The Government of India has opened many 'Anti-retroviral Therapy (ART)' centers to provide anti-retroviral therapy to the HIV/AIDS patients in the country. In addition to this several NGO's such as 'The Naz Foundation (India)', 'Desire Society', and 'SAATHII' are working towards bringing better awareness and knowledge regarding HIV, AIDS and TB in the Indian population.

1.4 Epidemiology of Tuberculosis (TB)

1.4.1 History

Tuberculosis (TB) is an infectious disease which has been severely affecting the human population for several decades. TB is a bacterial infection, primarily in the lungs (a pneumonia) and is caused by Mycobacterium tuberculosis (also called tubercle bacilli). It was first discovered in 1882 by a German physician, Robert Koch. He was awarded the Nobel Prize for Medicine in 1905 for his work and findings on tuberculosis. TB is observed as second only to HIV/AIDS as the largest killer worldwide. The first effective anti-TB antibiotic 'Para-Amino-Salicylic (PAS)' was discovered by Lehman in 1946. Thereafter, in 1952, an effective drug 'Isoniazid' was used to treat TB patients in New York, USA. Now a days, a combination of several drugs is used to treat patients with active TB and has proved to be helpful in controlling the disease significantly if it is supervised and completed adequately thorough the required duration of treatment course. Approximately one-third of the world population is infected with TB. TB accounts for more than one-quarter of all preventable adult deaths in developing countries. The rate of progression from TB infection to TB disease varies substantially. Around 10% of mycobacterium TB infected individuals are thought to develop noticeable clinical disease and about half

of them develop disease more than two years after infection; these cases are commonly named reactivation or post-primary TB. It has been declared as a notifiable disease in the countries with high tuberculosis incidence rate including India, notifiable disease means a disease that is mandatory by law to be reported to the associated government authorities so that the concerned authorities can monitor the disease and provide necessary early caution to stop possible transmission.

Tuberculosis has been declared as a global health emergency by the world health organization. The WHO estimated 8.8 million new TB cases in 2005, out of which 7.4 million cases were in Asia and sub-Saharan Africa. TB accounted for approximately 2 million adult deaths and has become the second largest contributor to adult mortality amongst infectious diseases, [5]. In 2012, WHO reported that about 8.6 million people became ill with TB and 1.3 million people died of it. More than 80% of the TB infected individuals live in 22 countries, mainly in sub-Saharan Africa and Asia, [15]. For several decades, a number of global initiatives were spear-headed by the WHO with the hope of reducing the burden of global TB transmission. The initiatives are designed to achieve the millennium development goal of halting and reversing the incidence of TB by 2015. The TB control strategies include 'Stop TB Partnership', 'International Standards of Tuberculosis Care and Patients Care' and the 'Global Plan to Stop TB', [8]. At present, India accounts for one-fifth of the global TB incident cases. Every year nearly 2 million people in India, develop TB, of which approximately 0.87 million are infectious cases. It is estimated that annually around 3, 30, 000 Indians die due to TB. So, it is a major health problem in India and one of the leading causes of mortality.

1.4.2 Transmission

TB spreads usually from person to person by breathing infected air during close contact. The bacteria usually attack the lungs but it can attacks any part of the body such as the

kidney, spine and brain. TB is an airborne infection and its bacteria spread in the air when a person with TB disease of the lungs or throat coughs, sneezes, speaks, or sings. People nearby may breathe in these bacteria and become infected. TB does not spread by shaking hands, sharing meals, touching bed linen or sharing toothbrushes, kissing, etc. The risk factors for acquiring TB include close-contact situations, alcohol and certain diseases (e.g. diabetes, cancer, and HIV, etc.) and occupations (e.g. health-care workers). The most common symptoms and signs of TB are fatigue, fever, weight loss, coughing and night sweats. The diagnosis of TB involves skin tests, chest X-rays, sputum analysis (i.e. smear and culture), and 'Polymerase Chain Reaction (PCR)' test to detect the genetic material of the causative bacteria. It can be noted that every person infected with TB bacteria does not become sick, it gives insight into the two different stages of TB depending on the medical status of the patient: i) Latent TB infection (LTBI) and ii) TB disease.

In latent TB infection, a person inhales the M. tuberculosis bacteria and the bacteria stay in the body without causing any sickness and in most of the cases body is able to fight against bacteria and stop them from multiplying. These patients do not show any symptoms and they are not even infectious so they cannot spread the bacteria to others. Many of the individuals who have latent TB infection never develop TB disease but there are some who develop TB disease soon after becoming infected with latent TB. The route from latent TB infection to TB disease is open only when the immune system gets weakened inherently or due to some other cause such as if someone is HIV infected. In such situations the bacteria multiply and this results in progression from latent TB infection to TB disease. Individuals with TB disease are capable of transmitting the bacteria to others. TB is a fatal disease if the patient is not able to access the treatment or does not have completed the treatment course properly. The factors that affect the transmission of TB include the number, viability, socioeconomic status, family size, poorly ventilated households, gathering and malnutrition.

1.4.3 Treatment

Tuberculosis is a disease which is preventable and curable. The inactive TB can be treated with an antibiotic ('Isoniazid (INH)'), to prevent the TB infection from becoming active. The active TB is treated, usually successfully, with INH in combination with one or more of several drugs, including Rifampin (Rifadin), Ethambu-tol (Myambutol), Pyrazinamide and Streptomycin. It can be noted here that an untreated TB patient can infect, on an average, between 10-15 people every year. TB cases are being decreased worldwide with the implementation of 'Directly Observed Treatment Short-course (DOTS)', [15], a program that was conducted by the British Medical Research Council, UK and the US Public Health Service. The DOTS strategy is one of the most effective 'Stop TB' strategies and it contains five basic components: i) political commitment with adequate and sustained financial support; ii) early case detection and diagnosis through quality-assured bacteriology; iii) standardized treatment with supervision and patient support; iv) effective drug supply and management; and v) monitor and evaluate performance and impact, [11]. The global DOTS strategy is now confronting various other obstacles, e.g. addressing the risk of HIV, diabetes and drug-resistant TB strains.

Drug-Resistant TB (DR TB):

TB bacteria can become resistant to the medicines which are used to treat TB disease. This means that the medicine can no longer kill the bacteria. The resistance to TB drugs can occur when these drugs are misused or mismanaged. Poor patient compliance, lack of detection of resistant strains and unavailable therapy are the key reasons for the development of drug resistant TB.

Multidrug-Resistant TB (MDR TB):

The MDR TB is TB that is resistant to at least two of the most powerful anti-TB drugs, isoniazid and rifampicin. These drugs are considered first-line drugs and are used to treat all persons with TB disease.

Extensively Drug-Resistant TB (XDR TB):

Extensively Drug-resistant TB (XDR TB): The XDR TB is a rare type of MDR TB and is defined as TB that is resistant to isoniazid and rifampin, plus resistant to any fluoroquinolone (e.g., oxofloxacin, levofloxacin) and at least one of three inject-able second-line drugs (i.e., amikacin, kanamycin, or capreomycin). As XDR TB is resistant to first-line and second-line drugs, so patients are left with very few effective treatment options.

1.5 HIV-TB co-infection

HIV-TB co-infection is considered as double-trouble for humankind. As discussed already, HIV infection causes a decrease in the immunity level of individuals, hence the people infected with HIV are more likely to get opportunistic infections. Tuberculosis is the most common opportunistic infection among the people living with HIV. The lifetime risk of developing active TB in immune-competent adults is estimated to be 5% -10% during their lifetime, but in HIV-positive individuals this risk is increased to 5%-15% annually. The depletion of $CD4^+$ T cells, which is a main feature of AIDS, is certainly an important contributor to the increased risk of reactivation of latent TB and susceptibility to new tuberculosis infection. There is also some evidence that $CD8^+$ T cells play a role in the control of latent TB. The occurrence of HIV has been responsible for the increased frequency of tuberculosis. However the control of HIV can substantially decrease the frequency of TB. The following section contains a brief survey of literature in mathematical modeling of the spread of infectious diseases with emphasis on HIV and TB, so that the research work on modeling and analysis of the problems presented in the thesis can be seen in its proper perspective.

1.6 Brief survey of literature on HIV, TB and HIV-TB co-infection

The transmission dynamics of HIV infection is affected by the latent period, the infectious period, the number of infected/infectious persons in the population having AIDS, type of sexual activity, type of mixing (homogeneous or heterogeneous) and various high risk groups, etc., [115]. The long and variable incubation period between the infection with HIV and collapse of the immunity system results in to development of AIDS [21]. In recent times, various mathematical modeling based researches have been carried out to describe and understand the transmission dynamics of HIV/AIDS, [17; 20; 32; 45; 52; 82; 85; 90; 91; 93; 94; 114; 116; 149; 160; 161; 164; 175]. In particular, Anderson *et al.* [19] described some preliminary attempts to use mathematical models for transmission of HIV in a homosexual community. May and Anderson [115] presented simple HIV transmission models of human immunodeficiency virus that foregrounded the relationship between various epidemiological factors and the overall pattern of the AIDS epidemic.

Blythe and Anderson in [41] considered the HIV transmission models with four forms for the distribution of incubation period. The authors derived the distributions reporting variation in the incubation and infectious periods of the HIV from a series of risk functions and analyzed the dynamics of the virus, compressing different assumptions concerning the distributed incubation and infectious periods.

Castillo-Chavez *et al.* [52] analyzed a model in which the mean rate of acquisition of new partners depends on the size of the sexually active population. Bailey [31] proposed a model for the HIV infection and AIDS in which infected people proceed through a sequence of stages to AIDS and then to death. These models involve only one population but the HIV transmission takes place in populations that are heterogeneous in a variety of ways. This particular aspect was incorporated in [81; 94].

Hyman and Stanley [87] formulated two simple models considering the association between infectiousness and the levels of HIV-1 RNA measured in serum and plasma and have investigated the impact of variation in infectiousness. Furthermore, the authors reported numerical simulations to analyze the relative significance of different stages of infection and chronic levels of virus in the transmission of the disease.

The demographic effect in general on infectious disease and on the spread of HIV in particular was studied by Busenberg *et al.* in [44]. The impact of the core risk group (i.e. commercial-sex workers) was discussed in [97; 144]. In these studies, the researchers suggested that prevention through behavioral changes among high-risk groups can result in the reduction of new infections. A detailed study considering the mixing of subpopulation structured to the basis of risk and age factors with attention on the spread of HIV/AIDS in sexually active homosexual population can be found in [44]. Inaba [92], considered an age-duration structured population model for HIV among the homosexual community and studied the invasion problem to establish basic reproduction number for HIV/AIDS.

Griffiths *et al.* [76] emphasized the fact that the virus which leads to AIDS is age dependent and hence they formulated a model considering age-profile from the homosexual population and analyzed the changing profiles over time of the susceptible, HIV infectives and AIDS cases. The authors have applied their work to the AIDS incidence in France and have carried out the comparison of actual data and the results obtained from model. They have also discussed the effectiveness of prevention campaigns and suggested to pay attention to the adult population.

Cai *et al.* investigated a four dimensional stage structured HIV/AIDS epidemic model with treatment using autonomous ordinary differential equations. The authors incorporated three of the several clinical stages (i.e. the asymptomatic phase - I, the symptomatic phase - J and the full blown AIDS - A) for the HIV infection. Also, the authors analyzed the effect of time delay on the stability of the endemic equilibrium.

Musgrave and Watmough [123] investigated the potential use of condoms to control HIV when withdrawal from sexual activity is included for individuals in the latent stage of HIV infection. A deterministic HIV/AIDS model incorporating condom use, screening through the 'HIV Counseling and Testing (HCT)', regular testing and treatment as control strategies was presented in [131]. Lima *et al.* [109] formulated a mathematical model to analyze the impact of increasing the rate of 'Highly Active Antiretroviral Therapy (HAART)' as a policy to decrease the HIV load at the population level on the transmission of HIV. Their results show that a higher HAART coverage consistently leads to decrease in the number of new HIV positive cases.

The epidemic models for HIV transmission have been developed to study the impact of various factors such as awareness, treatment, effect of drug therapy, response to immune system and effect of co-infection [37; 47; 48; 124; 137]. The various mathematical studies [88; 120; 128; 131] to analyze the effect and significance of screening to predict the HIV/AIDS epidemic have been reported. In [36; 120], the authors gave emphasis to stimulate the counseling and testing of HIV positive individuals as this may be helpful in reducing the risky sexual activities in resource limited communities. They have also suggested that the public health educational campaigns focused on HIV/AIDS transmission have a considerable impact on decreasing the transmission of the virus.

In the past, several models have been reported to study TB. Possibly, the first model for transmission dynamics of TB was reported by Waaler [171]. The aim of Waaler model was to record and study the patterns of reported TB data. A great deal of interest in analyzing the dynamics of TB using mathematical models can be found in the literature [40; 53; 54; 56; 66; 67; 140; 158].

Salpeter and Salpeter [152] constructed a model for the time delay between occurrences of latent infection to active disease and used epidemiologic data on tuberculosis generated from the case rate tables of USA to calculate the per annum fractional rate of change in the incidence of active tuberculosis. They also derived the estimates for effective repro-

ductive number and respective cumulative transmission. Feng *et al.* [66] formulated and analyzed a model for TB transmission dynamics with exogenous re-infection. A number of mathematical studies (e.g. Guo and Li [77] and McCluskey [118]) have performed rigorous global asymptotic stability analysis (using Lyapunov function theory) of the equilibria of TB models with mass-action incidence exogenous re-infection.

Aparicio and Castillo-Chavez [25], explored and discussed the strengths and constraints of using homogeneous mixing and heterogeneous mixing epidemic models in the transmission of tuberculosis. The authors focused on three types of TB models: a standard incidence homogeneous mixing model, a non-homogeneous mixing model incorporating household contacts and an age-structured model. Adewale *et al.* [16], presented the mathematical analysis of a model for TB spread using standard incidence function with exogenous re-infection of latent and recovered cases, in the presence of DOTS. Okuonghae and Korobeinikov [133] also formulated a mass-action model for TB in the presence of exogenous re-infection. Naresh *et al.* [125] discussed a model to study the effect of ecological factors incorporating variable human and bacteria populations and concluded that the equilibrium level of the infective population increases due to the presence of bacteria in the population.

Magombedze *et al.* [112] presented and exhibited the use of drug chemotherapy in TB infected individuals in the control and prevention of tuberculosis. Athithan and Ghosh [26] studied a mathematical model to study transmission dynamics of TB with case detection and treatment. Their model formulation is based on a simple mass action type incidence and their analysis suggested the need for sustained treatment strategy and accurate case detection to control the spread of TB.

Recently, some mathematical models [102; 124; 134; 142; 174] have been reported to study the complex HIV-TB co-infection dynamics. Kirschner [102] developed a cellular model to describe HIV-1 and TB co-infections inside a host. West and Thompson [174] proposed a model to study the joint dynamics of TB and HIV in the United States.

Naresh, *et al.* [126], formulated a mathematical model with focus on the transmission dynamics of HIV and treatable TB in varying size population. Porco *et al.* [140] considered a discrete event simulation model to analyze and predict the possible impact of HIV on the probability and the expected danger of TB outbreaks in the population.

The nonlinear model of tuberculosis and HIV/AIDS co-infection under treatment was formulated and analyzed by Sharomi *et al.* [155]. The authors simulated full model numerically to investigate the impact of various treatment strategies. Their study showed that if the resources are insufficient then one of the diseases should be targeted first using available resources and it will be surely beneficial in reducing new cases of co-infection.

As mentioned earlier, the combined effect of tuberculosis and HIV in a population is very critical and in this case the AIDS incubation period reduces drastically, leading to death. It is, therefore, essential to study the transmission of both HIV and TB to have better prediction about the number of infectives in the population.

1.7 Mathematical preliminaries

In this section, a brief description of the mathematical tools used in the thesis are described. In particular, the computation of reproduction number and the stability results for ordinary differential equations are revisited.

In the present thesis the next generation matrix method has been used for computation of basic reproduction number (R_0). This method was proposed by Van den Driessche *et al.* in [168]. The following subsection briefly describes the relevant details of the next generation matrix method.

1.7.1 Computation of R_0 using next generation matrix method

Next generation matrix is a non-negative matrix used to find the basic reproduction number which is given by the spectral radius of the next generation matrix. Consider a heterogeneous population whose individuals are distinguishable by age, behavior, spatial position and/or stage of disease, but can be grouped into n homogeneous compartments. Let $x = (x_1, x_2, ..., x_n)^t$ with each $x_i \geq 0$, be the number of individuals in each compartment. For clarity we sort the compartments so that the first m compartments correspond to infected individuals. The distinction between infected and uninfected compartments must be determined from the epidemiological interpretation of the model and cannot be deduced from the structure of the equations alone, as we shall discuss below. It is plausible that more than one interpretation is possible for some models. The basic reproduction number cannot be determined from the structure of the mathematical model alone, but depends on the definition of infected and uninfected compartments. We define X_s to be the set of all disease free states. That is

$$X_s = \{x \geq 0 | x_i = 0, i = 1, 2, ...m\}.$$

Let $\mathcal{F}_i(x)$ be the rate of appearance of new infections in compartment i, $\mathcal{V}_i^+(x)$ be the rate of transfer of individuals into compartment i by all other means, and $\mathcal{V}_i^-(x)$ be the rate of transfer of individuals out of compartment i. It is assumed that each function is continuously differentiable at least twice in each variable. The disease transmission model consists of non-negative initial conditions along with the following system of equations:

$$\frac{dx_i}{dt} = \mathcal{F}_i(x) - \mathcal{V}_i(x), \quad i = 1, 2, ..., n, \tag{1.1}$$

Further, F and V matrices are computed, where

F = Jacobian of $\mathcal{F}$ at disease-free equilibrium = $\left[\frac{\partial \mathcal{F}_i(x_0)}{\partial x_j}\right]$

V = Jacobian of $\mathcal{V}$ at disease-free equilibrium = $\left[\frac{\partial \mathcal{V}_i(x_0)}{\partial x_j}\right]$ with $1 \leq i,\ j \leq m$.

The matrices F contains the new infection terms whereas the matrix V contains the remaining transfer terms. The next generation matrix is defined as FV^{-1}. Thus $R_0 = \rho(FV^{-1})$, i.e., the spectral radius (or the largest eigenvalue in magnitude) of the next generation matrix.

1.7.2 Stability for ordinary differential equations

Linear stability : Consider the following system of ordinary differential equations:

$$\frac{dx}{dt} = G(x) \tag{1.2}$$

Here $x = (x_1, x_2, ..., x_n)^T$ and $G = (G_n, G_2, ..., G_n)^T$ and each G_i for $i = 1, 2, ..., n$ is a continuous functions from $\mathbb{R}^n$ to $\mathbb{R}$.

The *equilibrium point* for the above system (1.2) is found by setting $\frac{dx_i}{dt} = 0$, $i = 1, 2, ..., n$; which gives

$G_i(\bar{x_1}, \bar{x_2}, ..., \bar{x_n}) = 0$, $i \neq 1, 2, ..., n$, for $\bar{x} \equiv (\bar{x_1}, \bar{x_2}, ..., \bar{x_n})^T$ in $\mathbb{R}^n$.

To determine the *linear stability* of the equilibrium points (steady state solutions), we shift the origin to $\bar{x}$. i.e. using the transformation,

$X_i = x_i - \bar{x_i}, i = 1, 2, . . ., \ n.$

With this change of variable and neglecting higher order terms in equation (1.2), we get the following linearized system:

$\frac{dX}{dt} = AX,$

where $X = (X_1, X_2, ..., X_n)^T$ and $A = \left(\frac{\partial G_i}{\partial x_j})\right)_{x=\bar{x}}$ is called *Jacobian* matrix of the system (1.2).

The equilibrium point $x = \bar{x}$ of the dynamical system (1.2) is said to be linearly asymptotically stable if all the eigenvalues of the Jacobian matrix are with negative real

part. Hence the question of linear asymptotic stability of a equilibrium point reduces to finding the sign of the roots of the characteristic equation of the corresponding Jacobian matrix.

In this context, the Routh Hurwitz criterion [103] is very useful, which gives the necessary and sufficient condition for a polynomial to have all the roots with negative real part.

Routh Hurwitz criterion : Let a_1, a_2, . . .,a_n be n real numbers. The equation

$$\lambda^n + a_1\lambda^{n-1} + a_2\lambda^{n-2} + ... + a_n = 0, \tag{1.3}$$

has roots with negative real parts if and only if the values of the determinants of the matrices are positive,

$$H_1 = \begin{pmatrix} a_1 \end{pmatrix}, H_2 = \begin{pmatrix} a_1 & 1 \\ a_3 & a_2 \end{pmatrix}, H_3 = \begin{pmatrix} a_1 & 1 & 0 \\ a_3 & a_2 & a_1 \\ a_5 & a_4 & a_3 \end{pmatrix},$$

$$H_j = \begin{pmatrix} a_1 & 1 & 0 & . & 0 \\ a_3 & a_2 & a_1 & . & 0 \\ a_5 & a_4 & a_3 & . & 0 \\ . & . & . & . & . \\ a_{2j-1} & a_{2j-2} & a_{2j-3} & . & a_j \end{pmatrix}, \ . \ . \ ., H_n = \begin{pmatrix} a_1 & 1 & 0 & . & 0 \\ a_3 & a_2 & a_1 & . & 0 \\ a_5 & a_4 & a_3 & . & 0 \\ . & . & . & . & . \\ 0 & . & . & . & a_n \end{pmatrix}.$$

are all positive. Here $(l, m)th$, $l = 1, 2, ..., j$; $m = 1, 2, ..., j$, entry of the matrix H_j,

$j = 1, 2, ..., n$ is

$$\begin{cases} a_{2l-m}, & \text{for } 0 < 2l - m < n; \\ 1, & \text{for } 2l = m; \\ 0, & \text{for } 2l < m \text{ or } 2l > n + m. \end{cases}$$

In particular, for quadratic and cubic polynomials these conditions reduce to

(**i**) $a_1 > 0$, $a_2 > 0$, and

(**ii**) $a_1 > 0$, $a_3 > 0$, $a_1 a_2 - a_3 > 0$, respectively.

[for details see [103]; [104] and [138]]

1.7.3 Local stability analysis using Centre manifold theory

In this subsection, the centre manifold theory [50], as explained in [56] (Theorem 4.1), is stated and will be used later to prove the local asymptotic stability of the endemic equilibrium point.

Theorem 1.7.1: *Consider the following general system of ordinary differential equations with a parameter* ϕ

$$\frac{dx}{dt} = f(x, \phi), f : \mathbb{R}^n \times \mathbb{R} \to \mathbb{R} \quad \textit{and } C^2(\mathbb{R}^n \times \mathbb{R}), \tag{1.4}$$

where 0 is an equilibrium point of the system (that is, $f(0, \phi) \equiv 0$ *for all* ϕ *and assume*

A1 : $A = D_x f(0, 0) = (\frac{\partial f_i}{\partial x_j}(0, 0))$ *is the linearization matrix of the system (1.4) around the equilibrium 0 and* ϕ *evaluated at 0. Zero is a simple eigenvalue of A and other eigenvalues of A have negative real parts;*

A2 : *Matrix A has a right eigenvector w and a left eigenvector v (each corresponding to the zero eigenvalue);*

Let f_k *be the* k^{th} *component of f and*

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

The local dynamics of the system around 0 is totally determined by the signs of a and b.
i: $a > 0$, $b > 0$. *when* $\phi < 0$ *with* $|\phi| \ll 1$, *0 is locally asymptotically stable and there exists a positive unstable equilibrium; when* $0 < \phi \ll 1$, *0 is unstable and there exists a negative, locally asymptotically stable equilibrium;*
ii. $a < 0$, $b < 0$. *when* $\phi < 0$ *with* $|\phi| \ll 1$, *0 is unstable; when* $0 < \phi \ll 1$, *0 is locally asymptotically stable, and there exists a positive unstable equilibrium;*
iii. $a > 0$, $b < 0$. *when* $\phi < 0$ *with* $|\phi| \ll 1$, *0 is unstable and there exists a locally asymptotically stable negative equilibrium; when* $0 < \phi \ll 1$, *0 is stable, and a positive unstable equilibrium appears;*
iv. $a < 0, b > 0$ *when* ϕ *changes from negative to positive, 0 changes its stability from stable to unstable. Correspondingly a negative unstable equilibrium becomes positive and locally asymptotically stable.*

[See [50] for details].

1.7.4 Global stability of disease-free equilibrium

In this subsection, we describe the result and list two conditions that if met, guarantee the global asymptotic stability of the disease-free state. In order to study the global stability of disease-free equilibrium we shall make use of the theorem by Castillo-Chavez *et al.* [55] stated as below :

Theorem 1.7.2: *If the model system (1.2) can be written in the form:*

$$\begin{cases} X'(t) = F(X, Y), \\ Y'(t) = G(X, Y), \quad G(X, 0) = 0. \end{cases}$$

where $X \in \mathbb{R}^m{}_+$ *denotes the number of uninfected individuals and* $Y \in \mathbb{R}^n{}_+$ *denotes number of infected individuals including latent, infectious, etc.*

The disease-free equilibrium is denoted here by

$E_0 = (X_0, 0)$. *The conditions* (H_1) *and* (H_2) *below must met to guarantee global asymptotic stability of* E_0.

H_1: *For* $X'(t) = F(X_0, 0)$, X_0 *is globally asymptotically stable (g.a.s.),*

H_2: $G(X, Y) = AY - \widehat{G}(X, Y), \widehat{G}(X, Y) \geq 0$ *for* $(X, Y) \in \mathcal{D}$

where $A = D_Y G(X_0, 0)$ *is an M-matrix (the off diagonal elements of A are nonnegative) and* $\mathcal{D}$ *is the region where the model forms biological sense.*

If system (1.2) satisfies the above two conditions (H_1 and H_2) then the following Theorem 1.7.3 holds:

Theorem 1.7.3: *The fixed point* $E_0 = (X_0, 0)$ *is a globally asymptotically stable equilibrium of system (1.2) provided* $R_0 < 1$ *(locally asymptotically stable) and that the assumptions* H_1 *and* H_2 *are satisfied.*

Theorem 1.7.4: *(**Lasalle's Invariance Theorem**) Let* $\Omega \subset D$ *be a compact set that is positively invariant with respect to the system (1.2). Let* $V : D \to \mathbb{D}$ *be continuously differentiable function such that* $\frac{dV}{dt} \leq 0$ *in* Ω. *Let* $E = \left\{ x \mid \frac{dV}{dt} = 0, x \in \Omega \right\}$ *and* $\mathcal{M}$ *be the largest invariant set in E. Then every solution starting in* Ω *approaches* $\mathcal{M}$ *as* $t \to \infty$. *In particular, if* $\mathcal{M} = \{0\}$, *then the zero solution of (1.2) is asymptotically stable.*

[See [101] and [151] for details.]

1.8 Research objectives of the work

Following research objectives were set for the present work:

- To critical review and study the existing mathematical models for infectious diseases with emphasis on HIV and TB.

- To identify the important parameters for the improvement and extension of the existing mathematical models for HIV and TB.
- To develop new mathematical models to study the spread and prediction of HIV and TB based upon the identified important parameters.
- To analyze and simulate the developed models for HIV and TB.

1.9 Organization of the thesis

In this thesis we propose and analyze mathematical models for HIV, TB and HIV-TB co-infection. The role of various factors such as awareness, screening and treatment of infectives are studied.

Chapter 1 starts with a brief history of the spread of infectious diseases in the human population. Then, an overview of the epidemiological mathematical models and their role in the study of transmission dynamics of epidemics is given. After that a brief account of related mathematical models of the HIV, TB and HIV-TB co-infection by various authors from the recent literature is reported. Later, we provide some basic mathematical theories (definitions, theorems, lemmas and inequalities) and methodologies which are required in the analysis of the mathematical models discussed in subsequent chapters. Also, a brief plan of the results presented in the subsequent chapters is given towards the end of Chapter 1.

Chapter 2 examines the role of awareness and the effect of screening of infectives on the spread of the HIV/AIDS infection. A deterministic ordinary differential equation model for the HIV/AIDS is formulated by subdividing the whole sexually-active population into three disjoint compartments. The basic reproduction number (R_0) and different equilibria of the model are computed. The disease-free equilibrium is globally asymptotically stable for $R_0 < 1$ where as the endemic equilibrium point is globally stable under

some restrictions on parameter values. Primarily, the study emphasizes the need for mass awareness programs and screening centers to provide better counseling to the infectives who continue to participate in the transmission of the virus. Numerical simulations are performed for a varied set of parameter values to support the analytic findings.

Chapter 3, presents a nonlinear deterministic model for the HIV/AIDS by incorporating the role of female sex-workers in the transmission of HIV/AIDS. We observed that the female sex-workers is a core group responsible for the transmission of the HIV/AIDS epidemic among sex-workers, their clients and partners. We have shown that the global dynamics are completely determined by the basic reproduction number R_0. For $R_0 < 1$, the disease-free equilibrium is globally stable which leads to the eradication of disease from population whereas for $R_0 > 1$, the endemic equilibrium is globally asymptotically stable. Our analysis supported the need for preventive and curative services to guide and empower female sex workers so that they adopt healthier sex behavior which can reduce their risk of HIV infection. Finally, the analytic findings are validated with the help of numerical simulations.

Chapter 4 investigates a stage-structured HIV/AIDS model. The total population (N) is subdivided into eight compartments incorporating three different stages: children, adult and old population. Our study addresses the effect of awareness on the spread of HIV infection. The presented model exhibits two equilibria: disease-free equilibrium and endemic equilibrium. We show that disease-free equilibrium is globally asymptotically stable for $R_0 < 1$. We obtain the conditions on parameter values for existence and local stability of endemic equilibrium point and investigate the role of awareness in reducing the HIV/AIDS infection in the population. The theocratical findings are supported using numerical simulations.

Chapter 5 deals with the role of screening and treatment in the transmission of the TB disease. The equilibria and threshold of the model are obtained. The stability of different equilibria is also discussed. We observe that this model shows backward bifurcation, i.e.

in this case $R_0 < 1$ is not sufficient to eliminate the disease from the population. One needs to lower R_0 much below one to make the disease free equilibrium to be stable. We also demonstrate this fact numerically for different sets of parameters.

Chapter 6 presents a HIV/AIDS-TB co-infection model with treatment and screening of HIV infectives by considering simple mass action type incidence. The existence and stability of various equilibria are discussed and we observe from the analysis that the system always tends to TB-only equilibrium point or to HIV-only equilibrium point if both R_1 (reproduction number corresponding to TB) and R_2 (reproduction number corresponding to TB) are greater than one. The co-infection equilibrium point is always unstable whenever it exists. Our numerical simulation shows that the screening of HIV infected people plays a vital role in controlling the spread of this disease. Also, we show that the recovery rate of TB has positive impact on the reproduction number R_1 corresponding to TB, i.e. the reproduction number R_1 decreases with the increase in the recovery rate of TB infectives. If we increase the recovery rate constant and the rate of screening, both R_1 and R_2 can be reduced below one consequently leading to disease-free equilibrium to be stable. From the analysis we observe that a strong co-ordination between the national TB and the AIDS control programs is required for effective management of HIV-TB patients and to further lower the count of dual infections.

Chapter 7 deals with a non-linear mathematical model to study the transmission dynamics of the HIV-TB co-infection by considering standard incidence. Here too, the roles of screening and treatment are taken into account. The non-negative equilibria of the model are computed and the stability of these equilibria is discussed in detail. The basic reproduction numbers corresponding to both HIV and TB are found and we show that the disease-free equilibrium is stable only when the reproduction numbers for both the diseases are less than one. When both the reproduction numbers are greater than one, the co-infection equilibrium point may exist. The co-infection equilibrium is found to be locally stable whenever it exists. The TB-only and HIV-only equilibria are locally

asymptotically stable under some restriction on parameters incorporated in the model. The numerical simulation results are presented to support the analytical findings. We observe that the screening with proper counseling of HIV infectives results in a significant reduction in the number of individuals progressing to HIV. The analysis also shows that the screening of TB reduces the infection prevalence of TB disease. Our results reported in this thesis clearly indicate that a proper screening and counseling can check the spread of HIV and TB diseases and effective control strategies need to be formulated around screening with proper counseling.

Towards the end, the bibliography is followed by the future directions of this research area.

Chapter 2

Modelling the Role of Awareness and Screening of Infectives in the Transmission Dynamics of HIV [1]

2.1 Introduction

Acquired Immune Deficiency Syndrome (AIDS) was first identified as a distinct infectious disease in the year 1981 as per the report from the US Centers for Disease Control and Prevention. Two years later the causative virus named as the Human Immunodeficiency Virus (HIV) was identified. HIV is a retrovirus that infects and kills $CD4^+$ T-cells in a human body. It gradually destroys the immune cells and makes the body unable to fight infections. The deterioration of the immune system results in the development of opportunistic infections that lead to AIDS [117]. HIV infection, due to its various modes of infection, is the main matter of concern as it can be transmitted by having sex with an infected partner/person, by sharing needles for injection drug as well by blood transfusion. HIV/AIDS is a major health problem in many countries of the world, and is considered as a pandemic (i.e. a disease outbreak which is present over a large geographical area and that is actively spreading), [98]. A global report presented by UNAIDS in the year 2012 estimated that 35.3 (32.2–38.8) million people are living with HIV.

[1] This work has been communicated in *Differential Equations and Dynamical System*

It should be noticed that the HIV infected individuals undergo a long latency period (typically 5–10 years) prior to the surfacing of the disease. During this time span, the individuals remain unaware of their infected status, but remain infectious. Delayed diagnosis of HIV infection can be considered as the major contributor and an epidemiologically significant reason behind the growth of HIV. The high-risk sexual behavior is very common among HIV-positive individuals who are unaware of their infection status as compared to those who know they are HIV positive. The studies around the world show that the number of individuals who get tested for HIV infection have increased as compare to the previous year figures. However, the fear and misconceptions still prevent people from knowing their HIV status. As a result the undiagnosed infection remains a significant factor that fuels the transmission of the disease.

Although the HIV/AIDS is a pandemic and significant research of over 20 years has gone into development of effective control measures for HIV/AIDS, it remains a difficult target to invent a vaccine or drug that can cure it. Recently the use of Active Antiretroviral Drugs, in particular Highly Active Antiretroviral Therapy (HAART) remained successful in reducing its spread and AIDS related deaths among HIV infected patients. However, these life extending medicines are not extensively available in some countries which are in serious need of this therapy due to high HIV incidence and prevalence rates. Clearly, the disease is challenging as there is no effective medicine to cure HIV. Due to which the person who once get infected with this infection will remain infective for his/her life-time without any recovery. In the absence of curative treatment and due to severity of HIV infection, prevention is the only feasible way to reduce its spread.

The estimated cost of the available treatment and care of HIV/AIDS infected patients is somehow unaffordable in many of the developing countries. Public screening and education of HIV/AIDS is a powerful tool in combating the disease burden as it provides information to the individuals about causes of the disease that how it is transmitted, the precautionary measures that individuals can take to prevent the transmission of HIV, and

the steps to be taken after the detection of the disease among susceptible individuals. The prevention is about creating an environment of information and guiding people to adopt careful practices that will reduce their chances of getting infected.

The grim nature of this epidemic has motivated the researchers to develop mathematical models to understand its dynamical nature and the mechanism responsible to accelerate its growth on the population level. Mathematical modeling offers an efficient mode to create intelligent information that can help to develop suitable and effective policies. Since the recognition of the AIDS, various mathematical models have been developed to understand its immunological and epidemiological dynamics. The preliminary work in this regard is done by Anderson [21], Anderson and May [17; 24], Castillo-Chavez [51; 52], May and Anderson [115] and Schwager *et al.* [154]. Some researchers considered the proportional mixing of male population with different rates of contact with their new sexual partners in their mathematical model of HIV transmission [19; 115]. Various mathematical models to study the impact of sexual/social mixing structures are carried out and their results give emphasis on the urgency of understanding the mixing patterns to protect the future generations from the virus (see, e.g., [44; 62; 89; 94]). The impact of core risk group (such as commercial-sex workers) is discussed by several researchers [97; 144]. In these studies, the researchers have suggested that the prevention through behaviorial changes among high-risk groups can result in the reduction of new infections. Epidemic models for HIV transmission have also been developed to study the impact of awareness, treatment, effect of drug therapy, response to immune system and effect of co-infection [37; 47; 48; 88; 124; 128; 137].

In [36; 120], the authors have given emphasis on promoting counseling and testing of HIV positive patients as this may be helpful in reducing the risky sexual activities in resource limited communities. The parameters such as considerable variability of the infection rates for different sub populations at risk (e.g. homosexuals, heterosexuals, drug users, etc.); the long incubation period before the occurrence of symptoms; the

variability of the infection based on evolution of the infection in an individual; etc., are discussed in the *Lecture Notes in Biomathematics*, [49; 51]. Moreover, these parameters of HIV/AIDS infections imply a relevant impact on the demography of the population at risk. Tripathi *et al.* [166] proposed an epidemiological model to analyze the effect of screening of unaware infectives on the transmission of HIV infection with constant immigration of susceptibles in a homogeneous population. The model analysis has shown that the screening of unaware infectives has positive impact on reducing HIV prevalence.

To the best of our knowledge, relatively few studies have been carried out to mathematically analyze the impact of screening on the spread of HIV infection. In the present study, we have considered the impact of effective screening, i.e. the screening with proper counselling which plays a major role in the transmission dynamics of any infection in a homogeneous population. Here, by effective screening we mean screening and subsequent counseling which convinces HIV infectives not to transmit this disease to others. The effective screening acts as a powerful intervention in reducing the diagnostic delays and can help to initiate the timely treatment of the HIV infectives to suppress the viral load.

In the view of above facts, present chapter is devoted to analyze a nonlinear mathematical model to study the effect of awareness, screening of infectives and counseling on the spread of HIV infection in the endemic region. This model is formulated based on the basic principles developed by Anderson and May [17; 24] and May and Anderson [115]. These principles have been widely adopted to understand the dynamic nature and impact of the epidemic in various epidemiological and social environments.

The basic reproduction number R_0 of the model is determined by the method of next generation matrix. Mathematical analysis establishes that the global dynamics of the spread of the HIV infection is completely determined by the basic reproduction number R_0. The effect of awareness, screening of infectives and counseling on the transmission of HIV is demonstrated using numerical simulation and we show that all these have positive impact in reducing the transmission of HIV in the population. Furthermore, it is evident

that for some suitable choice of parameters corresponding to awareness, screening and counseling this disease can be eliminated from the population.

The remaining of this chapter is organized as follows: Section (2.2) is further divided into two subsections. The Subsection (2.2.1) describes the mathematical model (2.1) for HIV along with a discussion on the basic groundwork behind the formulation of present model. The Subsection (2.2.2) covers the basic properties of the model. Section (2.3) is also divided in two subsections, in Subsection (2.3.1) we derive the expression for basic reproduction number and thereafter Subsection (2.2.4) shows the existence and uniqueness of endemic equilibrium point. In Section (2.4) the local and global stability analysis of the equilibria is proved. In Section (2.5), some numerical simulations to support our analytical findings have been presented. Finally, in Section (2.6) the epidemiological significance of the observations obtained from the analysis have been discussed.

2.2 Mathematical model

2.2.1 Model description

In view of the discussion in Section 2.1, a mathematical model has been formulated to study the dynamics of HIV with emphasis on screening and treatment of infectives. Almost 90% of HIV infection occurs due to sexual transmission and the individuals between the age of 15-24 are the most vulnerable to this infection. Hence, in this study only the adult population has been taken into account. The whole population (and here whole population we means whole sexually active adult population) under consideration is divided into three compartments: susceptibles $S(t)$, who are not infected with HIV/AIDS, HIV infected individuals $I(t)$, who are infected with HIV and can transmit the virus, and AIDS $A(t)$, the total number of individuals who have fully developed AIDS, and thus they no longer take part in the transmission. The population of interest is homogeneously

mixed, that means all susceptible individuals are equally likely to become infected through an HIV positive person in case of effective contact. The following assumptions have been made while formulating the model:

- It is assumed that population is subjected to general awareness programme about HIV and there are several health centers where screening and subsequent counseling of HIV infectives is performed.
- The infected individuals who are unaware of having disease will transmit this infection to others unknowingly as they may not take precautionary measures to reduce the transmission. So, the rate of transmission due to this group of individuals will be comparatively more than the transmission due to aware HIV infectives.
- Further, it is assumed that in case of 100% effective counseling, the screened HIV infected individuals will not take part in the transmission of HIV. Whereas the infected individuals may take part in the transmission if counseling is not proper. It should be noticed that some orthodox/convetional people who never give consideration to counselors' advises (they actually give a deaf ear to the advisors) may also take part in the transmission of this disease. On the basis of these observations, we have taken different disease transmission rates through aware and unaware HIV infectives.

Additionally, general awareness about the transmission of this disease and possible consequences may influence individuals to take precautionary measures to protect themselves against HIV. In this way, the HIV infection through sexual transmission may lower down in this group of individuals. The discrimination and stigma are still associated with the illness and due to this some HIV infected patients develop psychological problems and they try to infect others around them with increased rate. So in this case, the rate of transmission in this group of screened HIV infectives will be very high as compared to normal rate of transmission. The transition diagram representing the disease dynamics is

shown in Figure 2.1.

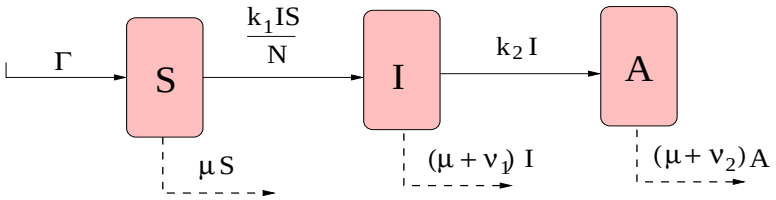

Figure 2.1: The transfer diagram for model system (2.2).

Assembling all the above mentioned observations and assumptions, the following standard incidence mathematical model governed by the system of ordinary differential equations is formulated as follows:

$$\begin{aligned}
\frac{dS}{dt} &= \Gamma - \frac{\beta_1\alpha(1-\gamma)I + \beta_2(1-\alpha)(1-\gamma)I + \beta_3(1-\epsilon)\gamma I}{N}\{(1-\alpha)+\eta\alpha\}S \\
&\quad -\mu S, \\
\frac{dI}{dt} &= \frac{\beta_1\alpha(1-\gamma)I + \beta_2(1-\alpha)(1-\gamma)I + \beta_3(1-\epsilon)\gamma I}{N}\{(1-\alpha)+\eta\alpha\}S \\
&\quad -\tau_1\delta\gamma I - \tau_2\{(1-\delta)\gamma+(1-\gamma)\}I - (\mu+\nu_1)I, \qquad (2.1)\\
\frac{dA}{dt} &= \tau_1\delta\gamma I + \tau_2\{(1-\delta)\gamma+(1-\gamma)\}I - (\mu+\nu_2)A, \\
S(0) &= S_0 > 0, \quad I(0) = I_0 \geq 0, \quad A(0) = A_0 \geq 0, \quad N = S(t)+I(t)+A(t).
\end{aligned}$$

The parameters used in the model have their physical interpretation. The descriptions of all parameters considered in model formulation are summarized in Table 2.1. The model (2.1) can be re-written as follows:

$$\begin{aligned}
\frac{dN}{dt} &= \Gamma - \mu N - \nu_1 I - \nu_2 A \\
\frac{dI}{dt} &= k_1\frac{I(N-I-A)}{N} - k_2 I - (\mu+\nu_1)I \qquad (2.2)\\
\frac{dA}{dt} &= k_2 I - (\mu+\nu_2)A,
\end{aligned}$$

where

$k_1 = \{\beta_1\alpha(1-\gamma) + \beta_2(1-\alpha)(1-\gamma) + \beta_3(1-\epsilon)\gamma\}\{(1-\alpha)+\eta\alpha\}$,

$k_2 = \tau_1\delta\gamma + \tau_2\{(1-\delta)\gamma + (1-\gamma)\}$.

Table 2.1: Description of parameters used in model system (2.1).

Parameter	Description
Γ	Recruitment rate into the population,
$\beta_i (i = 1; 2)$	Rates of transmission of infection by unscreened infectives to susceptibles,
β_3	Rate of transmission of infection by screened infectives who are not listening to counsellors,
μ	Natural death rate,
γ	Fraction of screening of unaware infectives,
α	Rate at which individuals are projected to general awareness programmes,
δ	Fraction of HIV infectives that are under treatment and are identified through screening test,
ϵ	Fraction of screened infectives not participating in the transmission of disease,
η	Fraction which reduces the transmission in aware susceptible individuals,
τ_1, τ_2	Progression rates to AIDS for treated and untreated HIV infectives, respectively,
ν_1, ν_2	Disease-induced mortality for HIV infection and AIDS, respectively.

2.2.2 Basic properties

Since the model under consideration monitors human populations, it is henceforth assumed that all the associated model variables and parameters are non-negative. This result is summarized in following lemma:

Lemma 2.2.1: *For all time $t \geq 0$, all the solutions of the system (2.1) are eventually confined in the compact subset $\mathcal{D} = \left\{(S, I, A) \in \mathbb{R}^3_+ : N = (S(t) + I(t) + A(t)) \leq \dfrac{\Gamma}{\mu}\right\}$; i.e. the closed set $\mathcal{D}$ is positively invariant for the model (2.1).*

Proof. We follow the following steps to show the positive invariance of $\mathcal{D}$ i.e. all the solutions of (2.1) which initiate in $\mathcal{D}$ remain in the region $\mathcal{D}$.

The rate of change of the total population N, is calculated by adding all the equations considered in model system (2.1), is given by

$$\frac{dN}{dt} = \Gamma - \mu N - \nu_1 I - \nu_2 A.$$

It follows that whenever $N > \dfrac{\Gamma}{\mu}$, then $\dfrac{dN}{dt} < 0$.

Since, $\dfrac{dN}{dt}$ is bounded by $\Gamma - \mu N$, therefore the standard comparison theorem [105] is

used to show, $N \leq \frac{\Gamma}{\mu}(1 - e^{-\mu t}) + N_0 e^{-\mu t}$, and for $t \to \infty$, we have

$$\lim_{t\to\infty} \sup N \leq \frac{\Gamma}{\mu}$$

In particular, $N(t) < \frac{\Gamma}{\mu}$ if $N(0) < \frac{\Gamma}{\mu}$. Clearly, it has been proved that all the solutions of (2.1) which initiate in $\mathbb{R}^3_+$ are confined in the region $\mathcal{D}$. Thus, $\mathcal{D}$ is positive-invariant and attracting. Hence the system considered is biologically and mathematically well posed in the region $\mathcal{D}$ [83]. ∎

2.3 Basic reproduction number and existence of equilibria

2.3.1 Basic reproduction number

The model has a disease-free equilibrium which is obtained by setting the right hand sides of the equations in the model (2.2) to zero, and I = 0 = A, given by $E_0 = (N_0, 0, 0)$ with $N_0 = \frac{\Gamma}{\mu}$. The stability of this equilibrium will be investigated by using the next generation matrix [61; 168]. Following the standard notation described by Van den Driessche and Watmough in [168] on the system (2.2), the matrices F and V, for the new infection terms and the remaining transfer terms, are, respectively, given by

$$F = \begin{pmatrix} 0 & 0 & 0 \\ 0 & k_1 & 0 \\ 0 & 0 & 0 \end{pmatrix} \quad \text{and} \quad V = \begin{pmatrix} \mu & \nu_1 & \nu_2 \\ 0 & (\nu_1 + \mu + k_2) & 0 \\ 0 & 0 & (\mu + \nu_2) \end{pmatrix}$$

Reproduction number is the spectral radius or the largest eigenvalue of its next generation matrix FV^{-1} and is computed as

$$R_0 = \rho(FV^{-1}) = \frac{k_1}{\nu_1 + k_2 + \mu}. \tag{2.3}$$

The threshold quantity R_0 is the basic reproduction number for HIV infection. It computes the average number of new HIV infections to be generated by a single infectious in a completely susceptible population. The disease-free equilibrium, E_0 of the re-written model system (2.2) is locally asymptotically stable whenever $R_0 < 1$ and unstable if $R_0 > 1$. This means that HIV might be eliminated from the population (when $R_0 < 1$) if the solutions of the population of system (2.2) are in the basin of attraction of the disease-free equilibrium E_0.

2.3.2 The existence and uniqueness of endemic equilibrium

For the model system (2.2) there exist two equilibria namely Disease-free equilibrium E_0 (as discussed in subsection (2.3.1)) and Endemic equilibrium E^*. Here we will discuss the existence of unique endemic equilibrium point $E^* = (N^*, I^*, A^*)$. The positive endemic equilibrium (steady state with $I > 0$) can be obtained by setting the right hand side of the equations in model (2.2) equal to zero, i.e.

$$\begin{aligned} \Gamma - \mu N - \nu_1 I - \nu_2 A &= 0 \\ k_1 \frac{I(N-I-A)}{N} - k_2 I - (\mu + \nu_1) I &= 0 \\ k_2 I - (\mu + \nu_2) A &= 0, \end{aligned}$$

which gives

$$N^* = \frac{\Gamma - \nu_1 I^* - \nu_2 A^*}{\mu} \tag{2.4}$$

$$A^* = \frac{k_2}{\mu + \nu_2} I^* \tag{2.5}$$

where

$$I^* = \frac{\Gamma(\mu + \nu_2)(k_2 + \mu + \nu_1)(R_0 - 1)}{k_1(\mu(\mu + \nu_2) + k_2\mu) + (R_0 - 1)(k_2 + \nu_1 + \mu)((\mu + \nu_2)\nu_1 + \nu_2 k_2)} \tag{2.6}$$

This ensures the existence of endemic equilibrium point E^* for $R_0 > 1$.

2.4 Stability analysis

In the following subsections, we shall discuss the local and global stability results of disease-free equilibrium point and endemic equilibrium point of the model (2.2), by using the standard linearization technique and the well-known Routh-Hurwitz criteria [103].

2.4.1 Stability analysis of disease-free equilibrium

Theorem 2.4.1: *The disease-free equilibrium E_0 of the system (2.2) is locally asymptotically stable when $R_0 \leq 1$.*

Proof. To study the stability of the system (2.2) at disease-free equilibrium (E_0), we have calculated Jacobian matrix at disease-free equilibrium E_0. The three eigenvalues are

$$-\mu,\ (R_0-1)(k_2+\mu+\nu_1) \ \text{ and } \ -(\mu+\nu_2).$$

Clearly, all the eigenvalues are negative for $R_0 < 1$, hence the system (2.2) is locally asymptotically stable around its disease-free equilibrium E_0. ∎

Theorem 2.4.2: *For $\dfrac{k_1}{\mu+\nu_1} < 1$, disease-free equilibrium E_0 is globally asymptotically stable.*

Proof. Consider a Lyapunov function $\dot{V} = \dot{I} + \dot{A}$. Then

$$\begin{aligned}
\dot{V} &= \dot{I} + \dot{A} \\
&= \frac{k_1 SI}{N} - (\mu+\nu_1)I - (\mu+\nu_2)A \\
&\leq [k_1 - (\mu+\nu_1)]I - (\mu+\nu_2)A \\
&= (\mu+\nu_1)[\frac{k_1}{(\mu+\nu_1)} - 1] - (\mu+\nu_2)A.
\end{aligned}$$

For $\dfrac{k_1}{\mu+\nu_1} < 1$, it is easy to obtain $\dot{V} \leq 0$. Hence by using LaSalle's Invariance Principle [151], the global stability of E_0 can be established. ∎

2.4.2 Stability analysis of endemic equilibrium

Theorem 2.4.3: *The endemic-equilibrium E^* of model (2.2) is locally asymptotically stable whenever it exists.*

Proof. The Jacobian matrix at E^* is given as

$$M = \begin{pmatrix} -\mu & -\nu_1 & -\nu_2 \\ m_{21} & m_{22} & m_{33} \\ 0 & k_2 & -(\mu+\nu_2) \end{pmatrix}$$

where, $m_{21} = \dfrac{\{k_1 - (k_2+\mu+\nu_1)\}I^*}{N^*}, m_{22} = -\dfrac{k_1 I^*}{N^*}, m_{23} = -\dfrac{k_1 I^*}{N^*}$.
The characteristic equation corresponding to the matrix M at disease-free equilibrium is given as follows:

$$\lambda^3 + a_2\lambda^2 + a_1\lambda + a_0 = 0,$$

where

$$\begin{aligned} a_2 &= 2\mu + \nu_2 + \frac{k_1 I^*}{N^*}, \\ a_1 &= \left(\mu + \frac{k_1 I^*}{N^*}\right)(\mu+\nu_2) + \frac{\nu_1(R_0-1)(k_2+\mu+\nu_1)I^*}{N^*} + \frac{k_1 I^*\mu}{N^*} + \frac{k_1 k_2 I^*}{N^*} \\ a_0 &= (\mu+\nu_2)\left[\frac{\nu_1(R_0-1)(k_2+\mu+\nu_1)I^*}{N^*} + \frac{k_1 I^*\mu}{N^*}\right] \\ &\quad + k_2\left[\frac{\nu_2(R_0-1)(k_2+\mu+\nu_1)I^*}{N^*} + \frac{k_1 I^*\mu}{N^*}\right]. \end{aligned}$$

It is clear from above that a_2, a_1 and a_0 are positive for $R_0 > 1$.

Here we obtain

$$\begin{aligned} a_2a_1 - a_0 &= (\mu - m_{22})\{(\mu - m_{22})(\mu + \nu_2) + (\nu_1 m_{21} - m_{22}\mu - k_2 m_{23}\} \\ &\quad + (\mu - m_{22})(\mu + \nu_2)^2 + \frac{k_2\nu_2(k_2 + \mu + \nu_1)I^*}{N^*}. \end{aligned}$$

Clearly, $(a_2a_1 - a_0) > 0$ for $R_0 > 1$. Thus the equilibrium point E^* is locally asymptotically stable whenever it exists. ∎

Theorem 2.4.4: *The endemic equilibrium E^* exists, then it is globally asymptotically stable, provided the following condition is satisfied:*

$$\max\left\{\frac{2\nu_1^2}{\mu}, \frac{k_2\nu_2^2}{2\mu(\mu + \nu_2)}\right\} < \frac{\mu}{2}. \tag{2.7}$$

Proof. Consider the positive definite function about endemic equilibrium E^*

$$V = \frac{1}{2}(N - N^*)^2 + l_1(I - I^* - I^* \ln \frac{I}{I^*}) + \frac{l_2}{2}(A - A^*)^2,$$

where the constant k_1, k_2 and k_3 are to be chosen suitably. The derivative of V along the solution of the system (2.2) can be written as

$$\frac{dV}{dt} = (N - N^*)\frac{dN}{dt} + l_1\frac{I - I^*}{I}\frac{dI}{dt} + l_2(A - A^*)\frac{dA}{dt}.$$

Some algebraic calculation result in simplification of $\frac{dV}{dt}$, which is given as

$$\begin{aligned} \frac{dV}{dt} &= -\mu(N - N^*)^2 - \frac{l_1k_1}{N^*}(I - I^*)^2 - l_2(\mu + \nu_2)(A - A^*)^2 \\ &\quad - \left[\nu_1 - \frac{k_1(I + A)}{NN^*}\right](I - I^*)(N - N^*) \\ &\quad -\nu_2(N - N^*)(A - A^*) + (l_2k_2 - \frac{l_1k_1}{N^*})(I - I^*)(A - A^*). \end{aligned}$$

Substituting $l_2 = \frac{l_1k_1}{k_2N^*}$, and thereafter rearranging the terms, the sufficient conditions

for $\frac{dV}{dt}$ to be negative definite come out as follows:

$$\begin{aligned} \nu_2^2 &< 2\mu l_2(\mu+\nu_2) \Rightarrow l_2 > \frac{\nu_2^2}{2\mu(\mu+\nu_2)} \Rightarrow l_1 > \frac{k_2\nu_2^2 N^*}{2k_1\mu(\mu\nu_2)} \\ \nu_1^2 &< \mu\frac{l_1k_1}{2N^*} \Rightarrow l_1 > \frac{2\nu_1^2N^*}{\mu k_1}, \\ \left\{\frac{k_1(I+A)l_1}{NN^*}\right\}^2 &< \frac{\mu l_1k_1}{2N^*}. \end{aligned}$$

On maximizing the last inequality, we obtain $l_1 < \frac{\mu N^*}{2k_1}$. Thus, the final condition for the negative definiteness of the derivative of the Lyapunov function V turns out to be

$$\max\left\{\frac{2\nu_1^2N^*}{\mu k_1}, \frac{k_2\nu_2^2N^*}{2k_1\mu(\mu+\nu_2)}\right\} < l_1 < \frac{\mu N^*}{2k_1}.$$

Hence, l_1 can be chosen arbitrarily satisfying the above inequality provided the condition stated in the theorem is satisfied. Thus, under the condition (2.7) the endemic equilibrium point E^* is globally stable. ∎

2.5 Numerical simulations

The system (2.2) is simulated numerically for various set of parameter values using XPP [65]. The primary purpose of the numerical simulation is to analyze the change in states of disease progression with time and to check the impact of various parameters on transmission dynamics of the virus. The stability of disease-free equilibrium point E_0 is shown in Figure 2.2-2.3, where the reproduction number R_0 is equal to 0.5094 which is less than one and parameter values are as follows:

$$\Gamma = 200, \beta_1 = 0.03, \beta_2 = 0.05, \beta_3 = 0.02, \alpha = 0.5, \eta = 0.1, \epsilon = 0.1,$$

$$\gamma = 0.3, \nu_1 = 0.01, \mu = 0.01666, \tau_1 = 0.005, \tau_2 = 0.01, \delta = 0.4, \nu_2 = 0.05$$

The phase portraits in N-I plane and N-A plane are shown in Figures 2.4-2.5, respectively

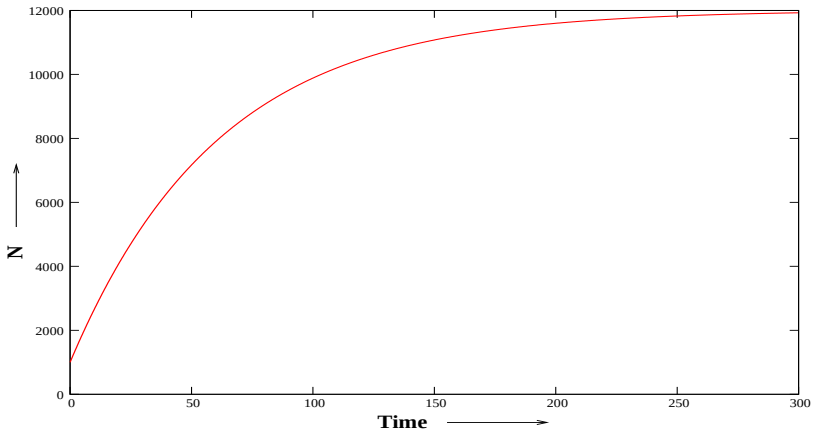

Figure 2.2: Variation of N with time, showing the stability of disease-free equilibrium point E_0 for $R_0 = 0.5094$.

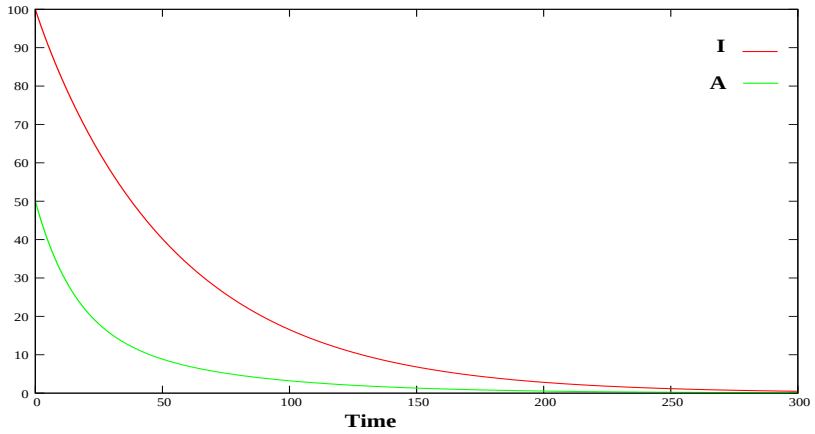

Figure 2.3: Variation of I and A with time, showing the stability of disease-free equilibrium point E_0 for $R_0 = 0.5094$.

for the following set of parameter values:

$$\Gamma = 200, \beta_1 = 0.2, \beta_2 = 0.8, \beta_3 = 0.02, \alpha = 0.5, \eta = 0.1, \epsilon = 0.1,$$

$$\gamma = 0.3, \nu_1 = 0.01, \mu = 0.01666, \tau_1 = 0.005, \tau_2 = 0.01, \delta = 0.4, \nu_2 = 0.05$$

For this set of parameter values, the endemic equilibrium point is stable. Here we find that the reproduction number $R_0 = 1.809817$ and the endemic equilibrium point E^* is given by

$$S^* = 8566.57, I^* = 3359.45, A^* = 473.73.$$

In Figures 2.6-2.7, the effect of parameter α is shown. The increase in the value of

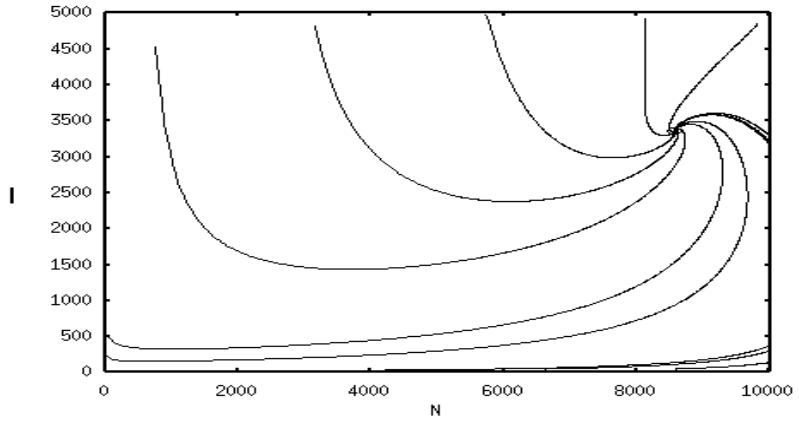

Figure 2.4: Phase portrait corresponding to stability of endemic equilibrium point in $N - I$ plane.

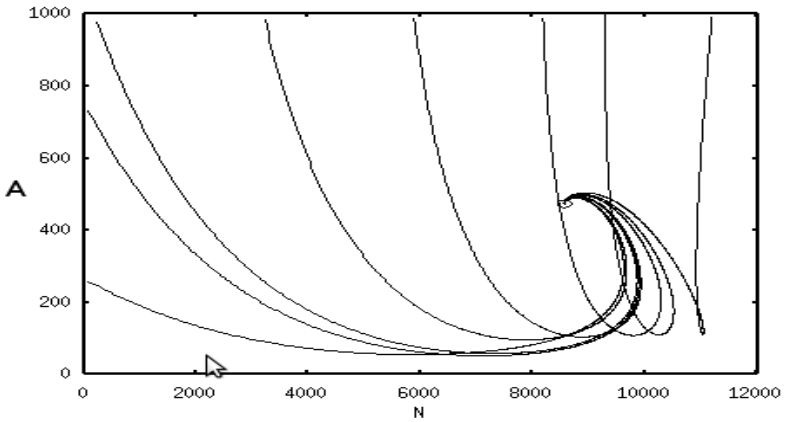

Figure 2.5: Phase portrait corresponding to stability of endemic equilibrium point in $N - A$ plane.

α shows significant reduction in the equilibrium level of infective population and AIDS patient. Figures 2.8-2.9 show the effect of γ on infectives and AIDS patients. Here again

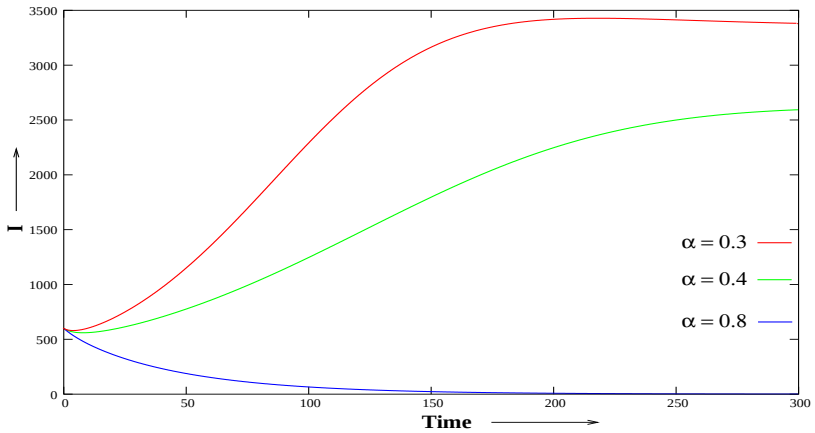

Figure 2.6: Effect of the fraction of individuals who are subject to general awareness α on the equilibrium level of I, where all other parameter values are same as used in plotting Figure 2.3.

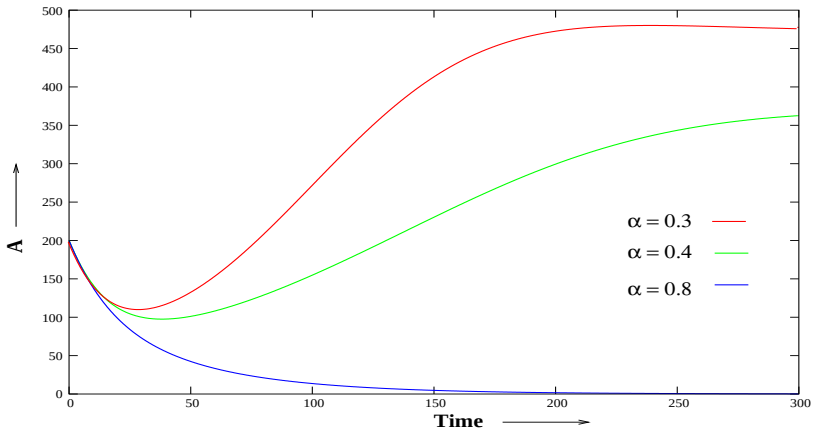

Figure 2.7: Effect of the fraction of individuals who are subject to general awareness α on the equilibrium level of A, where all other parameter values are same as used in plotting Figure 2.3.

the increase in γ decreases the equilibrium level of infectives and AIDS patients. Figure 2.10 shows the combined effect of α and γ where increase in these parameters causes the reduction of the basic reproduction number R_0 below one which forces the system towards disease-free equilibrium point. From these simulation, it is clear that general awareness and screening of HIV infectives play considerably important role in reducing the transmission of this disease. As discussed in Subsection (2.2.1), sometimes screened

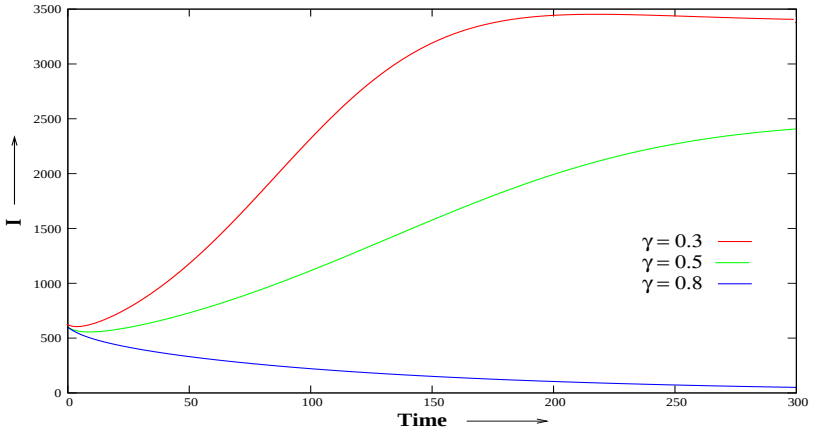

Figure 2.8: Effect of the fraction of individuals who are screened fγ on the equilibrium level of I, where all other parameter values are same as used in plotting Figure 2.3.

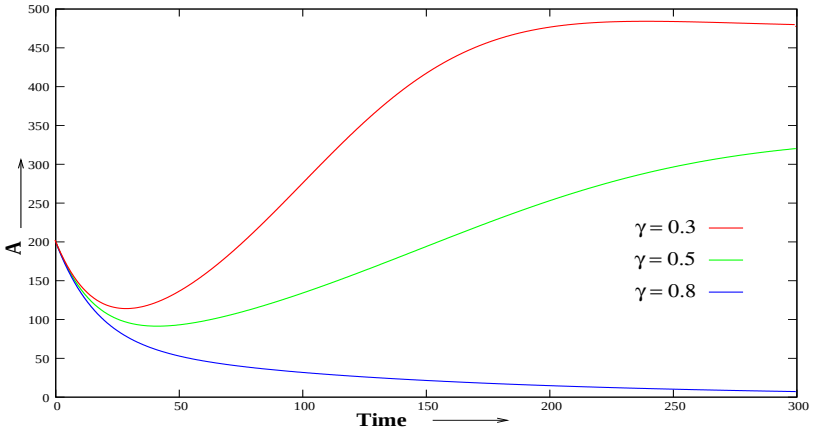

Figure 2.9: Effect of the fraction of individuals who are screened γ on the equilibrium level of A, where all other parameter values are same as used in plotting Figure 2.3.

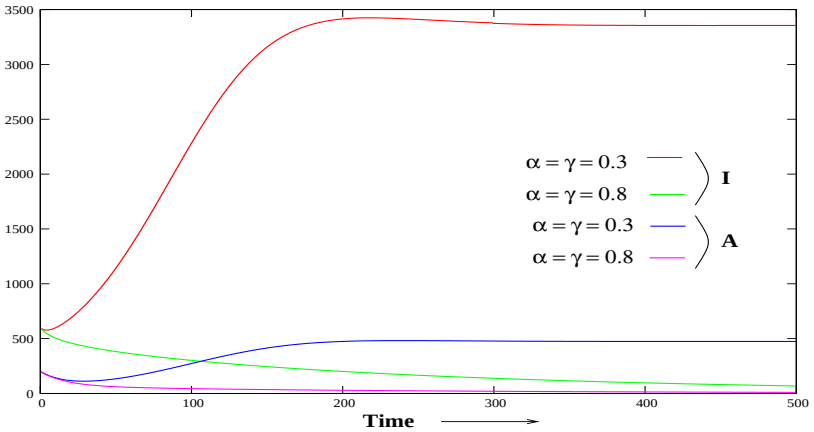

Figure 2.10: Combined effect of α and γ on the equilibrium level of I and A, where all other parameter values are same as used in plotting Figure 2.3.

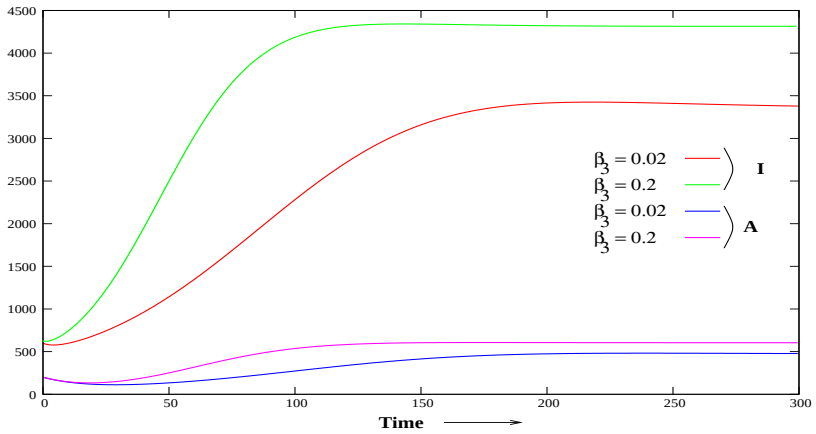

Figure 2.11: Effect of β_3 on the equilibrium level of I and A, where all other parameter values are same as used in plotting Figure 2.3.

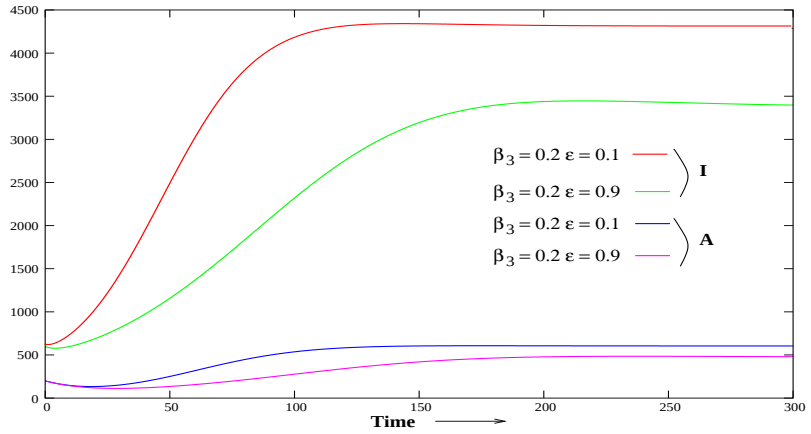

Figure 2.12: Effect of ϵ on the equilibrium level of I and A, with $\beta_3 = 0.2$, where all other parameter values are same as are used in Figure 2.3.

infectives develop psychological problems which forces them to transmit this disease to the individuals who come in their contact. In this case the rate of transmission β_3 will be large as compare to β_1 and β_2 and this is an alarming situation for the society leading to increased levels of HIV and AIDS patients. On the other hand, if counseling is 100% effective then ϵ should be one and if it is not at all effective then should be equal to zero. If counseling is partially effective then ϵ will be somewhere between zero and one. The effects of these parameters on the equilibrium level of HIV and AIDS are shown in Figures 2.11-2.12.

2.6 Conclusion

In this chapter, we formulated a mathematical model to investigate the impact of screening of unaware infectives, awareness and treatment of HIV/AIDS infectives on the transmission dynamics of the disease in a homogeneous population with constant immigration of susceptibles. It is observed that with appropriate screening and treatment, lives of many individuals can be changed. In particular, the quality of life of the people living with HIV can be improved. On the population-level, these changes can be framed with coordinated efforts by public health practitioners and with the support of government. The assurance of higher screening rates at all clinical settings serving population at risk of HIV can increase the number of cases detected and treated, and further it can reduce the harmful HIV consequences. The spread of the disease can be controlled, if the population under consideration presents constructive attitude towards prevention and control measures.

The community based educational programs must reach the general public to enhance the awareness about the disease and to extend the prevention and control techniques. Hence, the demand of time is to widen and effectively implement the prevention policies. The global health challenge that has come across us is to provide an overview of the pandemic to the individuals from high risk group that include the health, demo-

graphic, social, and economic effects of AIDS and the up-to-date information in prevention, care, and treatment of the disease. To disseminate the knowledge and awareness about this infection, awareness programs/camps incorporating screening of infectives can play a prominent role.

Chapter 3

Mathematical Analysis of the Transmission Dynamics of HIV/AIDS: Role of Female Sex Workers[1]

3.1 Introduction

UNAIDS [2] reported that 35.3 million [32.2 million –38.8 million] people were living with HIV in the year 2012. Among which, 32.1 million [29.1 million – 35.3 million] were adults and 17.7 million [16.4 million – 19.3 million] were women. The women population accounts for 52% of the total people living with HIV in low and middle-income countries, whereas men account for 48%, globally [2]. In the sub-Saharan Africa, which is considered as the center of global HIV epidemic, women comprise for approximately 57% of all people living with HIV.

Sexual intercourse is considered as the most common mode of HIV transmission in adult population. In the context of prostitution in developing and low-income countries, it is noted that the risk of female-to-male HIV transmission has been estimated as 2.4% per act and male-to-female transmission as 0.05% per act [42]. Women sex workers are

[1]A part of this work has been published in *Applied Mathematics & Information Sciences* 8(5) (2014) 2491-2501 (**SCI**)

among the key populations that have elevated the risk of acquiring HIV. In developing and low-income countries, the female sex workers are reported as one of the most vulnerable group participating widely in the transmission of HIV. In some of the recent studies, it has been noted that in high HIV-prevalent countries the female sex workers aged between 15-49 years are 13.5 times more likely to acquire HIV than all other women of this age group [33; 119]. From the available data, it has been estimated that the group sex events (GSEs) are common in developing and low income countries, e.g. Kenya, Bangladesh, India, and Argentina [27; 130; 167; 177]. In India, about 85% of new infections are associated with heterosexual transmission, especially with sex workers (SWs), their clients and the sexual partners of their clients [70; 136; 169]. Furthermore, since most of the male clients of female sex workers are married, hence the onward transmission of HIV is certain, specifically from HIV-positive men to their wives [69; 129].

The epidemiological modelling helps researchers to investigate how the system components are connected and how this connection may contribute to the growth or prevention of a specific disease. Several modelling studies have been published recently that are intended to provide information to policy makers for supporting the development of policies and strategies to reduce the overall transmission rate of the HIV infection. Mathematical models [47; 120; 128; 131; 166] have been developed to examine the effect of awareness, educational campaigns, screening and treatment of HIV infectives. Numerous epidemiological and evidence based studies have been carried out to explore and analyze the important role of various population groups and in particular female sex-workers in the transmission of HIV [13; 27; 86; 139; 145; 153; 170]. A survey of cohort study in Bangladesh [27] describes the high levels of risk behavior and pivotal similarities and differences in injecting and sexual risk activities among sex worker and non-sex worker female IDUs (Injecting Drug Users). Scheibe *et al.* [153] discussed the stigma, discrimination, violence associated with sex workers and their contribution to the high HIV incidence among female sex workers in Africa. They also provided a research report to showcase the available oppor-

tunities, barriers and suggestions to improve and extend the HIV prevention policies in the domain of sex work in Africa. Hsieh *et al.* [86] proposed and analyzed a theoretical model of HIV for a community with structure of two classes [direct (who work in brothels) and indirect (who are based in commercial places such as bars and massage parlors etc.)] of commercial sex workers (CSW), and two classes of sexually active male customers with different levels of sexual activity.

The multiple risk factors including multiple sexual partners, unprotected work conditions, barriers in negotiating the regular condom use, lack of access to appropriate health services, high prevalence of sexually transmitted infections (STIs) and sharing of injecting equipment, etc. increase the lifetime vulnerability of sex workers to get infected with HIV as compare to general population [7]. The environment and context in which sex-workers live and work do not support them to control the risk factors [145; 169]. Because of these reasons, sex-workers have been considered a key population responsible for HIV transmission. To control the epidemic spread, population specific interventions to guide and empower this specific group should be designed and implemented [139; 165]. The increasing testaments do suggest that the higher-risk behavior is substantially underreported in most of the HIV control and prevention surveys. Therefore, in the present analysis, attempts have been made to explore the role of female sex-workers and their clients in the transmission of HIV infection.

The chapter is organized as follows: Section (3.2) presents the formulation of nonlinear ODE model. This section has two subsections. In Subsection (3.2.1), HIV model with emphasis on female sex workers is described and formulated, thereafter in Subsection (3.2.2), basic properties of the model are described. Section (3.3) has three subsections. In Subsection (3.3.1) the computation of basic reproduction number is given. Subsection (3.3.2) defines the various non-negative equilibria associated with the model formulated in Section (3.2) and Subsection (3.3.3) deals with the existence and uniqueness of endemic equilibrium. Section (3.4) presents the stability analysis of the model. In Section (3.4)

we have two subsections. In Subsection (3.4.1), the local and global stability results for disease-free equilibrium are stated and proved and in Subsection (3.4.2) the global analysis of endemic equilibrium is performed. In Section (3.5), the numerical simulations to verify our theoretical results are shown, and finally Section (3.6) summarizes some of the key findings of our research.

3.2 Mathematical model

3.2.1 Model description

In this section, we formulated a deterministic model for heterosexual transmission of HIV infections. Heterosexual transmission means the population consisting of two groups of individuals: male and female, in which the susceptible male can become infected by an infectious female and vice versa. The model is formulated by dividing the total sexually active population N or $N(t)$ at time t into susceptible (S), HIV infected with no clinical symptoms of AIDS (I) and AIDS patients (A) compartments. There are total nine compartments in the final structure of the model. Each compartment is designed by splitting the aforementioned epidemiological disease status (S(t), I(t), A(t)) into mutually-exclusive sub-classes of the population groups acknowledged by their gender. The population groups used in the model formulation are : sexually active male, female and female sex worker population. The classes are distinguished by using suitable subscripts for male (m), female (f) and female sex workers (fs). The compartments are : HIV-susceptible male ($S_m(t)$), HIV-susceptible female ($S_f(t)$), HIV-susceptible female sex workers ($S_{fs}(t)$), HIV-infected male ($I_m(t)$), HIV-infected female ($I_f(t)$), HIV-infected female sex workers ($I_{fs}(t)$), AIDS-infected male ($A_m(t)$), AIDS-infected female ($A_f(t)$) and AIDS-infected female sex-workers ($A_{fs}(t)$). While formulating the model (3.1), it has been assumed that the new cases of disease occur at the rate $\beta_1 S_m I_f$, $\beta_2 S_m I_{fs}$, $\beta_3 S_f I_m$ and $\beta_4 S_{fs} I_m$ due to

interaction of susceptibles with HIV infectives. The transmission coefficient is used in same manner as it was used by Anderson and May in [18] and Jong *et al.* in [59]. It has been assumed that the AIDS patients are not taking part in the transmission of virus. The schematic flow diagram representing the disease dynamics is shown in Figure 3.1. By considering the above mentioned variables, a non-linear deterministic mathematical

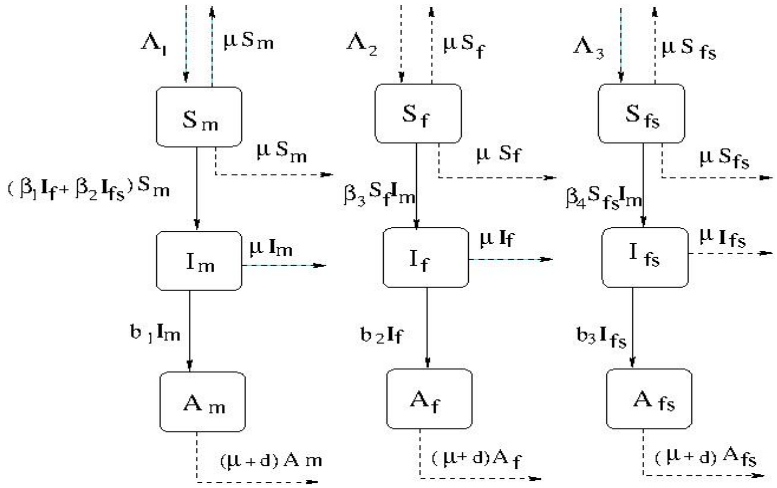

Figure 3.1: The schematic flow diagram for model system (3.1).

model to analyze the role of female sex workers in the transmission of HIV is proposed as follows:

$$\begin{aligned}
\frac{dS_m}{dt} &= \Lambda_1 - \beta_1 S_m I_f - \beta_2 S_m I_{fs} - \mu S_m \\
\frac{dI_m}{dt} &= \beta_1 S_m I_f + \beta_2 S_m I_{fs} - (b_1 + \mu) I_m \\
\frac{dA_m}{dt} &= b_1 I_m - (\mu + d) A_m \\
\frac{dS_f}{dt} &= \Lambda_2 - \beta_3 S_f I_m - \mu S_f \\
\frac{dI_f}{dt} &= \beta_3 S_f I_m - (b_2 + \mu) I_f \\
\frac{dA_f}{dt} &= b_2 I_f - (\mu + d) A_f \\
\frac{dS_{fs}}{dt} &= \Lambda_3 - \beta_4 S_{fs} I_m - \mu S_{fs} \\
\frac{dI_{fs}}{dt} &= \beta_4 S_{fs} I_m - (b_3 + \mu) I_{fs} \\
\frac{dA_{fs}}{dt} &= b_3 I_{fs} - (\mu + d) A_{fs}
\end{aligned} \tag{3.1}$$

Here

$S_m > 0, \quad S_f > 0, \quad S_{fs} > 0, \quad I_m \geq 0, \quad I_f \geq 0, \quad I_{fs} \geq 0, A_m \geq 0, \quad A_f \geq 0, A_{fs} \geq 0$ and

$N(t) = S_m + S_f + S_{fs} + I_m + I_f + I_{fs} + A_m + A_f + A_{fs}$.

The associated parameters are described in the Table 3.1.

Table 3.1: Description of parameters used in model system (3.1).

Parameter	Description
$\Lambda_1, \Lambda_2, \Lambda_3$	Recruitment rate into the population in male, female and female sex worker classes, respectively,
μ	Natural death rate,
$\beta_i (i = 1; 2; 3; 4)$	Transmission rate constants from HIV infected males, females and female sex workers to respective susceptible classes,
d	Disease induced mortality rate in AIDS classes $(A_m; A_f; A_{fs})$,
b_1, b_2, b_3	Progression rates from HIV infective male, female and female sex workers class to respective AIDS class.

3.2.2 Basic properties

The region of attraction corresponding to (3.1) is defined by,
$\mathcal{D} = \left\{ (S_m, S_f, S_{fs}, I_m, I_f, I_{fs}, A_m, A_f, A_{fs}) \in \mathbb{R}^9_+ : N \leq \frac{\Lambda}{\mu} \right\}$. It is positively invariant and all the solutions of (3.1) which initiate in $\mathcal{D}$ remain in the region $\mathcal{D}$. This result can be summarized in the following lemma:

Lemma 3.2.1: *For all time $t \geq 0$, all the solutions of the system (3.1) are eventually confined in the compact subset*
$\mathcal{D} = \left\{ (S_m, S_f, S_{fs}, I_m, I_f, I_{fs}, A_m, A_f, A_{fs}) \in \mathbb{R}^9_+ : N = \leq \frac{\Lambda}{\mu} \right\}$.

Proof. We have

$N(t) = S_m(t) + S_f(t) + S_{fs}(t) + I_m(t) + I_f(t) + I_{fs}(t) + A_m(t) + A_f(t) + A_{fs}(t)$.

The time derivative of $N(t)$ along the solution of (3.1) is

$$\begin{aligned}\frac{dN}{dt} &= \Lambda_1 + \Lambda_2 + \Lambda_3 - \mu N - d(A_m + A_f + A_{fs}) \\ &\leq (\Lambda_1 + \Lambda_2 + \Lambda_3) - \mu N.\end{aligned}$$

that implies, $\frac{dN}{dt} + \mu N \leq \Lambda$,
where

$\Lambda = \Lambda_1 + \Lambda_2 + \Lambda_3$, the total recruitment rate in the population under consideration. we obtain $N \leq \frac{\Lambda}{\mu}(1 - e^{-\mu t}) + N_0 e^{-\mu t}$, and for $t \to \infty$, we have

$$\lim_{t\to\infty} \sup N \leq \frac{\Lambda}{\mu}$$

Clearly, it has been proved that all the solutions of (3.1) which initiate in $\mathbb{R}^9_+$ remain confined that means approach, enter or stay in the region $\mathcal{D}$. Hence, solutions are bounded in the interval $[0, \infty)$. ∎

3.3 Basic reproduction number and existence of equilibria

3.3.1 Basic reproduction number

In this section, the computation of reproduction number (R_0) for the model system (3.1) is performed. It is computed using next generation matrix method [61; 168]. The system (3.1) has a disease-free equilibrium,
$E_0 = (S_m^0, S_f^0, S_{fs}^0, I_m^0, I_f^0, I_{fs}^0, A_m^0, A_f^0, A_{fs}^0) = \left(\frac{\Lambda_1}{\mu}, \frac{\Lambda_2}{\mu}, \frac{\Lambda_3}{\mu}, 0, 0, 0, 0, 0, 0\right)$.
Let $x = (I_m, I_f, I_{fs}, A_m, A_f, A_{fs})^T$. The terms representing infected population in the system (3.1) can be written as

$$x' = \mathcal{F} + \mathcal{V},$$

where

$$\mathcal{F} = \begin{pmatrix} \beta_1 S_m I_f + \beta_2 S_m I_{fs} \\ \beta_3 S_f I_m \\ \beta_4 S_{fs} I_m \\ 0 \\ 0 \\ 0 \end{pmatrix} \text{ and } \mathcal{V} = \begin{pmatrix} (b_1+\mu) I_m \\ (b_2+\mu) I_f \\ (b_3+\mu) I_{fs} \\ -b_1 I_m + (\mu+d) A_m \\ -b_2 I_f + (\mu+d) A_f \\ -b_3 I_{fs} + (\mu+d) A_{fs} \end{pmatrix}.$$

$$\text{F =Jacobian of } \mathcal{F} \text{ at } E_0 = \begin{pmatrix} 0 & \beta_1 S_m^0 & \beta_2 S_m^0 & 0 & 0 & 0 \\ \beta_3 S_f^0 & 0 & 0 & 0 & 0 & 0 \\ \beta_4 S_{fs}^0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \end{pmatrix}$$

and

$$\text{V=Jacobian of } \mathcal{V} \text{ at } E_0 = \begin{pmatrix} (b_1+\mu) & 0 & 0 & 0 & 0 & 0 \\ 0 & (b_2+\mu) & 0 & 0 & 0 & 0 \\ 0 & 0 & (b_3+\mu) & 0 & 0 & 0 \\ -b_1 & 0 & 0 & (\mu+d) & 0 & 0 \\ 0 & -b_2 & 0 & 0 & (\mu+d) & 0 \\ 0 & 0 & -b_3 & 0 & 0 & (\mu+d) \end{pmatrix}$$

Next generation matrix of the model system (3.1) is

$$FV^{-1} = \begin{pmatrix} 0 & \frac{\beta_1 \Lambda_1}{\mu(b_2+\mu)} & \frac{\beta_2 \Lambda_1}{\mu(b_3+\mu)} & 0 & 0 & 0 \\ \frac{\beta_3 \Lambda_2}{\mu(b_1+\mu)} & 0 & 0 & 0 & 0 & 0 \\ \frac{\beta_4 \Lambda_3}{\mu(b_1+\mu)} & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \end{pmatrix}$$

The spectral radius of the next generation matrix FV^{-1}, is the basic reproduction number of the model system (3.1) i.e., $R_0 = \rho(FV^{-1})$, hence

$$R_0 = \sqrt{\frac{\Lambda_1 \{\Lambda_2\beta_1\beta_3(b_3+\mu) + \Lambda_3\beta_2\beta_4(b_2+\mu)\}}{\mu^2(b_1+\mu)(b_2+\mu)(b_3+\mu)}}. \tag{3.2}$$

3.3.2 Equilibria of the model

In this section, the existence and stability of all possible equilibria of the model system (3.1) is discussed. It has been found that the system (3.1) has two possible non-negative equilibria: (i) Disease-free equilibrium denoted by E_0 and (ii) Endemic equilibrium denoted by E_1.

The disease-free equilibrium is always feasible as at this equilibrium infection is eradicated from the population. As stated above, the system (3.1) has a disease-free equilibrium given by,

$$\begin{aligned} E_0 &= (S_m^0, S_f^0, S_{fs}^0, I_m^0, I_f^0, I_{fs}^0, A_m^0, A_f^0, A_{fs}^0) \\ &= \left(\frac{\Lambda_1}{\mu}, \frac{\Lambda_2}{\mu}, \frac{\Lambda_3}{\mu}, 0, 0, 0, 0, 0, 0\right). \end{aligned} \tag{3.3}$$

3.3.3 The existence and uniqueness of endemic equilibrium

The endemic equilibrium point is denoted by $E_1 = (S_m^*, S_f^*, S_{fs}^*, I_m^*, I_f^*, I_{fs}^*, A_m^*, A_f^*, A_{fs}^*)$, where,

$$\begin{aligned}
S_m^* &= \frac{\Lambda_1 - (b_1+\mu)I_m^*}{\mu}, \\
S_f^* &= \frac{\Lambda_2}{\beta I_m^* + \mu}, \\
S_{fs}^* &= \frac{\Lambda_3}{\beta_4 I_m^* + \mu}, \\
I_f^* &= \frac{\Lambda_2\beta_3 I_m^*}{(\beta_3 I_m^* + \mu)(b_2+\mu)}, \\
I_{fs}^* &= \frac{\Lambda_3\beta_4 I_m^*}{(\beta_4 I_m^* + \mu)(b_3+\mu)}, \\
A_m^* &= \frac{b_1 I_m^*}{\mu + d}, \\
A_f^* &= \frac{b_2\Lambda_2\beta_3 I_m^*}{(\mu+d)(\beta_3 I_m^* + \mu)(b_2+\mu)}, \\
A_{fs}^* &= \frac{b_2\Lambda_3\beta_4 I_m^*}{(\mu+d)(\beta_4 I_m^* + \mu)(b_3+\mu)}.
\end{aligned}$$

It is easy to visualize that the variable values calculated above for endemic equilibrium point are positive if $I_m^* > 0$. Here I_m^* is given by the roots of the quadratic equation,

$$D_1 {I_m^*}^2 + D_2 I_m^* + D_3 = 0 \tag{3.4}$$

where

$$\begin{aligned}
D_1 &= \left[\Lambda_2\beta_1(b_3+\mu) + \Lambda_3\beta_2(b_2+\mu) + \mu(b_2+\mu)(b_3+\mu)\right]\beta_3\beta_4(b_1+\mu) > 0, \\
D_2 &= -\Lambda_1\Lambda_3\beta_2\beta_3\beta_4(b_2+\mu) - \Lambda_1\Lambda_2\beta_1\beta_3\beta_4(b_3+\mu) + \Lambda_2\beta_1\beta_3\mu(b_1+\mu)(b_3+\mu) \\
&\quad +\Lambda_3\beta_2\beta_4\mu(b_1+\mu)(b_2+\mu) + \mu^2(\beta_3+\beta_4)(b_1+\mu)(b_2+\mu)(b_3+\mu) \\
&= \mu^2\beta_4(b_1+\mu)(b_2+\mu)(b_3+\mu) \times \left[1 - \frac{\Lambda_1\left\{\Lambda_2\beta_1\beta_3(b_3+\mu) + \Lambda_3\beta_2\beta_3(b_2+\mu)\right\}}{\mu^2(b_1+\mu)(b_2+\mu)(b_3+\mu)}\right] \\
&\quad +\mu\beta_3(b_1+\mu)\left[\mu(b_2+\mu)(b_3+\mu) + \Lambda_2\beta_1(b_3+\mu)\right] + \Lambda_3\mu\beta_2\beta_4(b_1+\mu)(b_2+\mu), \\
D_3 &= \mu^3(b_1+\mu)(b_2+\mu)(b_3+\mu)(1-R_0^2).
\end{aligned}$$

The endemic nature of the equation (3.4) with above mentioned coefficient values is analyzed in following two cases:

(i) when $R_0 < 1$

(ii) when $R_0 > 1$.

Both the cases will be discussed one by one.

Explanation for case (i)

For $R_0 < 1$, we have $D_1 > 0$, and $D_3 > 0$. Notice that the rate of transmission in female sex worker β_4 is always greater than or equal to the rate of transmission in susceptible female β_3 i.e. $\beta_4 \geq \beta_3$.

Hence, $R_0 < 1$ implies that the first bracketed term in the expression of D_2 is positive. So in case (i) when $R_0 < 1$, there is no change in signs of D_1, D_2 and D_3. The Descartes's Rule of Signs ensures that there is no positive root of the above quadratic equation for $R_0 < 1$.

Explanation for case (ii)

For $R_0 > 1$, we have $D_1 > 0$ and $D_3 < 0$ whereas D_2 can be positive or negative. Again by using Descartes's Rule of Signs in this case, the quadratic equation (3.4) can have unique positive root irrespective of the sign of D_2. We have termed the positive root as I_m^*. Hence, existence of one positive real root (I_m^*) assures the positivity of endemic equilibrium point for $R_0 > 1$.

3.4 Stability analysis

In the following subsections, we discuss the local and global asymptotic stability properties of disease-free equilibrium point and endemic equilibrium point. First we evaluate the Jacobian matrix associated with the model (3.1) around the disease-free equilibrium point and there after the global stability results for the two equilibrium points are obtained and stated.

3.4.1 Stability analysis of disease-free equilibrium

Theorem 3.4.1: *The disease-free equilibrium E_0, is locally asymptotically stable when $R_0 < 1$ and unstable otherwise.*

Proof. The Jacobian matrix M_1 corresponding to the system (3.1) at disease-free equilibrium is calculated. We observe that the six eigenvalues of the matrix are $-\mu, -\mu, -\mu, -(\mu+d), -(\mu+d), -(\mu+d)$ and rest of the three eigenvalues are the roots of the following cubic equation:

$$a_0\lambda^3 + a_1\lambda^2 + a_2\lambda + a_3 = 0 \tag{3.5}$$

where

$$\begin{aligned}
a_0 &= 1, \\
a_1 &= x + y + z, \\
a_2 &= xy + yz + zx - \frac{\beta_1\beta_3\Lambda_1\Lambda_2}{\mu^2} - \frac{\beta_2\beta_4\Lambda_1\Lambda_3}{\mu^2}, \\
a_3 &= xyz - \frac{\beta_1\beta_3\Lambda_1\Lambda_2 z}{\mu^2} - \frac{\beta_2\beta_4\Lambda_1\Lambda_3 y}{\mu^2} \\
&= xyz(1 - R_0^2).
\end{aligned}$$

Here $x = b_1 + \mu, y = b_2 + \mu, z = b_3 + \mu$.

Clearly, $a_1 > 0, a_3 > 0$ for $R_0 < 1$ and $(a_1a_2 - a_3)$ is given as follows:

$$\begin{aligned}
a_1a_2 - a_3 &= (x+y+z)\left[xy + yz + zx - \frac{\beta_1\beta_3\Lambda_1\Lambda_2}{\mu^2} - \frac{\beta_2\beta_4\Lambda_1\Lambda_3}{\mu^2}\right] \\
&\quad -xyz + \frac{\beta_1\beta_3\Lambda_1\Lambda_2 z}{\mu^2} + \frac{\beta_2\beta_4\Lambda_1\Lambda_3 y}{\mu^2}, \\
&= (x+y)\left[x(y+z) - \frac{\beta_1\beta_3\Lambda_1\Lambda_2}{\mu^2} - \frac{\beta_2\beta_4\Lambda_1\Lambda_3}{\mu^2}\right] + \frac{y\Lambda_1\Lambda_3\beta_2\beta_4}{\mu^2} \\
&\quad +yz(y+z) + z\left[x(y+z) - \frac{\beta_2\beta_4\Lambda_1\Lambda_3}{\mu^2}\right].
\end{aligned}$$

It is easy to visualize that $(a_1a_2 - a_3)$ is positive for $R_0 < 1$ as the value of reproduction

number $R_0 < 1$ corresponds to,

$$x(y+z) > \frac{\beta_1\beta_3\Lambda_1\Lambda_2}{\mu^2} + \frac{\beta_2\beta_4\Lambda_1\Lambda_3}{\mu^2}.$$

Hence, by using Routh-Hurwitz criteria [103], the roots of the above cubic have negative real parts. Thus, E_0 is locally asymptotically stable for $R_0 < 1$. ∎

Now, the global stability of disease-free equilibrium using the following theorem by Castillo-Chavez *et al.* [55] is proved.

Theorem 3.4.2: *If the model system (3.1) can be written in the form:*

$$\begin{cases} X'(t) = F(X,Y), \\ Y'(t) = G(X,Y), \quad G(X,0) = 0. \end{cases} \tag{3.6}$$

where $X = S$ *and* $S = (S_m, S_f, S_{fs})^T$ *and* $Y = (I_m, I_f, I_{fs}, A_m, A_f, A_{fs})^T$ *with* $X \in \mathbb{R}^3{}_+$ *denoting the number of uninfected individuals and* $Y \in \mathbb{R}^6{}_+$ *denoting number of HIV infectives and AIDS patients.*

The disease-free equilibrium $E_0 = (X_0, 0) = \left(\frac{\Lambda_1}{\mu}, \frac{\Lambda_2}{\mu}, \frac{\Lambda_3}{\mu}, 0\right)$.

The conditions (H_1) *and* (H_2) *below must be met to guarantee global asymptotic stability of* E_0.

H_1*: For* $X'(t) = F(X_0, 0)$, X_0 *is globally asymptotically stable (g.a.s.),*

H_2*:* $G(X,Y) = AY - \widehat{G}(X,Y), \widehat{G}(X,Y) \geq 0$ *for* $(X,Y) \in \mathcal{D}$.

here $A = D_Y G(X_0, 0)$ *is an M-matrix (the off diagonal elements of A are non-negative) and* $\mathcal{D}$ *is the region where the model forms biological sense.*

If system (3.1) satisfies the conditions H_1 and H_2 mentioned in Theorem 3.4.2, then the fixed point $E_0 = (X_0, 0)$ is a globally asymptotic stable equilibrium of model system (3.1) provided $R_0 < 1$. For system (3.1) the result is stated and proved in following theorem:

Theorem 3.4.3: *The equilibrium point* $E_0 = (X_0, 0)$ *of the system* (3.1) *is globally asymp-*

totically stable provided $R_0 < 1$ (locally asymptotically stable) and that the assumption H_1 and H_2 are satisfied.

Proof. In Theorem 3.4.1, we have shown that for $R_0 < 1$, E_0 is locally asymptotically stable. Applying Theorem 3.4.2 to model system (3.1), we have

$F(X_0, 0) = \Gamma - \mu S$, where $\Gamma = (\Lambda_1, \Lambda_2, \Lambda_3)^T$,

$G(X, Y) = AY - \widehat{G}(X, Y)$,

where

$$A = \begin{pmatrix} -(b_1+\mu) & \beta_1 S_m^0 & \beta_2 S_m^0 & 0 & 0 & 0 \\ \beta_3 S_f^0 & -(b_2+\mu) & 0 & 0 & 0 & 0 \\ \beta_4 S_{fs}^0 & 0 & -(b_3+\mu) & 0 & 0 & 0 \\ b_1 & 0 & 0 & -(\mu+d) & 0 & 0 \\ 0 & b_2 & 0 & 0 & -(\mu+d) & 0 \\ 0 & 0 & b_3 & 0 & 0 & -(\mu+d) \end{pmatrix}$$

then

$$\widehat{G}(X, Y) = \begin{pmatrix} \widehat{G_1}(X, Y) \\ \widehat{G_2}(X, Y) \\ \widehat{G_3}(X, Y) \\ \widehat{G_4}(X, Y) \\ \widehat{G_5}(X, Y) \\ \widehat{G_6}(X, Y) \end{pmatrix} = \begin{pmatrix} \beta_1(S_m^0 - S_m)I_f + \beta_2(S_m^0 - S_m)I_{fs} \\ \beta_3(S_f^0 - S_f)I_m \\ \beta_4(S_{fs}^0 - S_{fs})I_m \\ 0 \\ 0 \\ 0 \end{pmatrix}$$

Here, $S_m^0 \geq S_m; S_f^0 \geq S_f; S_{fs}^0 \geq S_{fs}$, hence it is clear that $\widehat{G}(X, Y) \geq 0$ for all $(X, Y) \in \mathbb{R}_+^6$. We also notice that the matrix A is an M-Matrix since all its off-diagonal elements are non-negative. Hence, disease-free equilibrium E_0 is global asymptotically stability. ∎

3.4.2 Stability analysis of endemic equilibrium point

Theorem 3.4.4: *The endemic equilibrium, $E_1 = (S_m^*, S_f^*, S_{fs}^*, I_m^*, I_f^*, I_{fs}^*, A_m^*, A_f^*, A_{fs}^*)$, of model (3.1) is globally asymptotically stable for $R_0 > 1$.*

Proof. To prove global stability result we propose the following Lyapunov function:

$$\begin{aligned} V_1 &= c_1(S_m - S_m^* - S_m^* \ln \frac{S_m}{S_m^*}) + c_2(S_f - S_f^* - S_f^* \ln \frac{S_f}{S_f^*}) + c_3(S_{fs} - S_{fs}^* - S_{fs}^* \ln \frac{S_{fs}}{S_{fs}^*}) \\ &\quad + c_4(I_m - I_m^* - I_m^* \ln \frac{I_m}{I_m^*}) + c_5(I_f - I_f^* - I_f^* \ln \frac{I_f}{I_f^*}) + c_6(I_{fs} - I_{fs}^* - I_{fs}^* \ln \frac{I_{fs}}{I_{fs}^*}). \end{aligned}$$

The time derivative of V_1 is given by,

$$\begin{aligned} \dot{V_1} &= c_1 \left(1 - \frac{S_m^*}{S_m}\right) \dot{S_m} + c_2 \left(1 - \frac{S_f^*}{S_f}\right) \dot{S_f} + c_3 \left(1 - \frac{S_{fs}^*}{S_{fs}}\right) \dot{S_{fs}} + c_4 \left(1 - \frac{I_m^*}{I_m}\right) \dot{I_m} \\ &\quad + c_5 \left(1 - \frac{I_f^*}{I_f}\right) \dot{I_f} + c_6 \left(1 - \frac{I_m^*}{I_{fs}}\right) \dot{I_{fs}}. \\ &= c_1 \left(1 - \frac{S_m^*}{S_m}\right) [\Lambda_1 - \beta_1 S_m I_f - \beta_2 S_m I_{fs} - \mu S_m] + c_2 \left(1 - \frac{S_f^*}{S_f}\right) [\Lambda_2 - \beta_3 S_f I_m - \mu S_f] \\ &\quad + c_3 \left(1 - \frac{S_{fs}^*}{S_{fs}}\right) [\Lambda_3 - \beta_4 S_{fs} I_m - \mu S_{fs}] + c_4 \left(1 - \frac{I_m^*}{I_m}\right) [\beta_1 S_m I_f + \beta_2 S_m I_{fs} - (b_1 + \mu) I_m] \\ &\quad + c_5 \left(1 - \frac{I_f^*}{I_f}\right) [\beta_3 S_f I_m - (b_2 + \mu) I_f] + c_6 \left(1 - \frac{I_m^*}{I_{fs}}\right) [\beta_4 S_{fs} I_m - (b_3 + \mu) I_{fs}]. \end{aligned} \tag{3.7}$$

The model system (3.1) satisfy the following relations on the endemic equilibrium point:

$$\begin{aligned} \Lambda_1 &= \beta_1 S_m^* I_f^* + \beta_2 S_m^* I_{fs}^* + \mu S_m^*, \\ (b_1 + \mu) &= \beta_1 S_m^* \frac{I_f^*}{I_m^*} + \beta_2 S_m^* \frac{I_{fs}^*}{I_m^*}, \\ \Lambda_2 &= \beta_3 S_f^* I_m^* + \mu S_f^*, \\ (b_2 + \mu) &= \beta_3 S_f^* \frac{I_m^*}{I_f^*}, \\ \Lambda_3 &= \beta_4 S_{fs}^* I_m^* + \mu S_{fs}^*, \\ (b_3 + \mu) &= \beta_4 S_{fs}^* \frac{I_m^*}{I_{fs}^*}. \end{aligned}$$

On substituting the parameter values from Λ_1 to $(b_3+\mu)$ in (3.7), we obtain

$$\begin{aligned}
\dot{V}_1 &= c_1\left(1-\frac{S_m^*}{S_m}\right)[\beta_1 S_m^* I_f^* + \beta_2 S_m^* I_{fs}^* + \mu S_m^* - \beta_1 S_m I_f - \beta_2 S_m I_{fs} - \mu S_m] \\
&\quad + c_2\left(1-\frac{S_f^*}{S_f}\right)[\beta_3 S_f^* I_m^* + \mu S_f^* - \beta_3 S_f I_m - \mu S_f] \\
&\quad + c_3\left(1-\frac{S_{fs}^*}{S_{fs}}\right)[\beta_4 S_{fs}^* I_m^* + \mu S_{fs}^* - \beta_4 S_{fs} I_m - \mu S_{fs}] \\
&\quad + c_4\left(1-\frac{I_m^*}{I_m}\right)\left[\beta_1 S_m I_f + \beta_2 S_m I_{fs} - (\beta_1 S_m^* \frac{I_f^*}{I_m^*} + \beta_2 S_m^* \frac{I_{fs}^*}{I_m^*}) I_m\right] \\
&\quad + c_5\left(1-\frac{I_f^*}{I_f}\right)\left[\beta_3 S_f I_m - (\beta_3 S_f^* \frac{I_m^*}{I_f^*}) I_f\right] \\
&\quad + c_6\left(1-\frac{I_m^*}{I_{fs}}\right)\left[\beta_4 S_{fs} I_m - (\beta_4 S_{fs}^* \frac{I_m^*}{I_{fs}^*}) I_{fs}\right] \\
&= -c_1\mu\frac{(S_m - S_m^*)^2}{S_m} - c_2\mu\frac{(S_f - S_f^*)^2}{S_f} - c_3\mu\frac{(S_{fs} - S_{fs}^*)^2}{S_{fs}} \\
&\quad + c_1\left(1-\frac{S_m^*}{S_m}\right)(\beta_1 S_m^* I_f^* + \beta_2 S_m^* I_{fs}^* - \beta_1 S_m I_f - \beta_2 S_m I_{fs}) \\
&\quad + c_2\left(1-\frac{S_f^*}{S_f}\right)(\beta_3 S_f^* I_m^* - \beta_3 S_f I_m) \\
&\quad + c_3\left(1-\frac{S_{fs}^*}{S_{fs}}\right)(\beta_4 S_{fs}^* I_m^* - \beta_4 S_{fs} I_m) \\
&\quad + c_4\left(1-\frac{I_m^*}{I_m}\right)\left[\beta_1 S_m I_f + \beta_2 S_m I_{fs} - (\beta_1 S_m^* \frac{I_f^*}{I_m^*} + \beta_2 S_m^* \frac{I_{fs}^*}{I_m^*}) I_m\right] \\
&\quad + c_5\left(1-\frac{I_f^*}{I_f}\right)(\beta_3 S_f I_m - (\beta_3 S_f^* \frac{I_m^*}{I_f^*}) I_f) \\
&\quad + c_6\left(1-\frac{I_m^*}{I_{fs}}\right)(\beta_4 S_{fs} I_m - (\beta_4 S_{fs}^* \frac{I_m^*}{I_{fs}^*}) I_{fs}) \\
&= -c_1\mu\frac{(S_m - S_m^*)^2}{S_m} - c_2\mu\frac{(S_f - S_f^*)^2}{S_f} - c_3\mu\frac{(S_{fs} - S_{fs}^*)^2}{S_{fs}} \\
&\quad + f(x_1, x_2, x_3, x_4, x_5, x_6).
\end{aligned}$$

where
$\frac{S_m}{S_m^*} = x_1, \frac{S_f}{S_f^*} = x_2, \frac{S_{fs}}{S_{fs}^*} = x_3, \frac{I_m}{I_m^*} = x_4, \frac{I_f}{I_f^*} = x_5, \frac{I_{fs}}{I_{fs}^*} = x_6, S_m^* I_f^* = a, S_f^* I_m^* = b,$
$S_{fs}^* I_m^* = c, S_m^* I_{fs}^* = d.$

we get

$$\begin{aligned} f(x_1,x_2,x_3,x_4,x_5,x_6) &= (-c_1\beta_1 a + c_4\beta_1 a)x_1x_5 + (-c_5\beta_3 b + c_1\beta_1 a)x_5 + (-c_1\beta_2 d + c_4\beta_2 d)x_1x_6 \\ &\quad +(c_1\beta_2 d - c_6\beta_4 c)x_6 + (-c_2\beta_3 b + c_5\beta_3 b)x_2x_4 + (c_2\beta_3 b + c_3\beta_4 c - c_4\beta_1 a \\ &\quad -c_4\beta_2 d)x_4 + (-c_3\beta_4 c + c_6\beta_4 c)x_3x_4 + c_1\beta_1 a - c_1\beta_1 a\frac{1}{x_1} + c_1\beta_2 d \\ &\quad -c_1\beta_2 d\frac{1}{x_1} + c_2\beta_3 b - c_2\beta_3 b\frac{1}{x_2} + c_3\beta_4 c - c_3\beta_4 c\frac{1}{x_3} - c_4\beta_1 a\frac{x_1x_5}{x_4} \\ &\quad -c_4\beta_2 d\frac{x_1x_6}{x_4} + c_4\beta_1 a + c_4\beta_2 d - c_5\beta_3 b\frac{x_2x_4}{x_5} + c_5\beta_3 b - c_6\beta_4 c\frac{x_3x_4}{x_6} + c_6\beta_4 c. \end{aligned}$$

In order to determine c_1, c_2, c_3, c_4, c_5 and c_6, we set the coefficients of $x_1x_5, x_5, x_1x_6, x_6, x_2x_4, x_4$ and x_3x_4 equal to zero and solving the resulting equations, we obtain

$$c_1 = c_4; \quad c_2 = \frac{c_4\beta_1 a}{\beta_3 b} = c_5; \quad c_3 = \frac{c_4\beta_2 d}{\beta_4 c} = c_6.$$

Further by choosing $c_1 = c_4 = 1$,

we get

$$\begin{aligned} f(x_1,x_2,x_3,x_4,x_5,x_6) &= \beta_1 a\left[4 - \frac{1}{x_1} - \frac{x_1x_5}{x_4} - \frac{x_2x_4}{x_5} - \frac{1}{x_2}\right] \\ &\quad +\beta_2 d\left[4 - \frac{1}{x_1} - \frac{x_1x_6}{x_4} - \frac{x_3x_4}{x_6} - \frac{1}{x_3}\right]. \end{aligned}$$

Using arithmetic-geometric mean property, the arithmetic mean is greater than or equal to the geometric mean, hence we have,

$$\frac{1}{x_1} + \frac{x_1x_5}{x_4} + \frac{x_2x_4}{x_5} + \frac{1}{x_2} \geq 4,$$

and

$$\frac{1}{x_1} + \frac{x_1x_6}{x_4} + \frac{x_3x_4}{x_6} + \frac{1}{x_3} \geq 4.$$

Finally we obtained

$$\begin{aligned} \dot{V}_1 &= -\mu\frac{(S_m - S_m^*)^2}{S_m} - \mu\frac{\beta_1 a}{\beta_3 b}\frac{(S_f - S_f^*)^2}{S_f} - \mu\frac{\beta_2 d}{\beta_4 c}\frac{(S_{fs} - S_{fs}^*)^2}{S_{fs}} + \beta_1 a\left[4 - \frac{1}{x_1} - \frac{x_1x_5}{x_4}\right. \\ &\quad \left. -\frac{x_2x_4}{x_5} - \frac{1}{x_2}\right] + \beta_2 d\left[4 - \frac{1}{x_1} - \frac{x_1x_6}{x_4} - \frac{x_3x_4}{x_6} - \frac{1}{x_3}\right]. \end{aligned}$$

Thus, it implies $\dot{V}_1 \leq 0$ in $\mathcal{D}$. The equality $\dot{V}_1 = 0$ holds only for $x_1 = x_2 = x_3 = x_4 = x_5 =$

$x_6 = 1$ for which $S_m = S_m^*, S_f = S_f^*, S_{fs} = S_{fs}^*, I_m = I_m^*, I_f = I_f^*, I_{fs} = I_{fs}^*$. Hence, from the LaSalle's Invariance Principle [151], the global stability of unique endemic equilibrium E_1 of system (3.1) is ensured for $R_0 > 1$. ∎

3.5 Numerical simulation

The objective of these simulations is to illustrate some of the theoretical results obtained in this chapter. To show this, the system (3.1) is integrated using fourth order Runge-Kutta method for various set of parameter values using XPP [65]. In Figure 3.2, the stability of the disease-free equilibrium point E_0 is plotted for following set of parameter values:

$$\Lambda_1 = 80, \Lambda_2 = 60, \Lambda_3 = 50, \beta_1 = 0.00005, \beta_2 = 0.0002, \beta_3 = 0.0001,$$

$$\beta_4 = 0.0003, b_1 = 0.107261, b_2 = 0.0924, b_3 = 0.25, \mu = 0.0743, d = 0.123.$$

For this set of parameter values the basic reproduction number R_0 is computed as 0.939145. The equilibrium values corresponding to the disease-free equilibrium point have been found as

$S_m^0 = 1076.7, S_f^0 = 807.54, S_{fs}^0 = 672.95, I_m^0 = 0 = I_f^0 = I_{fs}^0 = A_m^0 = A_f^0 = A_{fs}^0$.

Figure 3.3, shows to the stability of the endemic equilibrium point E_1 for the following parameter values:

$$\Lambda_1 = 200, \Lambda_2 = 150, \Lambda_3 = 100, \beta_1 = 0.0002, \beta_2 = 0.0004, \beta_3 = 0.0002,$$

$$\beta_4 = 0.0004, b_1 = 0.4, b_2 = 0.3, b_3 = 0.5, \mu = 0.0463, d = 0.123$$

For this set of parameter values the basic reproduction number R_0 is evaluated as $R_0 = 1.460919$ and the endemic equilibrium values are obtained as

$$S_m^* = 1341.5, S_f^* = 1387.7, S_{fs}^* = 588.64, I_m^* = 308.96, I_f^* = 247.62,$$

$$I_{fs}^* = 133.16, A_m^* = 729.97, A_f^* = 438.77, A_{fs}^* = 393.27.$$

The phase portraits showing the variation of HIV infective male, female and female sex

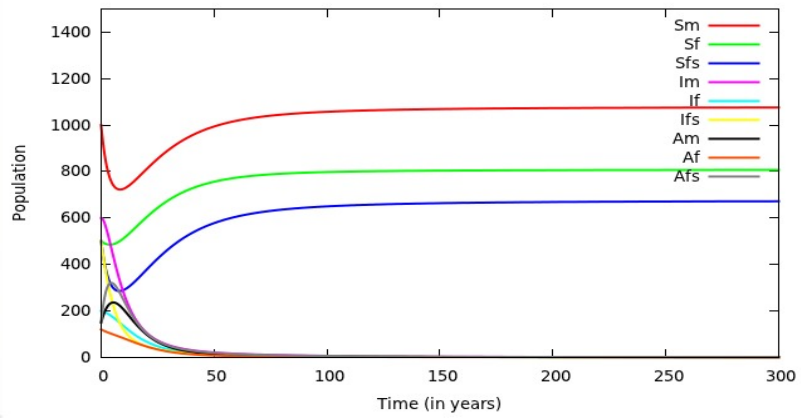

Figure 3.2: Stability of the disease-free equilibrium point E_0 for R_0= 0.939145.

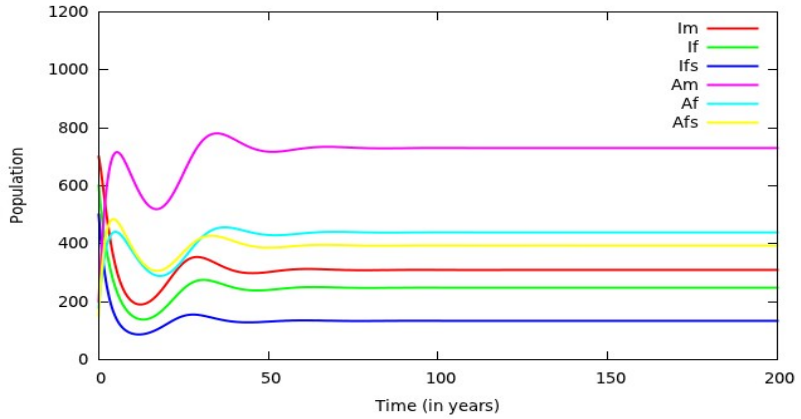

Figure 3.3: Stability of the endemic equilibrium point E_1 for R_0=1.460919.

worker population with susceptible male, female and female sex worker population (in $S_m - I_m$; $S_f - I_f$ and $S_{fs} - I_{fs}$ planes) are plotted in Figures. $3.4 - 3.6$. Figures 3.7-3.9 show the variation of different population groups (i.e. susceptible males, HIV infective males, AIDS infected males, AIDS infected females, AIDS infected female sex workers, respectively) for different values of β_2. It is observed that the number of HIV infectives increases with the increase in the parameter β_2, which corresponds to the rate of transmission due to female sex workers.

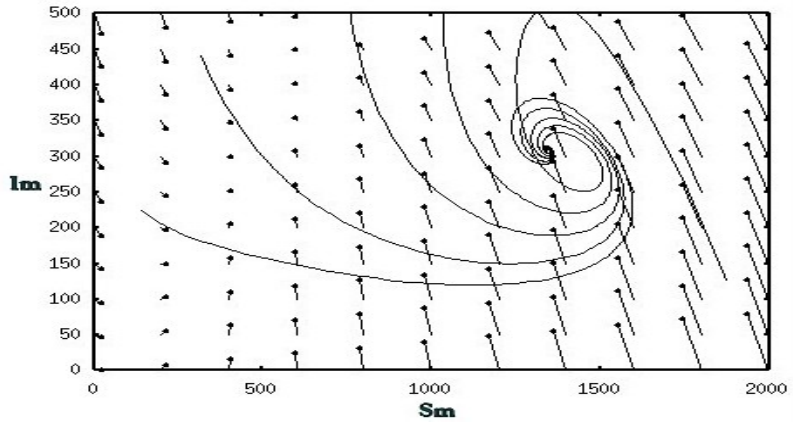

Figure 3.4: The phase portrait of endemic equilibrium point E_1 in $S_m - I_m$ plane.

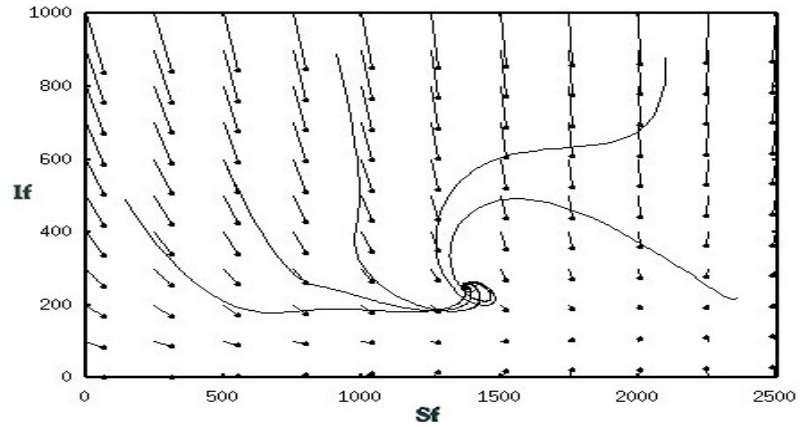

Figure 3.5: The phase portrait of endemic equilibrium point E_1 in $S_f - I_f$ plane.

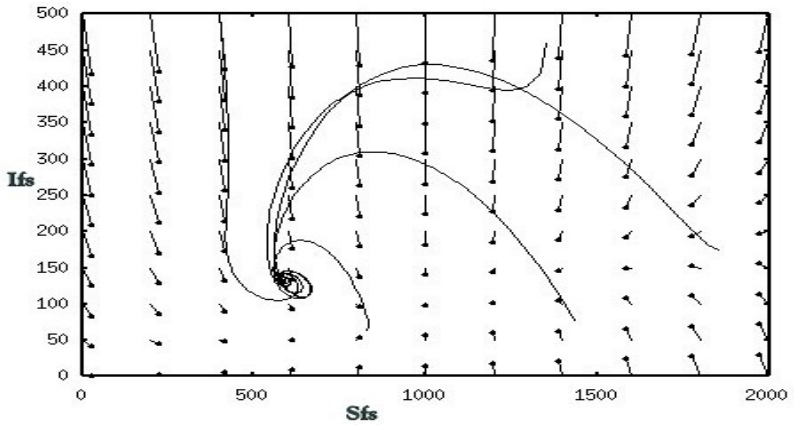

Figure 3.6: The phase portrait of endemic equilibrium point E_1 in $S_{fs} - I_{fs}$ plane.

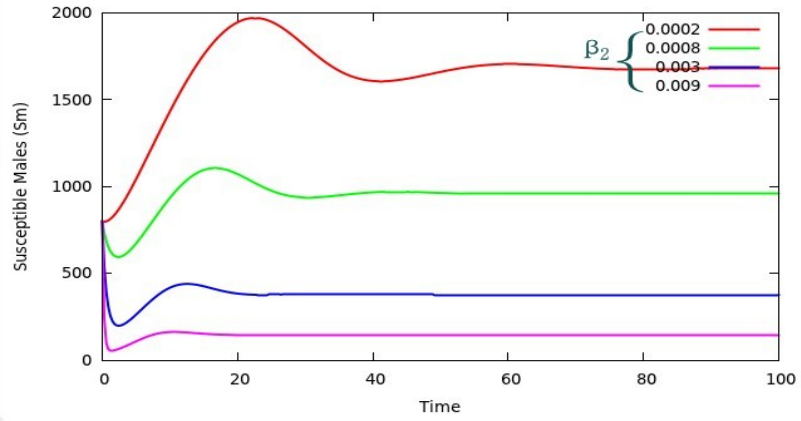

Figure 3.7: Variation of susceptible male population S_m for different values of β_2.

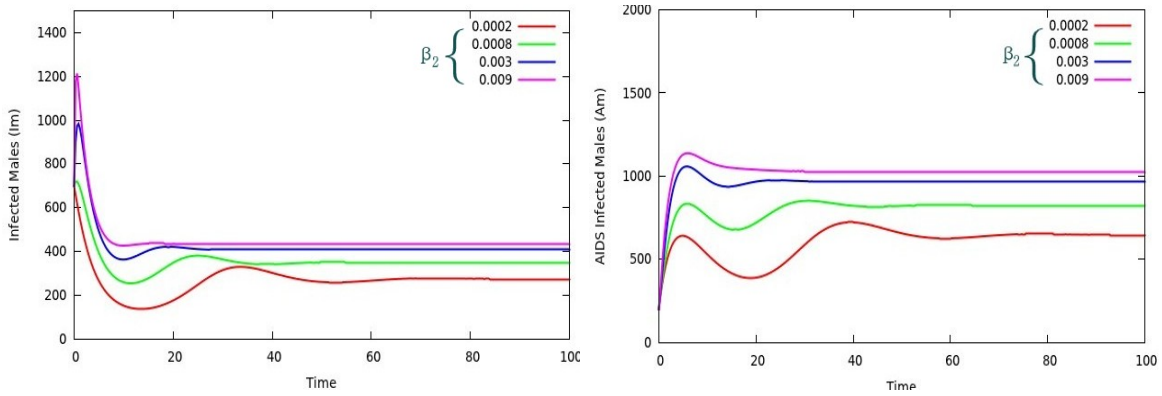

Figure 3.8: Variation of HIV infected male population I_m for different values of β_2 (Left panel) and variation of AIDS infected male population A_m for different values of β_2 (Right panel).

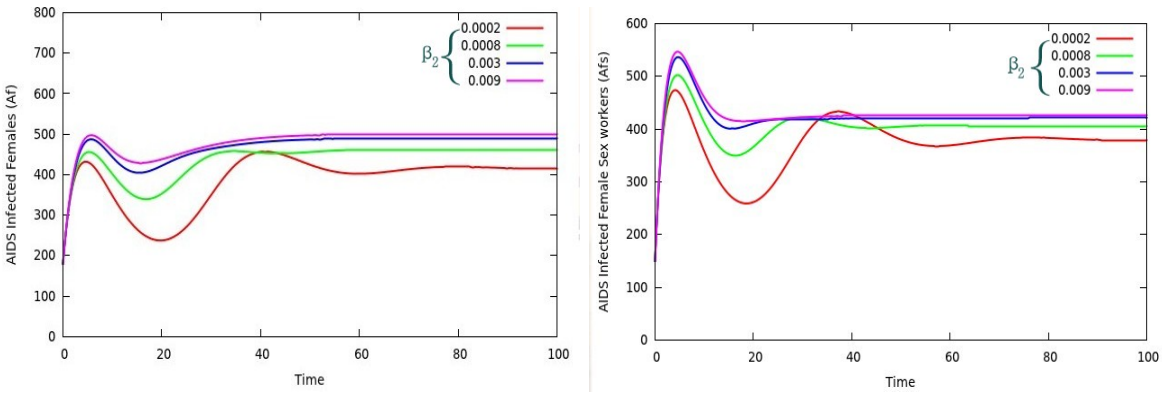

Figure 3.9: Variation of AIDS infected female population A_f for different values of β_2 (Left panel) and variation of AIDS infected female sex worker population A_{fs} for different values of β_2 (Right panel).

3.6 Conclusion

This chapter has been motivated by the importance in understanding the role of female sex-workers in transmission of the HIV, which is an observation widely accepted in all the major reports of the PLOS ONE and WHO (for reference see [141; 7]). In this work, the disease-free equilibrium is globally stable for $R_0 < 1$ whereas the endemic equilibrium is globally stable for $R_0 > 1$. The numerical simulations demonstrate that with the increase in the rate of transmission due to female sex workers, the total HIV infective population increases. Based upon the presented results, we conclude that to control the spread of HIV/AIDS epidemic, awareness among sex workers and their clients will play a very effective role which will certainly reduce the value of the rate of HIV infection transmission. Hence, the need is to make preventive and informed services for the sex workers. More widespread prevention efforts at a larger level with proper coverage are required that include changing the social and legal context of the sex workers.

Additionally, from the available research reports we have observed that the stigma and discrimination attached to sex workers are barriers in effective and equitable health care and treatment. Moreover, the criminalization of the sex workers restricts individuals from availing the health services which can improve their health and can increase their life span. In this regard, the available evidences suggest that the stigma reduction is critically important in efficient implementation of HIV prevention, care, and treatment policies. As discussed already, HIV transmission is strongly associated with un-protected sex. Keeping this point in focus the WHO (World Health Organization) has framed guidelines [7] for prevention and treatment of HIV and other sexually transmitted infections among sex workers in developing and low-income countries. As per these guidelines, the focus and emphasis is to be given on the decriminalization of sex workers.

Furthermore, these guidelines have outlined a set of interventions that includes: i) health services be made available, accessible and acceptable to sex workers grounded on

the principles of avoidance of stigma and non-discrimination; ii) to empower and make the sex workers aware and promote the correct and consistent use of condoms; iii) offering periodic screening for asymptomatic STIs to female sex workers; iv) voluntary HIV testing and counseling for couples and female sex-workers. Certainly, all these interventions can be helpful to reduce HIV transmission among female sex-workers and their clients. We believe that the analysis reported in this work can be strengthened by better understanding of limitations of the model and with appropriate real world data. The interventional programs and policies need to be designed to guide and empower female sex workers to adopt healthier sex behavior and to reduce their risk of HIV infection. Our future work will go in this direction and currently, this is under investigation.

Chapter 4

Modeling the Spread of HIV in a Stage Structured Population: Effect of Awareness [1]

4.1 Introduction

AIDS accounted for 1.6 million [1.4 million – 1.9 million] deaths in adults and 210 000 [190 000 – 250 000] deaths in children (< 15 years), as mentioned in UNAIDS (Joint United Nations Programme on HIV/AIDS) global report on AIDS for the year 2012. It has become a global pandemic because there is no vaccine or drug available to treat and cure it [75]. Scientists, epidemiologist and mathematical modelers are continuously working to understand the dynamics of HIV. Many studies have been performed to understand and analyze the transmission dynamics of HIV/AIDS [21; 52; 85; 115; 137; 164]. In [38], S. Blower shows that the overall HIV incidence rate can be reduced with increase in the availability of HIV treatment (HAART). This is shown only under the assumption that there will be a behaviorial change in the treated individuals and hence the levels of risky behavior will not increase. There are several studies incorporating treatment of HIV/AIDS [47; 48], effect of different age groups on transmission of AIDS [76] and role

[1] This work has been published in *International Journal of Biomathematics* 5(5) (2012) 1250040 (18 pages) DOI: 10.1142/S1793524511001829 (**SCI**)

of screening of unaware infectives [128; 166] without and with time delay and importance of media coverage [108] on prevalence level of HIV epidemic have been performed. The vertical transmission of HIV is incorporated in a study by Naresh et al. [127]. In this work, by keeping the essential biological and epidemiological factors in account, we have developed a nonlinear stage structured mathematical model incorporating the effect of awareness.

The chapter is organized as follows: In Section (4.2) we present the formulation and description of nonlinear stage structured model, ordinary differential equation model with awareness. Section (4.3) has four subsections. In Subsection (4.3.1) the computation of basic reproduction number is given. Subsection (4.3.2) defines the various non-negative equilibria associated with the model formulated in Section (4.2), thereafter Subsection (4.3.3) describes the existence of disease-free equilibrium and Subsection (4.3.4) defines the existences and uniqueness of endemic equilibrium. Section (4.4) presents the stability analysis corresponding to the two equilibria for the model. In Section (4.4) we have two subsections. The local and global stability results for disease-free equilibrium are stated and proved in Subsection (4.4.1) and in Subsection (4.4.2) the local stability conditions for endemic equilibrium point of the model are obtained. In Section (4.5), the numerical simulations to verify the theoretical results and to observe the effect of important parameters on the equilibrium level of infectives are shown, followed by the conclusion of the work in Section (4.6).

4.2 Mathematical model

In this section, a non-linear stage structured model for HIV is considered, where the whole population is divided into three different stages: child, adult and old. Here, we have considered three different classes for each stage: susceptible class, HIV infected class and the class of AIDS infected individuals. The total population at time t, denoted by

$N(t)$ is divided into mutually exclusive compartments, namely class of HIV susceptible children (X_1), HIV-susceptible adults (X_2), HIV-susceptible old X_3, HIV-infected children (Y_1), HIV-infected adults (Y_2), HIV-infected old (Y_3), AIDS-infected adults (Z_2), AIDS-infected old (Z_3). We have also included that children are acquiring HIV only by mode of vertical transmission (transmission from an infected mother to her offspring). It is assumed that new born children are susceptible and some fraction of total newborns are HIV infected at birth. Moreover, old age class is not taking part in the transmission of HIV and it is only the adult class which is involved in sexual transmission of HIV infection. The structural sub-division of the model system (4.1) and transfer diagram depicting model system (4.2) is shown in Figures 4.1 – 4.2. Note that, the AIDS patients

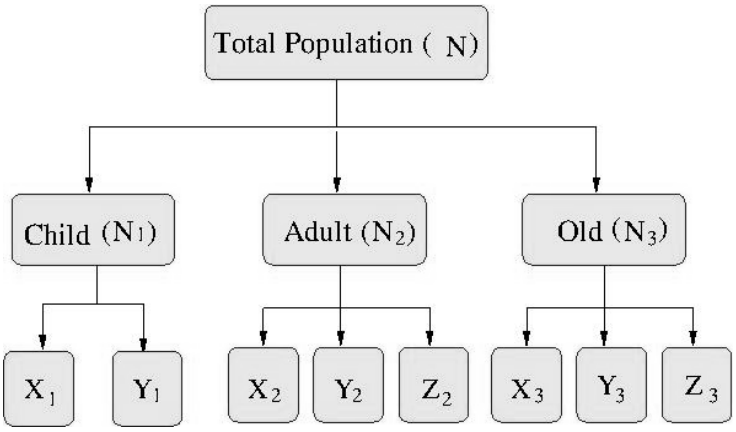

Figure 4.1: Structural description of model system (4.1)

(infected individuals) will not participate in the transmission of virus. A fraction of HIV infected individuals will further interact with susceptible adults and they will produce new HIV infected adults. We have already considered that a fraction $(1-\gamma)$ of unaware HIV infectives will give birth to HIV infected children via sexual contact with HIV susceptible individuals with a rate b. Also we have assumed that aware adults do not participate in the transmission of this disease. Some fraction of the infected but aware adults will go for treatment. Keeping the above assumptions in mind and by considering simple mass

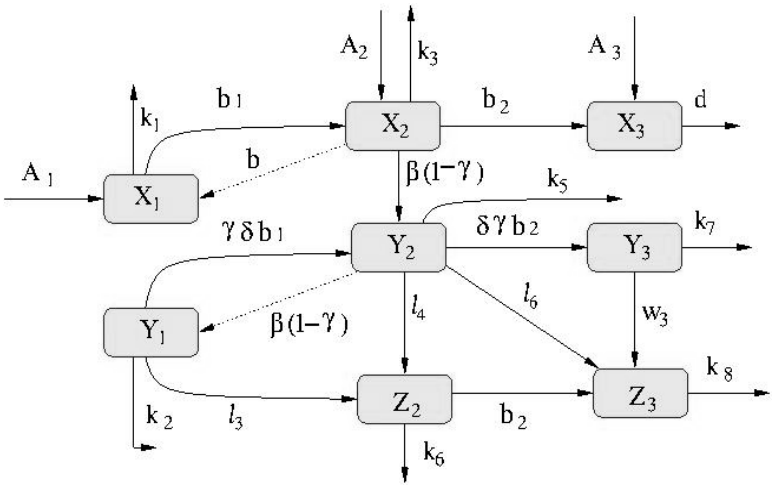

Figure 4.2: The transfer diagram of the model (4.2)

action interaction, a mathematical model is proposed as follows:

$$\begin{aligned}
\frac{dX_1}{dt} &= A_1 + bX_2 - b_1X_1 - dX_1,\\
\frac{dY_1}{dt} &= b\,(1-\gamma)\,Y_2 - \gamma\delta\,b_1\,Y_1 - \gamma(1-\delta)\,b_1\,Y_1 - (1-\gamma)\,b_1\,Y_1 - \alpha_1 Y_1 - dY_1,
\end{aligned}$$

$$\begin{aligned}
\frac{dX_2}{dt} &= A_2 + b_1X_1 - (d+b_2)\,X_2 - \beta(1-\gamma)\,X_2\,Y_2,\\
\frac{dY_2}{dt} &= \delta\gamma b_1\,Y_1 + \beta(1-\gamma)\,X_2\,Y_2 - \{\alpha_2 + \delta\gamma b_2 + (1-\delta)\gamma b_2 + (1-\gamma)b_2]\}\,Y_2\\
&\quad -\{w_1\{(1-\delta)\gamma + (1-\gamma)\} + w_2\gamma\delta + d\}\,Y_2,\\
\frac{dZ_2}{dt} &= \{[(1-\gamma) + (1-\delta)\gamma]b_1\}\,Y_1 + \{w_1[(1-\delta)\gamma + (1-\gamma)]\\
&\quad +w_2\delta\gamma\}\,Y_2 - (b_2 + \alpha_3 + d)\,Z_2,
\end{aligned} \tag{4.1}$$

$$\begin{aligned}
\frac{dX_3}{dt} &= A_3 + b_2\,X_2 - d\,X_3,\\
\frac{dY_3}{dt} &= \delta\gamma b_2\,Y_2 - (d + \alpha_4 + w_3)\,Y_3,\\
\frac{dZ_3}{dt} &= [(1-\delta)\gamma\,b_2 + (1-\gamma)b_2]\,Y_2 + b_2\,Z_2 + w_3\,Y_3 - (\alpha_5 + d)\,Z_3.
\end{aligned}$$

The descriptions of all parameters considered in model formulation are summarized in Table 4.1. Here the term transmission coefficient is used in the same context as used by Anderson and May in [18], which means that the new infections from the disease occur at the rate βXY due to interaction of susceptibles with the infectives.

Table 4.1: Description of parameters used in model system (4.1).

Parameter	Description
A_1, A_2, A_3	Recruitment rate into the child, adult, old stages of the population, respectively,
d	Natural death rate,
β	Transmission coefficient,
b	Birth rate which is proportional to number of adults,
$b(1-\gamma)$	Rate at which number of infected child will be produced by unaware adult infectives,
b_1	Rate of maturation from HIV infected child class to HIV infected adult class,
b_2	Rate of maturation from HIV infected adults class to HIV infected old class,
$\alpha_1, \alpha_2, \alpha_4$	Disease induced mortality rate in HIV classes ($Y_1,\ Y_2,\ Y_3$),
α_3, α_5	Disease induced mortality rate in AIDS classes (Z_2, Z_3),
γ	Fraction of individuals that are aware and this fraction is same in each class,
δ	Fraction of HIV infectives under treatment,
w_1, w_2	Progression rate from HIV infective (adults) class to AIDS class in untreated and treated adult classes, respectively,
w_3	Progression rate from HIV infective (old) class to AIDS individuals in old class.

Remark: The variables and parameters used in the formulation of the model system (4.1) are all non-negative for all $t \geq 0$. Since these variables and parameters are governing human-population. It can be seen that the region of attraction

$$\mathcal{D} = \left\{ (X_1, Y_1, X_2, Y_2, Z_2, X_3, Y_3, Z_3) \in \mathbb{R}^8_+ :\ 0 \leq N \leq \frac{A_1 + A_2 + A_3}{d} \right\},$$

is positively invariant and all solutions starting in this region $\mathcal{D}$ approach, enter or stay in the region $\mathcal{D}$. The continuity of right hand sides of (4.1) and its derivatives imply that unique solution exists [78].

To perform further analysis, we have re-written the model (4.1) in the following equivalent

system:

$$\begin{aligned}
\frac{dX_1}{dt} &= A_1 + bX_2 - k_1X_1, \\
\frac{dY_1}{dt} &= l_1Y_2 - k_2Y_1, \\
\frac{dX_2}{dt} &= A_2 + b_1X_1 - k_3X_2 - k_4X_2Y_2, \\
\frac{dY_2}{dt} &= l_2Y_1 + k_4X_2Y_2 - k_5Y_2, \\
\frac{dZ_2}{dt} &= l_3Y_1 + l_4Y_2 - k_6Z_2, \\
\frac{dX_3}{dt} &= A_3 + b_2X_2 - dX_3, \\
\frac{dY_3}{dt} &= l_5Y_2 - k_7Y_3, \\
\frac{dZ_3}{dt} &= l_6Y_2 + b_2Z_2 + w_3Y_3 - k_8Z_3.
\end{aligned} \tag{4.2}$$

$X_1(0) > 0,\ Y_1(0) \geq 0,\ X_2(0) > 0,\ Y_2(0) \geq 0,\ Z_2(0) \geq 0,\ X_3(0) > 0,$

$Y_3(0) \geq 0,\ Z_3(0) \geq 0.$

$k_1 = d + b_1,\ k_2 = d + \gamma\delta b_1 + \gamma(1-\delta)b_1 + (1-\gamma)b_1 + \alpha_1 = k_1 + \alpha_1,$

$k_3 = (d + b_2),\ k_4 = \beta(1-\gamma),$

$k_5 = \alpha_2 + \delta\gamma b_2 + (1-\delta)\gamma b_2 + w_1[(1-\delta)\gamma + (1-\gamma)] + w_2\gamma\delta + (1-\gamma)b_2 + d,$

$\quad = k_3 + \alpha_2 + w_1(1-\gamma\delta) + w_2\gamma\delta$

$k_6 = b_2 + \alpha_3 + d,\ k_7 = (d + \alpha_4 + w_3),\ k_8 = \alpha_5 + d,$

$l_1 = b(1-\gamma),\ l_2 = \delta\gamma b_1,\ l_3 = (1-\gamma)b_1 + (1-\delta)\gamma b_1,$

$l_4 = w_1[(1-\delta)\gamma + (1-\gamma)] + w_2\delta\gamma,\ l_5 = \gamma\delta b_2,\ l_6 = (1-\delta)\gamma b_2 + (1-\gamma)b_2.$

4.3 Basic reproduction number and existence of equilibria

4.3.1 Basic reproduction number

The model (4.2) has two possible non negative equilibria namely, the disease-free equilibrium E_0 and the endemic equilibrium E_1.

4.3.2 Disease-free equilibrium

For our model (4.2) we obtain the disease-free equilibrium $E_0(X_1^*, 0, X_2^*, 0, 0, X_3^*, 0, 0)$, which exists when $k_1k_3 > bb_1$. Here X_1^*, X_2^* and X_3^* are as follows:

$$\begin{aligned} X_1^* &= \frac{A_1 + \frac{bA_2}{k_3}}{k_1 - \frac{bb_1}{k_3}} \\ X_2^* &= \frac{A_2 + \frac{b_1A_1}{k_1}}{k_3 - \frac{bb_1}{k_1}} \\ X_3^* &= \frac{A_3 + b_2X_2^*}{d} \end{aligned} \tag{4.3}$$

Remark: As population size cannot be negative so throughout, our analysis it is obvious to assume $k_1k_3 > bb_1$. In this section, the basic reproduction number for the model (4.2) is calculated by using next generation matrix method as defined by Diekmann *et al.* in [61]. For the model system (4.2), the next generation matrix is described as follows:

$$M = \begin{pmatrix} Y_1 \to Y_1 & Y_2 \to Y_1 & Y_3 \to Y_1 \\ Y_1 \to Y_2 & Y_2 \to Y_2 & Y_3 \to Y_2 \\ Y_1 \to Y_3 & Y_2 \to Y_3 & Y_3 \to Y_3 \end{pmatrix} \tag{4.4}$$

Here $Y_i \to Y_j$ denotes the number of new individuals in Y_j class generated by single individual of Y_i class in his/her whole infectious period.

For our model, we get

$$\begin{aligned}
Y_1 \to Y_1 &= P(Y_1 \to Y_2)T(Y_2)l_1 = \frac{l_2}{k_2}\frac{l_1}{k_5}, \\
Y_1 \to Y_2 &= P(Y_1 \to Y_2)T(Y_2)(R(Y_2 : X_2)) = \frac{l_2}{k_2}\frac{1}{k_5}k_4X_2^*, \\
Y_1 \to Y_3 &= P(Y_1 \to Y_2)[1 + T(Y_2)(R(Y_2 : X_2))]P(Y_2 \to Y_3) \\
&\quad \times P(Y_2 \to Y_3), \\
&= \frac{l_2l_5}{k_2k_5} + \frac{l_2l_5k_4X_2^*}{k_2k_5^2}, \\
Y_2 \to Y_1 &= T(Y_2)l_1 = \frac{l_1}{k_5}, \\
Y_2 \to Y_2 &= T(Y_2)(R(Y_2 : X_2)) = \frac{1}{k_5}k_4X_2^*, \\
Y_2 \to Y_3 &= [1 + T(Y_2)(R(Y_2 : X_2)]P(Y_2 \to Y_3) = \frac{l_5}{k_5} + \frac{l_5k_4X_2^*}{k_5^2}, \\
Y_3 \to Y_1 &= 0, \quad Y_3 \to Y_2 = 0, \quad Y_3 \to Y_3 = 0,
\end{aligned}$$

where

$\mathrm{T}(Y_2)$ = Time when HIV infected adult remains infectious $= \dfrac{1}{k_5}$,

$\mathrm{P}(Y_1 \to Y_2)$ = Probability that HIV infected child becomes HIV infected adult $= \dfrac{l_2}{k_2}$,

$\mathrm{P}(Y_2 \to Y_3)$ = Probability that HIV infected adult becomes HIV infected old $= \dfrac{l_5}{k_5}$,

$\mathrm{R}(Y_2 : X_2)$ = Rate at which HIV infected adult infects HIV susceptible adult $= k_4X_2^*$,

where X_2^* corresponds to disease-free equilibrium level of the population in X_2 class.

After substituting above mentioned values we get the next generation matrix M for model system (4.2) evaluated at disease-free equilibrium as follows:

$$M = \begin{pmatrix} \dfrac{l_2}{k_2}\dfrac{l_1}{k_5} & \dfrac{l_1}{k_5} & 0 \\ \dfrac{l_2}{k_2}\dfrac{1}{k_5}k_4X_2^* & \dfrac{1}{k_5}k_4X_2^* & 0 \\ \dfrac{l_2l_5}{k_2k_5} + \dfrac{l_2l_5k_4X_2^*}{k_2k_5^2} & \dfrac{l_5}{k_5} + \dfrac{l_5k_4X_2^*}{k_5^2} & 0 \end{pmatrix} \tag{4.5}$$

The spectral radius of this matrix is called the basic reproduction number. We see that one of the eigenvalues is zero and rest of the two eigenvalues are the roots of following

quadratic equation:

$$(m_{11}-\lambda)(m_{22}-\lambda)-m_{12}m_{21}=0$$

$$\lambda^2-(m_{11}+m_{22})\lambda+m_{11}m_{22}-m_{12}m_{21}=0$$

$$\lambda^2-(\frac{l_1l_2}{k_2k_5}+\frac{k_4X_2^*}{k_5})\lambda=0$$

$$\text{this gives,}\quad \lambda=0,\frac{l_1l_2}{k_2k_5}+\frac{k_4X_2^*}{k_5}.$$

Hence, the reproduction number of the model is given by

$$R_0=\frac{l_1l_2}{k_2k_5}+\frac{k_4X_2^*}{k_5}. \tag{4.6}$$

Alternatively, one can find the reproduction number R_0 by using the method described by Van den Driessche and Watmough in [168] and following the same notation as in [168] the matrices $\mathcal{F}$, $\mathcal{V}$, F and V are, respectively, given by

$$\mathcal{F}=\begin{pmatrix} l_1Y_2 \\ k_4X_2Y_2 \\ 0 \\ 0 \\ 0 \end{pmatrix},$$

$$\mathcal{V}=\begin{pmatrix} k_2Y_1 \\ -l_2Y_1+k_5Y_2 \\ -(l_3Y_1+l_4Y_2-k_6Z_2) \\ -l_5Y_2+k_7Y_3 \\ -l_6Y_2-b_2Z_2-w_3Y_3+k_8Z_3 \end{pmatrix},$$

$$\text{F= Jacobian of } \mathcal{F} \text{ at } E_0=\begin{pmatrix} 0 & l_1 & 0 & 0 & 0 \\ 0 & k_4X_2^* & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \end{pmatrix},$$

$$\text{V=Jacobian of } \mathcal{V} \text{ at } E_0 = \begin{pmatrix} k_2 & 0 & 0 & 0 & 0 \\ -l_2 & k_5 & 0 & 0 & 0 \\ -l_3 & -l_4 & k_6 & 0 & 0 \\ 0 & -l_5 & 0 & k_7 & 0 \\ 0 & -l_6 & -b_2 & -w_3 & k_8 \end{pmatrix}$$

Thus, the matrix FV^{-1} is given by

$$FV^{-1} = \begin{pmatrix} \frac{l_1 l_2}{k_2 k_5} & \frac{l_1}{k_5} & 0 & 0 & 0 \\ \frac{X_2^* k_4 l_2}{k_2 k_5} & \frac{X_2^* k_4}{k_5} & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \end{pmatrix}$$

The eigenvalues of the matrix FV^{-1} are obtained as 0 and $\frac{l_1 l_2}{k_2 k_5} + \frac{X_2^* k_4}{k_5}$.

The spectral radius of the matrix FV^{-1} represents the reproduction number R_0, given by

$$R_0 = \frac{l_1 l_2}{k_2 k_5} + \frac{X_2^* k_4}{k_5}. \tag{4.7}$$

4.3.3 Equilibria of the model

As $X_1 + Y_1 = N_1, X_2 + Y_2 + Z_2 = N_2, X_3 + Y_3 + Z_3 = N_3$, it is sufficient to consider the equations of rate of change of $N_1, N_2, N_3, Y_1, Y_2, Y_3, Z_2$ and Z_3 only.

$$\begin{aligned}
\frac{dN_1}{dt} &= A_1 - k_1N_1 + bN_2 + (k_1 - k_2)Y_1 + (l_1 - b)Y_2 - bZ_2, \\
\frac{dY_1}{dt} &= l_1Y_2 - k_2Y_1, \\
\frac{dN_2}{dt} &= A_2 + b_1N_1 - k_3N_2 + (l_2 + l_3 - b_1)Y_1 + (k_3 + l_4 - k_5)Y_2 \\
&\quad +(k_3 - k_6)Z_2, \\
\frac{dY_2}{dt} &= l_2Y_1 + k_4N_2Y_2 - k_4Y_2^2 - k_4Z_2Y_2 - k_5Y_2, \\
\frac{dZ_2}{dt} &= l_3Y_1 + l_4Y_2 - k_6Z_2, \\
\frac{dN_3}{dt} &= A_3 + b_2N_2 - dN_3 + (l_5 + l_6 - b_2)Y_2 + (d + w_3 - k_7)Y_3 \\
&\quad +(d - k_8)Z_3, \\
\frac{dY_3}{dt} &= l_5Y_2 - k_7Y_3, \\
\frac{dZ_3}{dt} &= l_6Y_2 + w_3Y_3 + b_2Z_2 - k_8Z_3.
\end{aligned} \tag{4.8}$$

The model (4.8) has two possible non negative equilibria namely, the disease-free equilibrium E_0 and the endemic equilibrium E_1.

4.3.4 Disease-free equilibrium

As mentioned already, model system (4.8) we obtain the disease-free equilibrium $E_0(N_1^*, 0, N_2^*, 0, 0, N_3^*)$ which exists when $k_1k_3 > bb_1$. Here N_1^*, N_2^* and N_3^* are as follows:

$$\begin{aligned} X_1^* &= N_1^* = \frac{A_1 + \dfrac{bA_2}{k_3}}{k_1 - \dfrac{bb_1}{k_3}} \\ X_2^* &= N_2^* = \frac{A_2 + \dfrac{b_1A_1}{k_1}}{k_3 - \dfrac{bb_1}{k_1}} \\ X_3^* &= N_3^* = \frac{A_3 + b_2X_2^*}{d} \end{aligned} \tag{4.9}$$

Remark: As population size cannot be negative so throughout, our analysis it is obvious to assume $k_1k_3 > bb_1$.

4.3.5 Existence and uniqueness of endemic equilibrium

For our model (4.8), the endemic equilibrium is $E_1(\hat{N_1}, \hat{Y_1}, \hat{N_2}, \hat{Y_2}, \hat{Z_2}, \hat{N_3}, \hat{Y_3}, \hat{Z_3})$, where

$$\begin{aligned}
\hat{N_1} &= \frac{A_1}{k_1} + \frac{l_1}{k_2}\hat{Y_2} + \frac{b}{k_1}\left(\frac{k_2k_5 - l_1l_2}{k_2k_4}\right) \\
\hat{Y_1} &= \frac{l_1}{k_2}\hat{Y_2} \\
\hat{N_2} &= \left[1 + \frac{l_1l_3 + l_4k_2}{k_2k_6}\right]\hat{Y_2} + \left(\frac{k_2k_5 - l_1l_2}{k_2k_4}\right) \\
\hat{Z_2} &= \left[\frac{l_1l_3 + l_4k_2}{k_2k_6}\right]\hat{Y_2} \\
\hat{N_3} &= \frac{1}{d}\left[(l_5 + l_6) + \frac{(l_1l_3 + l_4k_2)b_2}{k_2k_6} + \frac{(d - k_7 + w_3)l_5}{k_7} + \frac{(d - k_8)(k_7l_6 + l_5w_3)}{k_7k_8}\right. \\
&\quad \left. + \frac{(d - k_8)(l_1l_3 + k_2l_4)b_2}{k_2k_6k_8}\right]\hat{Y_2} + \frac{A_3}{d} + \frac{b_2}{dk_4}\left[\frac{k_2k_5 - l_1l_2}{k_2}\right] \qquad (4.10) \\
&= \left[\frac{l_5}{k_7} + \frac{l_6}{k_8} + \frac{l_5w_3}{k_7k_8} + \frac{(l_1l_3 + k_2k_4)b_2}{k_2k_6k_8}\right]\hat{Y_2} + \frac{A_3}{d} + \frac{b_2}{dk_4}\left[\frac{k_2k_5 - l_1l_2}{k_2}\right] \\
\hat{Y_3} &= \frac{l_5}{k_7}\hat{Y_2} \\
\hat{Z_3} &= \left[\frac{l_6}{k_8} + \frac{w_3l_5}{k_7k_8} + \frac{b_2l_1l_3 + b_2l_4k_2}{k_2k_6k_8}\right]\hat{Y_2} \\
\hat{Y_2} &= \frac{A_2 + \frac{b_1A_1}{k_1} + \left(\frac{bb_1}{k_1} - k_3\right)\frac{k_2k_5 - l_1l_2}{k_2k_4}}{\frac{k_2k_5 - l_1l_2}{k_2}} = \frac{k_2(k_1k_3 - bb_1)(R_0 - 1)}{k_1k_4k_5(k_2k_5 - l_1l_2)}.
\end{aligned}$$

$\hat{Y_2}$ is positive when R_0 is greater than one as $k_2k_5 > l_1l_2$ and also using the assumption $k_1k_3 > bb_1$. Hence, the existence of unique positive endemic equilibrium point is guaranteed under the condition $R_0 > 1$.

4.4 Stability analysis

In the following subsections, we first discuss the local and global asymptotic stability properties of disease-free equilibrium and the local stability analysis for endemic equilibrium. Thereafter the stability results for the two equilibria are obtained and stated.

4.4.1 Stability analysis of disease-free equilibrium

Theorem 4.4.1: *If $R_0 < 1$, the disease-free equilibrium E_0 is locally asymptotically stable and unstable if $R_0 > 1$.*

Proof. The Jacobian matrix M^* of the model system (4.7) evaluated at disease-free equilibrium E_0 is given by

$$M^* = \begin{pmatrix} m_{11} & m_{12} & m_{13} & m_{14} & m_{15} & 0 & 0 & 0 \\ 0 & m_{22} & 0 & m_{24} & 0 & 0 & 0 & 0 \\ m_{31} & m_{32} & m_{33} & m_{34} & m_{35} & 0 & 0 & 0 \\ 0 & m_{42} & 0 & m_{44} & 0 & 0 & 0 & 0 \\ 0 & m_{52} & 0 & m_{54} & m_{55} & 0 & 0 & 0 \\ 0 & 0 & m_{63} & m_{64} & 0 & m_{66} & m_{67} & m_{68} \\ 0 & 0 & 0 & m_{74} & 0 & 0 & m_{77} & 0 \\ 0 & 0 & 0 & m_{84} & m_{85} & 0 & m_{87} & m_{88} \end{pmatrix}$$

where

$m_{11} = -k_1,\ m_{12} = k_1 - k_2,\ m_{13} = b,\ m_{14} = l_1 - b,\ m_{15} = -b,$

$m_{22} = -k_2,\ m_{24} = l_1,$

$m_{31} = b_1,\ m_{32} = l_2 + l_3 - b_1,\ m_{33} = -k_3,\ m_{34} = l_4 + k_3 - k_5,\ m_{35} = k_3 - k_6,$

$m_{42} = l_2,\ m_{43} = 0,\ m_{44} = k_4 N_2^* - k_5,\ m_{45} = 0$

$m_{52} = l_3,\ m_{54} = l_4,\ m_{55} = -k_6,$

$m_{63} = b_2,\ m_{64} = l_5 + l_6 - b_2,\ m_{66} = -d,\ m_{67} = d + w_3 - k_7,\ m_{68} = d - k_8,$

$m_{74} = l_5,\ m_{77} = -k_7,$

$m_{84} = l_6,\ m_{85} = b_2,\ m_{87} = w_3,\ m_{88} = -k_8.$

From the Jacobian matrix, it has been found that four roots of the characteristic equation are given by $-d, -k_6, -k_7, -k_8$ and other four roots are the solution of following quadratic

equations:

$$\lambda^2 + (k_1 + k_3)\lambda + (bb_1 + k_1k_3) = 0, \tag{4.11}$$

$$\lambda^2 + (k_2 + k_5 - k_4N_2^*)\lambda + (k_2k_5 - k_2k_4N_2^* - l_1l_2) = 0. \tag{4.12}$$

The equilibrium point E_0 will be locally asymptotically stable if eigenvalues of characteristic equation are either negative or have negative real parts. Here in equation (4.11), coefficient of λ and constant term are positive. The coefficient of λ i.e.$(k_2 + k_5 - k_4N_2^*)$ and the constant term $(k_2k_5 - k_2k_4N_2^* - l_1l_2)$ in equation (4.12) are also positive under the condition $R_0 = \dfrac{l_1l_2}{k_2k_5} + \dfrac{X_2^*k_4}{k_5} < 1$ as $N_2^* = X_2^*$ in absence of disease. Hence, both quadratic equations will have roots with negative real parts. This implies the stability of the disease free equilibrium under the condition $R_0 < 1$. ∎

Now, the global stability of the disease-free equilibrium point E_0 is established using Theorem 2 of [168] and stated in following theorem.

Theorem 4.4.2: *If $R_0 < 1$, the disease-free equilibrium E_0 is globally asymptotically stable and unstable if $R_0 > 1$.*

Proof. We will prove global stability of E_0 by using comparison theorem [105]. The rate of change of the variables representing the infected components of system (4.2) can be rewritten as

$$\begin{pmatrix} Y_1' \\ Y_2' \\ Z_2' \\ Y_3' \\ Z_3' \end{pmatrix} = (F - V) \begin{pmatrix} Y_1 \\ Y_2 \\ Z_2 \\ Y_3 \\ Z_3 \end{pmatrix} - \begin{pmatrix} 0 \\ k_4Y_2(X_2^* - X_2) \\ 0 \\ 0 \\ 0 \end{pmatrix}$$

The matrices F and V are defined by the expressions in (4.6).

However, since $X_2 \leq X_2^* = N_2^*$, hence

$$\begin{pmatrix} Y_1' \\ Y_2' \\ Z_2' \\ Y_3' \\ Z_3' \end{pmatrix} \leq (F - V) \begin{pmatrix} Y_1 \\ Y_2 \\ Z_2 \\ Y_3 \\ Z_3 \end{pmatrix} \tag{4.13}$$

Three eigenvalues of the matrix $F - V$ are $-k_6, \ -k_7, \ -k_8$ and other two eigenvalues are given by the roots of the quadratic equation,

$$\lambda^2 + \{k_2 + k_5 - k_4 X_2^*\}\lambda + \{k_2(k_5 - k_4 X_2^*) - l_1 l_2\} = 0 \tag{4.14}$$

It is easy to verify here that for $R_0 < 1$ the constant term as well as the co-efficient of λ in the last quadratic equation are positive which implies the roots of the quadratic equation have negative real parts. Thus, the inequality (4.12) is stable for $R_0 < 1$ (see for result of Lemma 1 in [168]). Thus, it follows that $(Y_1, Y_2, Z_2, Y_3, Z_3) \to (0, 0, 0, 0, 0)$ as $t \to \infty$. By the comparison theorem in [105] it follows that $(Y_1, Y_2, Z_2, Y_3, Z_3) \to (0, 0, 0, 0, 0)$. Also, from the expressions in (4.8) it is found that $X_1 \to X_1^* = N_1^*, X_2 \to X_2^* = N_2^*$ and $X_3 \to X_3^* = N_3^*$ whenever $Y_1 = 0 = Y_2 = Z_2 = Y_3 = Z_3$.

Thus, for $R_0 < 1$, the disease-free equilibrium point $E_0(N_1^*, 0, N_2^*, 0, 0, N_3^*, 0, 0)$ is globally asymptotically stable. ∎

4.4.2 Stability analysis of endemic equilibrium

Theorem 4.4.3: *If $R_0 > 1$, the endemic equilibrium $E_1(\hat{N}_1, \hat{Y}_1, \hat{N}_2, \hat{Y}_2, \hat{Z}_2, \hat{N}_3, \hat{Y}_3, \hat{Z}_3)$ is locally asymptotically stable provided*

$$a_4 > 0, \quad \begin{vmatrix} a_4 & a_2 \\ 1 & a_3 \end{vmatrix} > 0, \quad \begin{vmatrix} a_4 & a_2 & a_0 \\ 1 & a_3 & a_1 \\ 0 & a_4 & a_2 \end{vmatrix} > 0,$$

$$\begin{vmatrix} a_4 & a_2 & a_0 & 0 \\ 1 & a_3 & a_1 & 0 \\ 0 & a_4 & a_2 & a_0 \\ 0 & 1 & a_3 & a_1 \end{vmatrix} > 0, \quad \begin{vmatrix} a_4 & a_2 & a_0 & 0 & 0 \\ 1 & a_3 & a_1 & 0 & 0 \\ 0 & a_4 & a_2 & a_0 & 0 \\ 0 & 1 & a_3 & a_1 & 0 \\ 0 & 0 & a_4 & a_2 & a_0 \end{vmatrix} > 0.$$

where a_0, a_1, a_2, a_3 and a_4 are given in the proof of this theorem.

Proof. The Jacobian matrix, $\hat{M}$ corresponding to the system (4.2) at endemic equilibrium $E_1(\hat{N_1}, \hat{Y_1}, \hat{N_2}, \hat{Y_2}, \hat{Z_2}, \hat{N_3}, \hat{Y_3}, \hat{Z_3})$ is given by

$$\hat{M} = \begin{pmatrix} n_{11} & n_{12} & n_{13} & n_{14} & n_{15} & 0 & 0 & 0 \\ 0 & n_{22} & 0 & n_{24} & 0 & 0 & 0 & 0 \\ n_{31} & n_{32} & n_{33} & n_{34} & n_{35} & 0 & 0 & 0 \\ 0 & n_{42} & n_{43} & n_{44} & n_{45} & 0 & 0 & 0 \\ 0 & n_{52} & 0 & n_{54} & n_{55} & 0 & 0 & 0 \\ 0 & 0 & n_{63} & n_{64} & 0 & n_{66} & n_{67} & n_{68} \\ 0 & 0 & 0 & n_{74} & 0 & 0 & n_{77} & 0 \\ 0 & 0 & 0 & n_{84} & n_{85} & 0 & n_{87} & n_{88} \end{pmatrix}$$

where

$n_{11} = -k_1,\ n_{12} = k_1 - k_2,\ n_{13} = b,\ n_{14} = l_1 - b,\ n_{15} = -b,$

$n_{22} = -k_2,\ n_{24} = l_1,$

$n_{31} = b_1,\ n_{32} = l_2 + l_3 - b_1,\ n_{33} = -k_3,\ n_{34} = l_4 + k_3 - k_5,\ n_{35} = k_3 - k_6,$

$n_{42} = l_2,\ n_{43} = k_4\hat{Y_2},\ n_{44} = (\hat{N_2} - 2\hat{Y_2} - \hat{Z_2})k_4 - k_5 = -k_4\hat{Y_2} - \frac{l_2\hat{Y_1}}{\hat{Y_2}},\ n_{45} = -k_4\hat{Y_2},$

$n_{52} = l_3,\ n_{54} = l_4,\ n_{55} = -k_6,$

$n_{63} = b_2,\ n_{64} = l_5 + l_6 - b_2,\ n_{66} = -d,\ n_{67} = d + w_3 - k_7,\ n_{68} = d - k_8,$

$n_{74} = l_5,\ n_{77} = -k_7,$

$n_{84} = l_6,\ n_{85} = b_2,\ n_{87} = w_3,\ n_{88} = -k_8.$

The Jacobian matrix gives three negative eigenvalues as $-d, -k_7, -k_8$ and other five eigen-

values are the solutions of the following fifth-degree equation,

$$\lambda^5 + a_4\lambda^4 + a_3\lambda^3 + a_2\lambda^2 + a_1\lambda + a_0 = 0. \tag{4.15}$$

where

$$\begin{aligned}
a_4 &= -(n_{11} + n_{22} + n_{33} + n_{44} + n_{55}),\\
a_3 &= -[n_{13}n_{31} + n_{24}n_{42} + n_{34}n_{43} + n_{45}n_{54} - n_{11}(n_{22} + n_{33} + n_{44} + n_{55}) - n_{22}(n_{33}\\
&\quad +n_{44} + n_{55}) - n_{33}(n_{44} + n_{55}) - n_{44}n_{55}],\\
a_2 &= -[-n_{24}n_{42}(n_{11} + n_{33} + n_{55}) - n_{24}n_{32}n_{43} + n_{24}n_{45}n_{52} - n_{22}n_{45}n_{54} + n_{35}n_{43}n_{54} - n_{11}n_{45}n_{54}\\
&\quad -n_{33}n_{45}n_{54} + n_{22}n_{55}(n_{11} + n_{33} + n_{44}) - n_{34}n_{43}(n_{22} + n_{55}) + n_{11}(n_{22}n_{33} + n_{22}n_{44}\\
&\quad +n_{33}n_{55} + n_{44}n_{55}) + n_{33}n_{44}(n_{11} + n_{22} + n_{55}) + n_{14}n_{31}n_{43} - n_{11}n_{34}n_{43}\\
&\quad -n_{13}n_{31}(n_{22} + n_{44} + n_{55})],\\
a_1 &= -[n_{24}n_{42}n_{55}(n_{11} + n_{33}) - n_{24}n_{32}n_{43}(n_{11} + n_{55}) - n_{24}n_{52}(n_{35}n_{43} + n_{11}n_{45} + n_{33}\\
&\quad n_{45}) + n_{22}n_{54}(n_{11}n_{45} - n_{35}n_{43} + n_{22}n_{45}) + n_{43}n_{54}(n_{15}n_{31} - n_{11}n_{35}) + n_{45}n_{54}(n_{11}n_{33}\\
&\quad -n_{13}n_{31}) + n_{22}n_{55}(-n_{11}n_{33} - n_{11}n_{44} + n_{13}n_{31} - n_{33}n_{44} + n_{34}n_{43}) - n_{14}n_{31}n_{43}(n_{22}\\
&\quad +n_{55}) + n_{11}n_{34}n_{43}(n_{22} + n_{55}) + n_{13}n_{31}n_{44}(n_{22} + n_{55}) - n_{11}n_{33}n_{44}(n_{22} + n_{55})],\\
a_0 &= -[n_{24}(n_{13}n_{31}n_{42}n_{55} - n_{11}n_{33}n_{42}n_{55} + n_{12}n_{31}n_{43}n_{55} + n_{11}n_{32}n_{43}n_{55} + n_{15}n_{31}\\
&\quad n_{43}n_{52} - n_{11}n_{35}n_{43}n_{52} - n_{13}n_{31}n_{45}n_{52} + n_{11}n_{33}n_{45}n_{52}) - n_{15}n_{22}n_{31}n_{43}n_{54} + n_{11}n_{22}\\
&\quad (n_{35}n_{43}n_{54} + n_{13}n_{22}n_{31}n_{45}n_{54}) - n_{11}n_{22}n_{33}n_{45}n_{54} + n_{14}n_{22}n_{31}n_{43}n_{55} - n_{13}n_{22}n_{31}\\
&\quad n_{44}n_{55} - n_{11}n_{22}n_{34}n_{43}n_{55} + n_{11}n_{22}n_{33}n_{44}n_{55}].
\end{aligned}$$

With the help of well-known Routh-Hurwitz criteria [103], we have obtained that the equilibrium point E_1 will be locally asymptotically stable if the following conditions are satisfied:

$$a_4 > 0, \quad \begin{vmatrix} a_4 & a_2 \\ 1 & a_3 \end{vmatrix} > 0, \quad \begin{vmatrix} a_4 & a_2 & a_0 \\ 1 & a_3 & a_1 \\ 0 & a_4 & a_2 \end{vmatrix} > 0,$$

$$\begin{vmatrix} a_4 & a_2 & a_0 & 0 \\ 1 & a_3 & a_1 & 0 \\ 0 & a_4 & a_2 & a_0 \\ 0 & 1 & a_3 & a_1 \end{vmatrix} > 0, \quad \begin{vmatrix} a_4 & a_2 & a_0 & 0 & 0 \\ 1 & a_3 & a_1 & 0 & 0 \\ 0 & a_4 & a_2 & a_0 & 0 \\ 0 & 1 & a_3 & a_1 & 0 \\ 0 & 0 & a_4 & a_2 & a_0 \end{vmatrix} > 0.$$

Clearly $a_4 > 0$, thus the endemic equilibrium E_1 is locally asymptotically stable if other four inequalities are satisfied. ∎

4.5 Numerical simulation

In this section, we present some numerical simulations to validate the analytical findings obtained in Section (4.3). The system (4.7) is simulated for different set of parameter values satisfying the condition of local asymptotic stability of equilibria E_0 and E_1. To see the dynamic behavior of the model for disease-free equilibria the system is integrated numerically by fourth order Runge-Kutta method. The parameter values used here are for the illustration purpose only.

Figure. 4.3 shows the stability of disease-free equilibrium using following set of parameter values

$$A_1 = 20, A_2 = 20, A_3 = 10, b = 0.01, b_1 = 0.071, b_2 = 0.025,$$

$$d = 0.0166, \delta = 0.4, \gamma = 0.7, \beta = 0.00008, \alpha_1 = 0.01, \alpha_2 = 0.02,$$

$$\alpha_3 = 0.05, \alpha_4 = 0.03, \alpha_5 = 0.1, w_1 = 0.05, w_2 = 0.01, w_3 = 0.06.$$

We have chosen the parameters in such a way that R_0 remains less than one and we are able to visualize the local stability of disease-free equilibrium (E_0). The reproduction number is evaluated as R_0=0.948483.

Here, Figure. 4.4 corresponds to the stability of the endemic equilibrium point E_1 for the

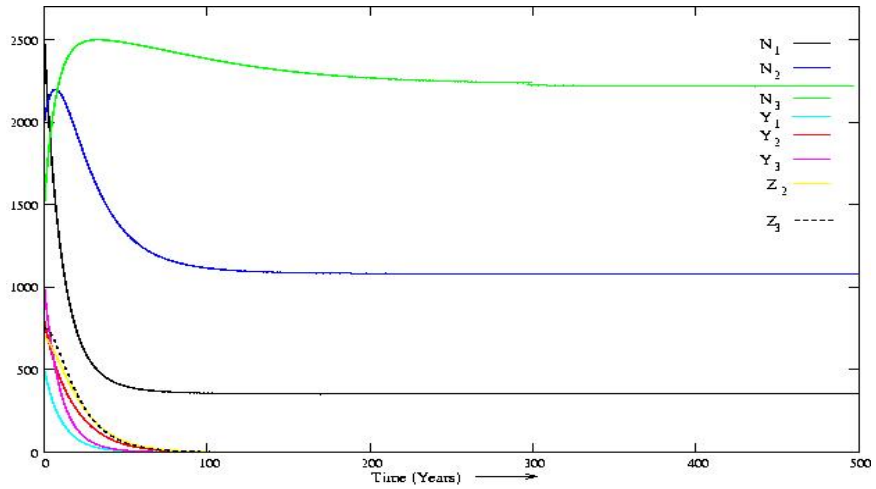

Figure 4.3: Stability of the disease-free equilibrium point E_0 for $R_0 = 0.948483$

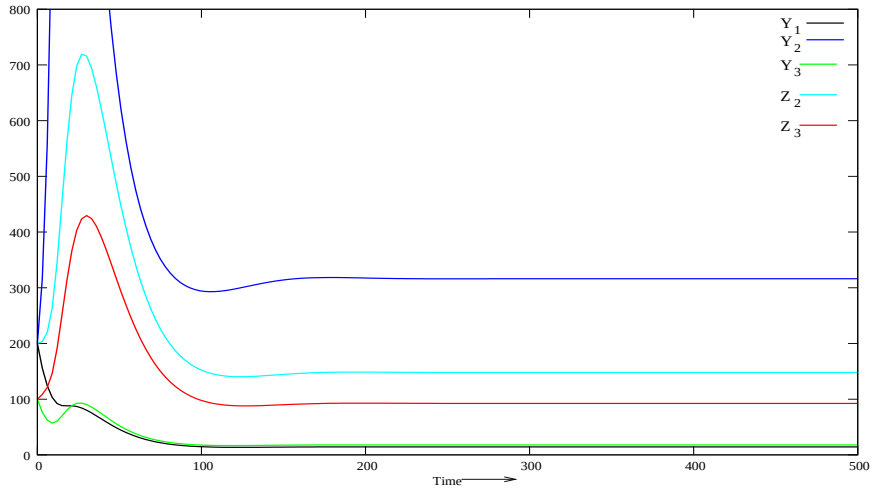

Figure 4.4: Stability of the endemic equilibrium point E_1 for R_0= 2.123477

parameter values

$$A_1 = 30, A_2 = 30, A_3 = 20, b = 0.01, b_1 = 0.071, b_2 = 0.025,$$

$$d = 0.0166, \delta = 0.4, \gamma = 0.6, \beta = 0.0003, \alpha_1 = 0.001, \alpha_2 = 0.02,$$

$$\alpha_3 = 0.05, \alpha_4 = 0.03, \alpha_5 = 0.1, w_1 = 0.05, w_2 = 0.01, w_3 = 0.06.$$

For this set of parameter values reproduction number is evaluated as R_0=2.123477. In

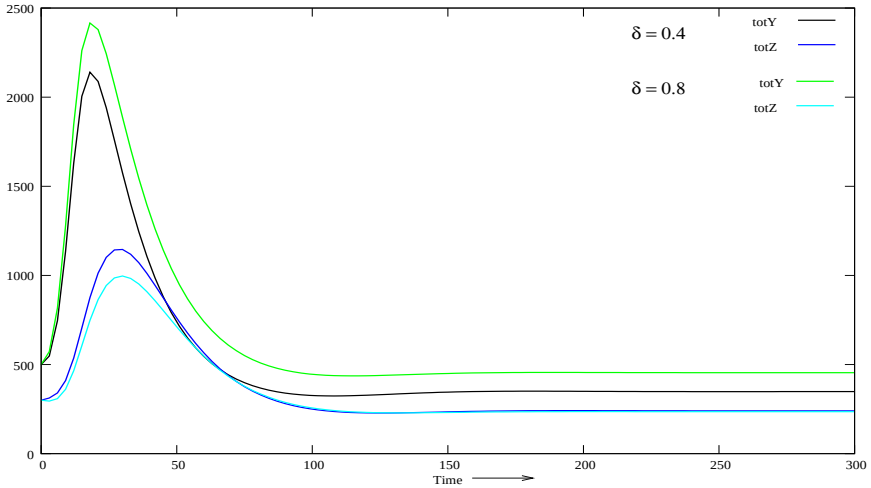

Figure 4.5: Effect of the fraction of infectives under treatment δ on endemic prevalence

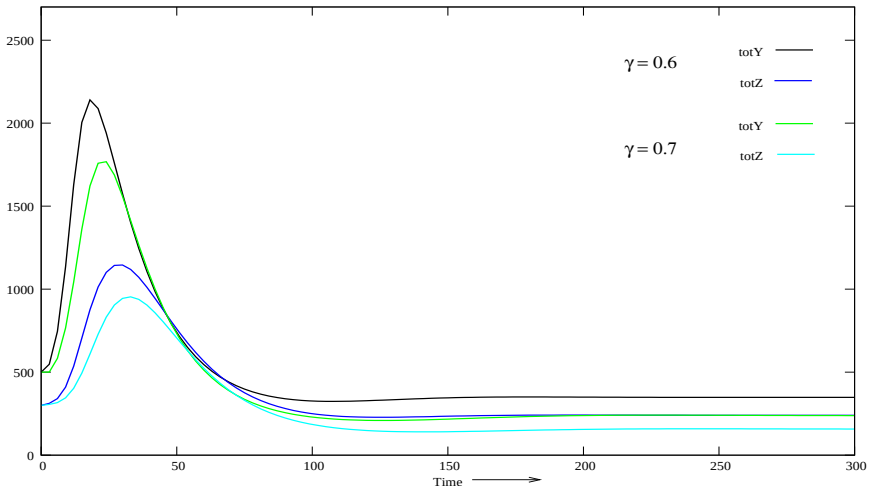

Figure 4.6: Effect of the fraction of infectives that are aware γ on endemic prevalence

Figure 4.5, the effect of fraction of infectives under treatment δ has been shown for δ = 0.4 and 0.8. The Figure 4.6, shows the effect of fraction of individuals that are aware γ on

endemic prevalence and the plot is drawn for $\gamma = 0.6$ and 0.7. Notice that the equilibrium level of HIV infectives increases with the increase in the fraction of individuals under treatment δ. This corresponds to the observed medical fact that the adequate treatment of HIV infective patients under ART prolongs the life of the infective and also enhances the quality of life. Hence, the increase in fraction of individuals under treatment increases the waiting time for HIV infected individuals in HIV class with which the per capita contact rate of susceptibles with infectives also get increased. This observation can be visualized in Figure 4.5. Also it has been shown that the equilibrium level of AIDS infectives decreases with the increase in the fraction of individuals under treatment δ. From Figure 4.6 we can see that the equilibrium level of HIV as well as AIDS patients have a significant decrease with increase in the fraction of individuals who are aware γ. Finally, it can be clearly depicted that awareness, along with treatment, is helpful in reducing the transmission of HIV/AIDS.

4.6 Conclusion

In this chapter, we have formulated and analyzed a stage structured model for HIV and the effect of awareness has also been studied. The proposed model has two equilibria: the disease-free equilibrium point E_0 and the endemic equilibrium point. The disease-free equilibrium is locally asymptotically stable when $R_0 < 1$ and is unstable for $R_0 > 1$. In fact the equilibrium point E_0 is globally stable under the condition $R_0 < 1$. Thereafter the conditions for existence and local stability of the endemic equilibrium point are obtained. Numerical simulation are carried out for different set of parameter values and it has also been shown that the infection prevalence of HIV and AIDS can be reduced by increasing the fraction of individuals that are aware of the disease in adult class. The HIV/AIDS prevention and control programmes should focus on the aim to spread awareness on the causes and consequences of the HIV/AIDS, which may help in changing individual be-

havior, in particular of those at risk of infection. The programmes should promote (i) the consistent use of condoms for safe sex; (ii) to stop sharing of injection equipment; and (iii) to provide access to antiretroviral drugs among HIV positive pregnant women/mothers to protect their babies from the infection. Hence providing adequate awareness regarding the spread of disease and its preventive measures is the most constructive way to decrease the incidence level of HIV/AIDS.

Chapter 5

Analysis of a Simple TB Model with Exogenous Reinfection and Case Detection [1]

5.1 Introduction

Tuberculosis (TB) is known for causing distressing illness for centuries and claiming so many lives. It is potentially fatal, infectious disease caused by Mycobacterium Tuberculosis (also called tubercle bacilli). Although, it can affect any part of the human body, it mainly infects lungs. Most of the people remain latent with TB and are at risk of developing TB disease as a consequence of either exogenous reinfection (i.e., recurrent infection by a different strain) or endogenous reactivation (i.e., re-activation of a pre-existing dormant infection) of latent bacilli. A small fraction of individuals can develop progressive TB disease following primary infection. TB is described as a slow disease due to its long and variable latency period distribution and short infectious period [3; 6]. Social factors including HIV prevalence and increasing drug resistant TB strains have dramatically accelerated the TB epidemic. With the present medical interventions, TB can be treated, cured, and can be prevented if individuals at risk take certain drugs. Although scientists and medical practitioners have been trying hard to prevent the transmission of TB but

[1] This work is under minor revision in *Model Assisted Statistics and Applications*

unable to eradicate this disease.

The number of new cases and deaths due to TB have been declining since 2006, and new cases have decreased since 2002, [6]. However, the global burden of this ancient disease is still extensive. According to the World Health Organization (WHO), in year 2012, about 8.6 million people became infected with TB and 1.3 million people died because of the disease. Every year approximately 500, 000 children develop TB and around 74, 000 die from the disease. The co-infection of HIV with TB is the major cause of death for HIV-positive individuals. Furthermore, a number of cases of 'Multi Drug-Resistant (MDR)' and 'Extensively Drug-Resistant (XDR)' TB strains have also been detected and they are seriously affecting the global TB control efforts.

The biomedical and epidemiological researches are essential to improve global TB prevention and control interventions. In this regard, the epidemiological models to study the transmission dynamics of TB disease have been investigated by several researchers, (see [43; 56; 66; 132; 134; 143; 163]). In [39; 40; 66], authors analyzed mathematical models incorporating a long and variable rate of progression of tuberculosis. The mathematical models for multi strains tuberculosis have also been investigated by many authors [40; 53]. In the case of TB, endogenous reactivation and exogenous reinfection are well-reported sources that can lead towards the progression of active TB infection. The endogenous reactivation is a mechanism that has been considered as the major suspect responsible behind the progression to tuberculosis [162]. The exogenous reinfection is important source of TB recurrence among TB cured individuals and this observation has been incorporated, studied and supported in some of the recent modeling studied reported on TB, (e.g. [25; 57; 66; 156; 173]). The extent at which exogenous reinfection may occur is determined by the prevalence level of the disease, that means higher the prevalence, greater the possibility of exogenous reinfection [147]. Moreover, it has been noticed that the exogenous reinfection plays a significant role on the transmission dynamics of TB in the environment where tuberculosis infectivity and prevalence rates are high.

The mathematical models are very useful in predicting the future dynamics of any infectious disease provided that the parameters used in the model are very close to the real life parameters. Of course, to get real life parameters is not so easy, more so in developing countries like India - where there are many unreported cases. There are people who do not complete their treatment and go back to work. This situation is very dangerous if an individual is infected by an infectious disease. So the case detection needs to be considered as an important parameter while framing any mathematical model for a developing country. In [26], the authors studied a simple mathematical model for TB with case detection and treatment. However, the model formulation in [26] is based on simple mass action type incidence but mathematical models with standard incidence are also extensively used and are useful in predicting the disease dynamics. In this chapter, this has been addressed and the mathematical study of simple TB model with exogenous reinfection and case detection is done considering standard incidence type interaction between susceptibles and infectives.

The remaining of this chapter is organized as follows: Section (5.2) has been described and formulated. Section (5.3) deals with equilibrium analysis. Section (5.4) presents the stability analysis of the various equilibria. In Section (5.5) the numerical simulations to illustrate analytical findings and to see the effect of various parameters on the transmission dynamics of HIV are discussed. Section (5.6) ends the chapter with brief discussion.

5.2 Mathematical model

In this section, we formulate an SEIR model to study the transmission dynamics of TB by incorporating exogenous reinfection. The total host population is divided into the four epidemiological classes: susceptibles (S), exposed (E, latently infected with TB but not infectious), infectious (I), and effectively treated and recovered (R, still susceptible) individuals. N denotes the total population which is assumed to be varying and ho-

mogenously mixed. It is assumed that some of the individuals from the population are projected to general awareness programmes about TB. So they may take some precautionary measures while interacting with sick individuals. Additionally, TB infectives are screened at a rate γ and some of these identified TB patients are opting for treatment at a rate δ. It is assumed that the rate of transmission due to screened and under treatment infectives will be less as compared to those infectives who are not identified or those who are not taking any treatment for TB. The rate of transmission of TB could be fast or slow depending upon the immunity level of individuals who come into contact with TB infectives. Hence it is assumed that a fraction $0 < p < 1$ of the total individuals with new infection develops TB faster and directly joins infected class whereas $(1-p)$ fraction of individuals with new infection moves to exposed class first and then gradually moves to infected class. In the same manner, if exposed individual comes into contact with TB infectives, he/she becomes infectious. Keeping in view the above facts and considering the standard incidence type interaction a nonlinear mathematical model for TB is formulated as follows:

$$\begin{aligned}
\frac{dS}{dt} &= \Lambda - \frac{\beta\{\delta(1-\gamma)+(1-\delta)+\eta_2\delta\gamma\}I}{N}\{(1-\alpha)+\eta_1\alpha\}S - \mu S \\
\frac{dE}{dt} &= (1-p)\frac{\beta\{\delta(1-\gamma)+(1-\delta)+\eta_2\delta\gamma\}I}{N}\{(1-\alpha)+\eta_1\alpha\}S \\
&\quad -\eta_3\frac{\beta\{\delta(1-\gamma)+(1-\delta)+\eta_2\delta\gamma\}I}{N}\{(1-\alpha)+\eta_1\alpha\}E - (\mu+\theta)E \qquad (5.1)\\
\frac{dI}{dt} &= p\frac{\beta\{\delta(1-\gamma)+(1-\delta)+\eta_2\delta\gamma\}I}{N}\{(1-\alpha)+\eta_1\alpha\}S \\
&\quad +\eta_3\frac{\beta\{\delta(1-\gamma)+(1-\delta)+\eta_2\delta\gamma\}I}{N}\{(1-\alpha)+\eta_1\alpha\}E + \theta E - (\mu+\mu_1+\nu\epsilon)I \\
\frac{dR}{dt} &= \nu\epsilon I - \mu R,
\end{aligned}$$

$S(0) > 0, E(0) \geq 0, I(0) \geq 0, R(0) \geq 0$ and $N = S(t) + E(t) + I(t) + R(t)$.
The descriptions of all parameters considered in model formulation are summarized in Table 5.1.

Here it is to be noted that $\eta_3 > 1$ is the modification parameter which states that the rate of transmission of TB due to reinfection will be more.

Table 5.1: Description of parameters used in model system (5.1).

Parameter	Description
Λ	Recruitment rate into the population,
α	Rate at which individual are projected to general awareness programmes,
γ	Fraction of unaware infectives who are screened,
δ	Fraction of TB infectives under treatment who are identified through screening test,
β	Rate of transmission of infection from TB infectives to susceptible,
η_1	Fraction which reduces the transmission in aware susceptible individuals,
η_2	Fraction which reduces the transmission in screened and treated infected individuals,
η_3	Modification parameter corresponding to TB reinfection,
θ	Rate at which an individual leaves the latent class by becoming infectious,
$\nu\epsilon$	Fraction of screened and sucessfully treated TB infectives,
μ	Natural death rate,
μ_1	Disease induced death rate,
p	Rate of fast progression to infection.

The above system (5.1) can be simplified as follows:

$$\begin{aligned}
\frac{dS}{dt} &= \Lambda - \frac{kSI}{N} - \mu S \\
\frac{dE}{dt} &= (1-p)\frac{kSI}{N} - \eta_3\frac{kEI}{N} - (\mu+\theta)E \\
\frac{dI}{dt} &= p\frac{kSI}{N} + \eta_3\frac{kEI}{N} + \theta E - (\mu+\mu_1+\nu\epsilon)I \\
\frac{dR}{dt} &= \nu\epsilon I - \mu R.
\end{aligned} \tag{5.2}$$

where $k = \beta\{\delta(1-\gamma) + (1-\delta) + \eta_2\delta\gamma\}\{(1-\alpha) + \eta_1\alpha\}$.

As $N = S + E + I + R$, the last system can be represented by the following system:

$$\begin{aligned}
\frac{dN}{dt} &= \Lambda - \mu N - \mu_1 I \\
\frac{dE}{dt} &= (1-p)\frac{k(N-E-I-R)I}{N} - \eta_3\frac{kEI}{N} - (\mu+\theta)E \\
\frac{dI}{dt} &= p\frac{k(N-E-I-R)I}{N} + \eta_3\frac{kEI}{N} + \theta E - (\mu+\mu_1+\nu\epsilon)I \\
\frac{dR}{dt} &= \nu\epsilon I - \mu R.
\end{aligned} \tag{5.3}$$

The schematic flow diagram of the model system (5.2) is shown in Figure 5.1. Since the

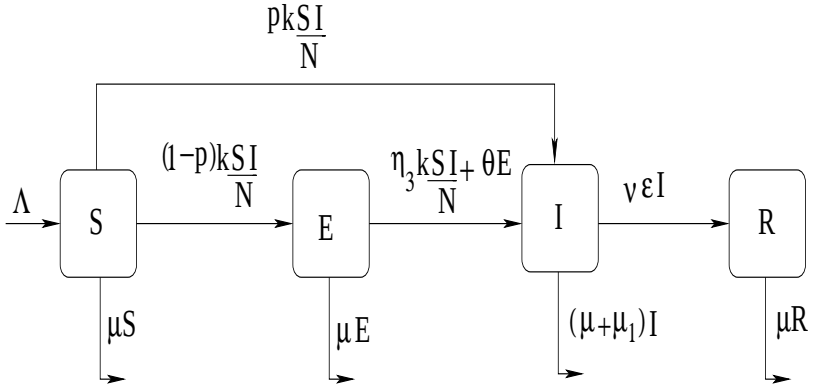

Figure 5.1: Transfer diagram of the model (5.2)

system (5.2) monitors human populations, hence the variables and parameters which are considered in this model are non-negative. The system (5.2) will therefore be analyzed in the biologically-feasible region given by

$$\mathcal{D} = \left\{ (S, E, I, R) \in R_+^4 : N \leq \frac{\Lambda}{\mu} \right\}.$$

It is positively invariant and all the solutions of (5.2) which initiate in $\mathcal{D}$ remain in the region $\mathcal{D}$. This result can be summarized in the following lemma:

Lemma 5.2.1: *For all time $t \geq 0$, all the solutions of the system (5.2) are eventually confined in the compact subset*

$$\mathcal{D} = \left\{ (S, E, I, R) \in R_+^4 : N \leq \frac{\Lambda}{\mu} \right\}.$$

Proof. We follow the following steps to show the positive invariance of $\mathcal{D}$ i.e. all the solutions of (5.2) which initiate in $\mathcal{D}$ remain in the region $\mathcal{D}$.

We have $N(t) = S(t) + E(t) + I(t) + R(t)$. The rate of change of total population is obtained by adding all the equations considered in model system (5.2) given by

$$\frac{dN}{dt} = \Lambda - \mu N - \mu_1 I.$$

It follows that, whenever $N > \Lambda/\mu$, $dN/dt < 0$. Notice that $\dfrac{dN}{dt}$ is bounded by $\Lambda - \mu N$.

By using standard comparison theorem, (for details see [105]) it can be shown that,
$0 \leq N(t) \leq \frac{\Lambda}{\mu}(1 - e^{-\mu t}) + N(0)e^{-\mu t}$.
In particular, $N(t) \leq \frac{\Lambda}{\mu}$, if $N(0) \leq \frac{\Lambda}{\mu}$.

Therefore the solutions of the model system (5.2) with initial conditions in $\mathcal{D}$ remain in $\mathcal{D}$ for all $t > 0$. Thus the region $\mathcal{D}$ is positively invariant for the system (5.2). Hence the system considered is biologically and mathematically well posed. ∎

5.3 Basic reproduction number and existence of equilibria

5.3.1 Basic reproduction number

The system (5.2) has a disease-free equilibrium $E_0 = \left(\frac{\Lambda}{\mu}, 0, 0, 0\right)$ obtained by equating the right hand sides of the equations in model to zero. The stability of E_0 can be established using the next generation operator method (see [168]), on the system (5.2). Following the notations described in [168], the matrices F and V, for the new infection terms and the remaining transfer terms, are given, respectively by

$$F = \begin{pmatrix} 0 & k(1-p) \\ 0 & kp \end{pmatrix}$$

and

$$V = \begin{pmatrix} (\mu + \theta) & 0 \\ -\theta & (\mu + \mu_1 + \nu\epsilon) \end{pmatrix}$$

thus

$$FV^{-1} = \begin{pmatrix} \frac{k(1-p)\theta}{(\mu+\theta)(\mu+\mu_1+\nu\epsilon)} & \frac{k(1-p)}{(\mu+\mu_1+\nu\epsilon)} \\ \frac{kp\theta}{(\mu+\theta)(\mu+\mu_1+\nu\epsilon)} & \frac{kp}{(\mu+\mu_1+\nu\epsilon)} \end{pmatrix}$$

The associated basic reproduction number, denoted by R_0 is the spectral radius of the matrix FV^{-1} (i.e. $R_0 = \rho(FV^{-1})$) and is calculated as follows:

$$R_0 = \frac{k(p\mu + \theta)}{(\mu + \theta)(\mu + \mu_1 + \nu\epsilon)}. \tag{5.4}$$

Thus, the result on local stability of the disease-free equilibrium E_0 of model system (5.2) follows from Theorem 2 of [168] and is stated below:

Theorem 5.3.1: *The disease-free equilibrium E_0 of the model system (5.2), is locally asymptotically stable if $R_0 < 1$, and unstable if $R_0 > 1$.*

The threshold quantity R_0 is the basic reproduction number for the TB model. It measures the average number of secondary infections produced by a single infected individual during the mean course of infection in a completely susceptible population. In biologically sense, Theorem 5.3.1 implies that TB can be eliminated from the community when $R_0 < 1$, if the initial sizes of the sub-populations of the model are in the considered basin of attraction of disease-free equilibrium E_0.

From Theorem 5.3.1, it has been established that if the disease-free equilibrium exists, it is locally asymptotically stable, if and only if, $R_0 < 1$. Notice that the disease-free equilibrium may not be globally asymptotically stable even if $R_0 < 1$. For $R_0 < 1$, there could be a possibility of backward bifurcation (bi-stability) when a stable endemic equilibrium may co-exist with the disease-free equilibrium.

5.3.2 Equilibria of the model

The model system (5.2) has following non-negative:
(I) Disease-free equilibrium denoted by E_0,
(II) Endemic equilibrium denoted by E^*, which exists only when $R_0 > 1$.
(III) Endemic equilibria E_1 and E_2, which exists only when $R_0 < 1$ and the parameters satisfy some conditions as discussed below:

To find the endemic equilibrium (S^*, E^*, I^*, R^*) of the system (5.2), we assume that $x = \dfrac{kI^*}{N^*}$. Then we have following:

$$\begin{aligned} S^* &= \frac{\Lambda}{\mu + x}, \\ E^* &= \frac{(1-p)S^*x}{\eta_3 x + \mu + \theta}, \\ I^* &= \left(\frac{xS^*}{\mu + \mu_1 + \nu\epsilon}\right)\left(\frac{p\mu + \theta + \eta_3 x}{\eta_3 x + \mu + \theta}\right), \\ R^* &= \frac{\nu\epsilon}{\mu} I^*. \end{aligned}$$

and x is the root of the following quadratic equation:

$$Ax^2 + Bx + C = 0. \tag{5.5}$$

Here

$$\begin{aligned} A &= \left(1 + \frac{\nu\epsilon}{\mu}\right)\eta_3 > 0, \\ B &= \left(1 + \frac{\nu\epsilon}{\mu}\right)\theta + (1+\eta_3)(\mu + \mu_1 + \nu\epsilon) - p\mu_1 - k\eta_3, \\ C &= (\mu + \mu_1 + \nu\epsilon)(\mu + \theta) - k(p\mu + \theta) = (\mu + \mu_1 + \nu\epsilon)(\mu + \theta)(1 - R_0). \end{aligned}$$

As all the variables S, E, I and R are positive for $x > 0$, so we can draw following conclusion depending upon the signs of B and C.

The system (5.2)

(i) has a unique endemic equilibrium when $C < 0$, i.e., when $R_0 > 1$,

(ii) has a unique endemic equilibrium when $B < 0$ and either $C = 0$ or $B^2 - 4AC = 0$,

(iii) has two endemic equilibria when $B < 0$, $C > 0$, (i.e.,$R_0 < 1$) and $B^2 - 4AC > 0$,

(iv) has no endemic equilibrium when $B > 0$ and $C > 0$.

Hence, it is clear that system may have two endemic equilibria for some set of parameters satisfying the conditions stated in (iii) above, which leads to backward bifurcation.

It should be noticed that in case the condition stated in (iii) holds then we will have two equilibria, namely E_1 and E_2. The equilibrium point E_1 corresponds to x which is coming

from $\frac{(-B+\sqrt{(B^2-4AC)})}{(2A)}$ and E_2 when x takes second root of the quadratic equation (5.5), i.e. $\frac{(-B-\sqrt{(B^2-4AC)})}{(2A)}$.

It is also clear that if the parameter $\eta_3 = 0$, the quadratic equation reduces to the linear equation, giving only one root. Hence if there is no exogenous reinfection then there is no chance of backward bifurcation.

Thus, the following expression is derived:
$R_0^c = 1 - \frac{B^2}{4A(\mu+\mu_1+\nu\epsilon)(\mu+\theta)}$, for $R_0 < 1$.
For $B^2 - 4AC > (= or <)0$ if $R_0 > (= or <)R_0^c$, here R_0^c is the point of backward bifurcation and it can be shown that backward bifurcation takes place for values of R_0 in the range $R_0^c < R_0 < 1$ this supports the point (iii) given above. Here E_0 and E_1 are stable and E_2 is unstable for $R_0^c < R_0 < 1$.
The Jacobian matrix of the system (5.1), at E_0 is given by

$$J(E_0) = \begin{pmatrix} -\mu & 0 & -\mu_1 & 0 \\ 0 & -(\mu+\theta) & (1-p)k & 0 \\ 0 & \theta & pk-(\mu+\mu_1+\nu\epsilon) & 0 \\ 0 & 0 & \nu\epsilon & -\mu \end{pmatrix}$$

The two eigenvalues of the matrix are $-\mu$ and $-\mu$. Other two eigenvalues are the roots of the quadratic equation

$$\lambda^2 + a_1\lambda + a_0 = 0,$$

where

$$\begin{aligned} a_1 &= [(\mu+\theta)+(\mu+\mu_1+\nu\epsilon)-pk] \\ a_0 &= -(\mu+\theta)(pk-(\mu+\mu_1+\nu\epsilon)) - \theta(1-p)k \\ &= -(p\mu+\theta)k + (\mu+\theta)(\mu+\mu_1+\nu\epsilon) \\ &= (\mu+\theta)(\mu+\mu_1+\nu\epsilon)(1-R_0). \end{aligned}$$

Here $a_0 > 0$ for $R_0 < 1$ and if $a_1 > 0$, then the equilibrium E_0 will be locally asymptotically stable. Here it is easy to observe that $R_0 < 1$ corresponds $\mu[pk - (\mu + \mu_1 + \nu\epsilon)] + \theta[k - (\mu + \mu_1 + \nu\epsilon)] < 0$. And for this inequality to be true we must need $pk < (\mu + \mu_1 + \nu\epsilon)$ as $p < 1$. Thus a_1 is also greater than 0 for $R_0 < 1$. Hence the equilibrium point E_0 is always locally asymptotically stable whenever $R_0 < 1$.

5.4 Bifurcation analysis

The mathematical models, to study TB transmission dynamics with exogenous reinfection exhibit the phenomenon of backward bifurcation [56; 66], where the stable disease-free equilibrium co-exists with a stable endemic equilibrium. To demonstrate it for our model, let us assume $N = x_1, E = x_2, I = x_3$ and $R = x_4$, where $S = x_1 - x_2 - x_3 - x_4$. Using the vector notation $\mathbf{X} = (x_1, x_2, x_3, x_4)^T$, the model system (5.2) can be written in the form $\frac{d\mathbf{X}}{dt} = F(\mathbf{x})$, where $F = (f_1, f_2, f_3, f_4)^T$, as follows:

$$\begin{aligned}
\frac{dx_1}{dt} &= f_1 = \Lambda - \mu x_1 - \mu_1 x_3 \\
\frac{dx_2}{dt} &= f_2 = (1-p)\frac{k(x_1 - x_2 - x_3 - x_4)x_3}{x_1} - \eta_3 \frac{k x_2 x_3}{x_1} - (\mu + \theta)x_2 \\
\frac{dx_3}{dt} &= f_3 = p\frac{k(x_1 - x_2 - x_3 - x_4)x_3}{x_1} + \eta_3 \frac{k x_2 x_3}{x_1} + \theta x_2 - (\mu + \mu_1 + \nu\epsilon)x_3 \\
\frac{dx_4}{dt} &= f_4 = \nu\epsilon x_3 - \mu x_4.
\end{aligned} \tag{5.6}$$

The Jacobian matrix of system (5.3) or the equivalent system (5.6) evaluated at disease-free equilibrium E_0 is given by

$$J(E_0) == \begin{pmatrix} -\mu & 0 & -\mu_1 & 0 \\ 0 & -(\mu + \theta) & (1-p)k & 0 \\ 0 & \theta & pk - (\mu + \mu_1 + \nu\epsilon) & 0 \\ 0 & 0 & \nu\epsilon & -\mu \end{pmatrix}$$

The basic reproduction number associated with system (5.2) is given by

$$R_0 = \frac{k(p\mu + \theta)}{(\mu + \theta)(\mu + \mu_1 + \nu\epsilon)},$$

where $k = \beta\{\delta(1-\gamma) + (1-\delta) + \eta_2\delta\gamma\}\{(1-\alpha) + \eta_1\alpha\}$.

Suppose p is chosen as bifurcation parameter. Then setting the expression of R_0 equal to 1 (i.e. $R_0 = 1$) and solving for p gives

$$p = p^* = \frac{(\mu + \theta)(\mu + \mu_1 + \nu\epsilon) - \theta k}{\mu k}.$$

The eigenvalues of the matrix $J(E_0)$ are $-\mu, -\mu, \{pk - (\mu + \theta) - (\mu + \mu_1 + \nu\epsilon)\}$ and 0. It is to be noted that the above linearized system of transformed system (5.6) with $p = p^*$, has a zero eigenvalue which is simple.

Here we will use the center manifold theory [50], as described in Theorem 4.1 of [56] to analyze the dynamics of (5.6) near $p = p^*$ and to show that the system (5.6) exhibits backward bifurcation.

Eigenvectors of $\mathbf{J}(\mathcal{E}_0)|_{p=p^*}$

The Jacobian of (5.6) at $p = p^*$ (we denote it by J_{p^*}) has a right eigenvector (associated with the zero eigenvalue) given by $w = [w_1, w_2, w_3, w_4]^T$, where

$$w_1 = -\frac{kw_3}{\mu}$$

$$w_2 = \frac{(1-p^*)kw_3}{(\mu + \theta)}$$

$$w_3 = w_3 > 0,$$

$$w_4 = \frac{\nu\epsilon w_3}{\mu}.$$

Further, J_{p^*} has a left eigenvector $v = [v_1, v_2, v_3, v_4]$ (associated with the zero eigenvalue), where

$$v_1 = 0 = v_4,$$

$$v_2 = \frac{\theta}{(\mu + \theta)}v_3,$$

$$v_3 = v_3 > 0.$$

The Theorem 4.1 given in [56] is stated below, which will be used for further analysis is stated below:

Theorem 5.4.1: *Consider the following general system of ordinary differential equations with a parameter* ϕ

$$\frac{dx}{dt} = f(x, \phi), f : \mathbb{R}^n \times \mathbb{R} \to \mathbb{R} \quad \textit{and } C^2(\mathbb{R}^n \times \mathbb{R}), \tag{5.7}$$

where 0 is an equilibrium point of the system (that is, $f(0, \phi) \equiv 0$ *for all* ϕ *and assume*

A1 : $A = D_x f(0,0) = (\frac{\partial f_i}{\partial x_j}(0,0))$ *is the linearization matrix of the system (5.7) around the equilibrium 0 and* ϕ *evaluated at 0. Zero is a simple eigenvalue of A and other eigenvalues of A have negative real parts;*

A2 : *Matrix A has a right eigenvector w and a left eigenvector v (each corresponding to the zero eigenvalue);*

Let f_k *be the* k^{th} *component of f and*

$$a = \sum_{k,j,i=1}^{n} v_k w_i w_j \frac{\partial^2 f_k}{\partial x_i \partial x_j}(0,0), \qquad b = \sum_{k,i=1}^{n} v_k w_i \frac{\partial^2 f_k}{\partial x_i \partial \phi}(0,0) \tag{5.8}$$

The local dynamics of the system around 0 is totally determined by the signs of a and b.

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

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

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

iv. $a < 0, b > 0$ *when* ϕ *changes from negative to positive, 0 changes its stability from stable to unstable. Correspondingly a negative unstable equilibrium becomes positive and*

locally asymptotically stable.

Now, taking p as bifurcation parameter, and using Theorem 5.4.1, further calculations are carried out to determine the signs of a and b.

Computations of a and b:

$$\begin{aligned}
a &= v_2 \sum_{i,j=1}^{4} w_i w_j \frac{\partial^2 f_2}{\partial x_i \partial x_j} + v_3 \sum_{i,j=1}^{4} w_i w_j \frac{\partial^2 f_3}{\partial x_i \partial x_j} \\
&= -2\{w_2 w_3 + w_3^2 + w_3 w_4\} \left[v_2 \frac{(1-p)k\mu}{\Lambda} + v_3 \frac{pk\mu}{\Lambda} \right] \\
&\quad +2w_2 w_3 (v_3 - v_2) \frac{\eta_3 k\mu}{\Lambda} \\
&= -2\{w_2 w_3 + w_3^2 + w_3 w_4\} \frac{k\mu}{\Lambda} \frac{\mu p^*}{\theta} v_2 + 2w_2 w_3 \frac{\mu}{\theta} \frac{\eta_3 k\mu}{\Lambda} v_2 \\
&= -2v_2 w_3^2 \left[\frac{(1-p^*)k}{(\mu+\theta)} + 1 + \frac{\nu\epsilon}{\mu} \right] \left(\frac{k\mu^2 p^*}{\theta\Lambda} \right) + 2v_2 w_3^2 \left(\frac{k^2\mu^2\eta_3}{\theta\Lambda} \right) \frac{(1-p^*)}{(\mu+\theta)} \\
&= 2v_2 w_3^2 \left(\frac{k\mu^2}{\theta\Lambda} \right) \left[\eta_3 \frac{(1-p^*)k}{(\mu+\theta)} - p^* \left\{ \frac{(1-p^*)k}{(\mu+\theta)} + 1 + \frac{\nu\epsilon}{\mu} \right\} \right] \\
&= 2v_2 w_3^2 \left(\frac{k\mu^2}{\theta\Lambda} \right) \frac{(1-p^*)k}{(\mu+\theta)} \left[\eta_3 - p^* \left\{ 1 + \left(1 + \frac{\nu\epsilon}{\mu} \right) \frac{(\mu+\theta)}{(1-p^*)k} \right\} \right].
\end{aligned}$$

From this it can be noted that $a > 0$ for $\eta_3 > p^* \left\{ 1 + \left(1 + \frac{\nu\epsilon}{\mu} \right) \frac{(\mu+\theta)}{(1-p^*)k} \right\}$.

$$\begin{aligned}
b &= v_2 \sum_{i=1}^{4} w_i \frac{\partial^2 f_2}{\partial x_i \partial p^*} + v_3 \sum_{i=1}^{4} w_i \frac{\partial^2 f_3}{\partial x_i \partial p^*} \\
&= v_2 w_3 (-k) + v_3 w_3 k \\
&= w_3 k (v_3 - v_2) = \frac{k\mu}{\theta} w_3 v_2.
\end{aligned}$$

Clearly, $b > 0$. Thus, the following result is established:

Theorem 5.4.2: *If*

$$\eta_3 > p^* \left\{ 1 + \left(1 + \frac{\nu\epsilon}{\mu} \right) \frac{(\mu+\theta)}{(1-p^*)k} \right\},$$

then the model system (5.6) of the transformed system (5.3) undergoes a backward bifurcation at $R_0 = 1$.

5.4.1 Local stability of endemic equilibrium

Theorem 5.4.3: *The endemic equilibrium (E^*) of model (5.2), which exists for $R_0 > 1$, is locally asymptotically stable when $a_2a_1 - a_0 > 0$, where a_2, a_1 and a_0 are given in the proof of this theorem.*

Proof. To prove this result, the Jacobian matrix M corresponding to the endemic equilibrium point $E^*(N^*, E^*, I^*, R^*)$ corresponding to the model (5.3) is calculated as follows:

$$M = \begin{pmatrix} -\mu & 0 & -\mu_1 & 0 \\ b_{21} & b_{22} & b_{23} & b_{24} \\ b_{31} & b_{32} & b_{33} & b_{34} \\ 0 & 0 & \nu\epsilon & -\mu \end{pmatrix}$$

here

$b_{21} = \dfrac{(1-p)k(E^* + I^* + R^*)I^*}{N*^2} + \dfrac{\eta_3 k E^* I^*}{N*^2}$, $b_{22} = -\dfrac{(1-p)kI^*}{N^*} - (\mu + \theta) - \dfrac{\eta_3 k I^*}{N^*}$,

$b_{23} = -\dfrac{2(1-p)kI^*}{N^*} + \dfrac{(1-p)k(N^* - E^* - R^*)}{N^*} - \dfrac{\eta_3 k E^*}{N^*}$, $b_{24} = \dfrac{-(1-p)kI^*}{N^*}$,

$b_{31} = \dfrac{pk(E^* + I^* + R^*)I^*}{N*^2} - \dfrac{\eta_3 k E^* I^*}{N*^2}$, $\quad b_{32} = -\dfrac{pkI^*}{N^*} + \theta + \dfrac{\eta_3 k I^*}{N^*}$,

$b_{33} = -\dfrac{2pkI^*}{N^*} + \dfrac{pk(N^* - E^* - R^*)}{N^*} + \dfrac{\eta_3 k E^*}{N^*} - (\mu + \mu_1 + \nu\epsilon) = \dfrac{-pkI^*}{N^*} - \dfrac{\theta E^*}{I^*}$, $b_{34} = \dfrac{-pkI^*}{N^*}$.

The Jacobian matrix M has one eigenvalue as $-\mu$ and other three eigenvalues are given by the roots of the following cubic equation:

$$\lambda^3 + \ a_2\lambda^2 + a_1\lambda + a_0 = 0. \tag{5.9}$$

where

$a_2 = \mu - (b_{22} + b_{33})$,

$a_1 = (b_{22}b_{33} - b_{23}b_{32} - \mu(b_{22} + b_{33}) - \nu\epsilon b_{34} + b_{31}\mu_1$,

$a_0 = \mu(b_{22}b_{33} - b_{23}b_{32}) + \nu\epsilon(b_{34}b_{22} - b_{24}b_{32}) + \mu_1(b_{21} - b_{32} - b_{31}b_{22})$.

Using Routh-Hurwitz criteria, the endemic equilibrium will be locally asymptotically stable if the following inequalities are satisfied:

$a_2 > 0$ and $\begin{vmatrix} a_2 & a_0 \\ 1 & a_1 \end{vmatrix} > 0.$

Clearly $a_2 > 0$, hence E^* is locally asymptotically stable if second inequality is also satisfied. ∎

5.5 Numerical simulation

In this section, numerical simulations are performed in XPP [65] to visualize the dynamics of the model system (5.2) for various set of parameters. First we consider the following set of parameters:

$$\Lambda = 50, \mu = 0.075, \eta_1 = .57, \eta_2 = 0.57, \eta_3 = 4, \alpha = 0.7$$

$$\delta = 0.4, \theta = 0.001, p = 0.75, \nu = 0.02, \epsilon = 0.15, \gamma = 0.7, \beta = 0.3, \mu_1 = 0.1.$$

For this set of parameters $R_0 = 0.780$ which is less than $R_0^c = 0.972$ and in this case only the disease-free equilibrium point $E_0(666.666, 0, 0, 0)$ exists and is stable. This observation is demonstrated by the $S-I$ phase plane shown in Figure 5.2. The stability of the endemic

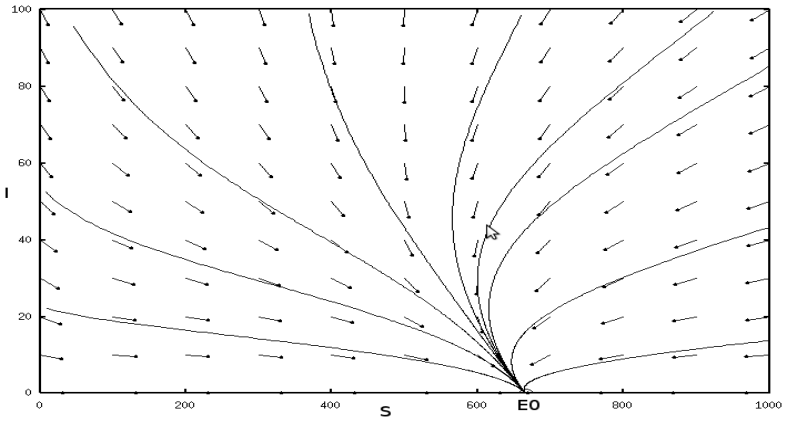

Figure 5.2: $S - I$ phase plane for $R_0 < R_0^c < 1$.

equilibrium E^* is shown in the Figure 5.3 for the following set of parameters:

$$\Lambda = 50, \mu = 0.075, \eta_1 = .57, \eta_2 = 0.57, \eta_3 = 4, \alpha = 0.7$$

$$\delta = 0.4, \theta = 0.001, p = 0.75, \nu = 0.02, \epsilon = 0.15, \gamma = 0.7, \beta = 0.42, \mu_1 = 0.1.$$

Here $R_0 = 1.0928 > 1$ and in this case both the disease-free equilibrium $E_0(666.666, 0, 0, 0)$ and the endemic equilibrium $E^*(77.651, 17.733, 114.304, 4.572)$ exist but only the equilibrium E^* is stable. Further the system (5.2) is simulated by changing the parameter

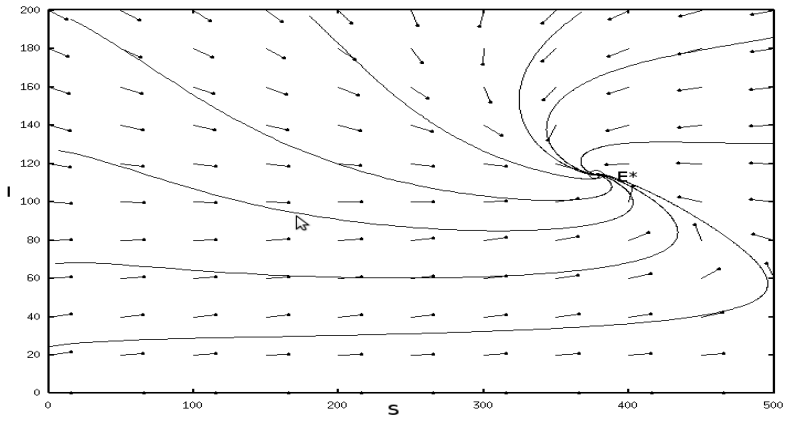

Figure 5.3: $S - I$ phase plane for $R_0 > 1$.

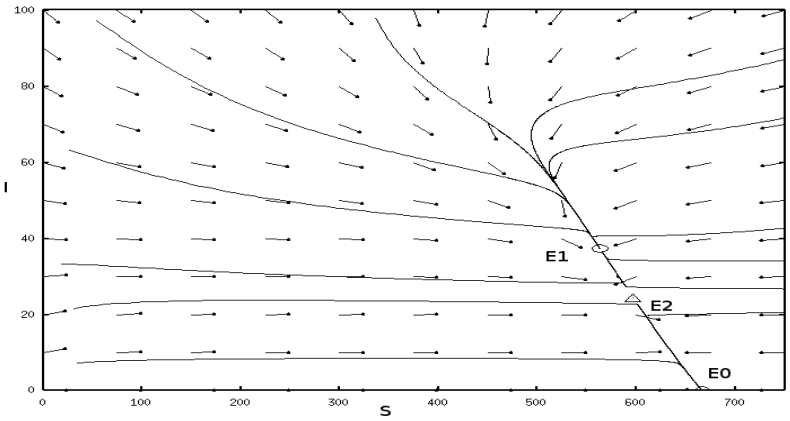

Figure 5.4: $S - I$ phase plane for $R_0^c < R_0 < 1$ showing bi-stability.

β from 0.42 to 0.37 and keeping all other parameters as in Figure 5.3. For this set of parameters $R_0 = 0.9627$ which is greater than $R_0^c = 0.9608$ and less than 1.

Hence in this case all three equilibria $E_0(666.666, 0, 0, 0)$, $E_1(596.739, 11.7955, 24.493, 0.979)$ and $E_2(563.131, 14.801238, 37.387, 1.4955)$ exist but only the equilibrium E_1 and E_0 are locally stable and the equilibrium E_2 is unstable. This fact is demonstrated in Figure 5.4. This observation is more clear from the Figure 5.5, which shows the bifurcation diagram

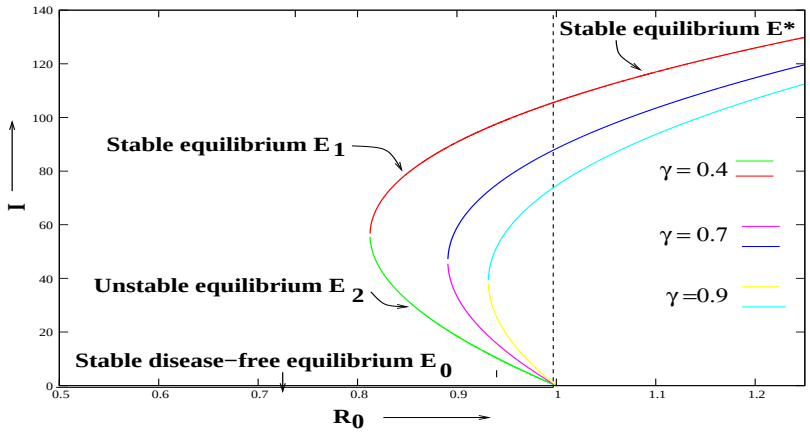

Figure 5.5: Bifurcation diagram by considering the bifurcation parameter as p and showing the effect of the fraction of screened individuals γ.

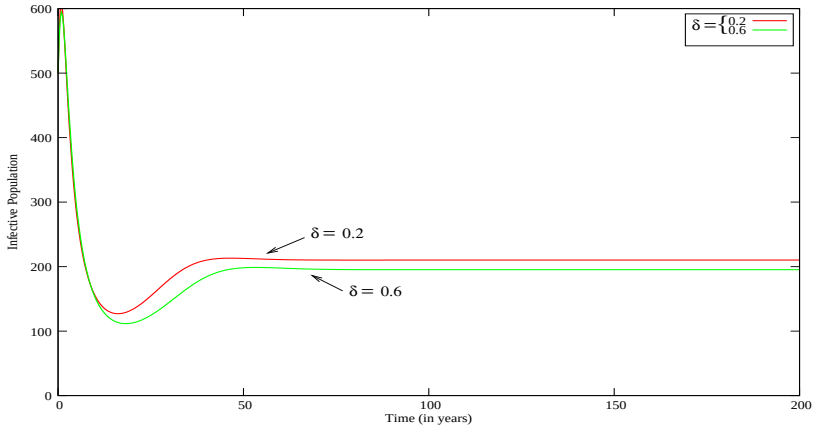

Figure 5.6: Variation of infective population with time for different values of δ where $\Lambda = 100, \mu = 0.0545, \eta_1 = 0.57, \eta_2 = 0.57, \eta_3 = 4, \alpha = 0.7, \theta = 0.001, p = 0.75, \nu = 0.02, \epsilon = 0.15, \gamma = 0.7, \beta = 0.672, \mu_1 = 0.1$.

by considering the fast progression rate of the disease p as the bifurcation parameter. This figure is obtained for the following set of parameters. The parameter p is chosen as bifurcation parameter and the parameter γ takes three different values as shown in Figure 5.5:

$$\Lambda = 50, \mu = 0.075, \eta_1 = .57, \eta_2 = .57, \eta_3 = 4, \alpha = 0.7$$

$$\delta = 0.4, \theta = 0.001, \nu = 0.02, \epsilon = 0.15, \beta = 0.4, \mu_1 = 0.1.$$

Here horizontal axis is representing the basic reproduction number R_0 which is obtained by corresponding value of p. The vertical axis is showing the equilibrium level of the infectives I. It is observed that when the reproduction number R_0 is between 0 to R_0^c, the disease-free equilibrium E_0 alone is stable, for $R_0^c < R_0 < 1$ we have bi-stability, where

either the infection free equilibrium is stable or one of the endemic equilibria is stable. To see the effect of fraction of screening of unaware infective γ on the dynamics of TB, bifurcation diagram is obtained for three different values of γ. From this figure, it is easy to see that with the increase in γ, the bifurcation diagram shifts towards right implying the increase in R_0^c value. This indicates that the backward bifurcation may not occur if the fraction of screening of unaware infectives is large enough. So in this situation, by making $R_0 < 1$, this disease can be eliminated from the population. Here Figure 5.6

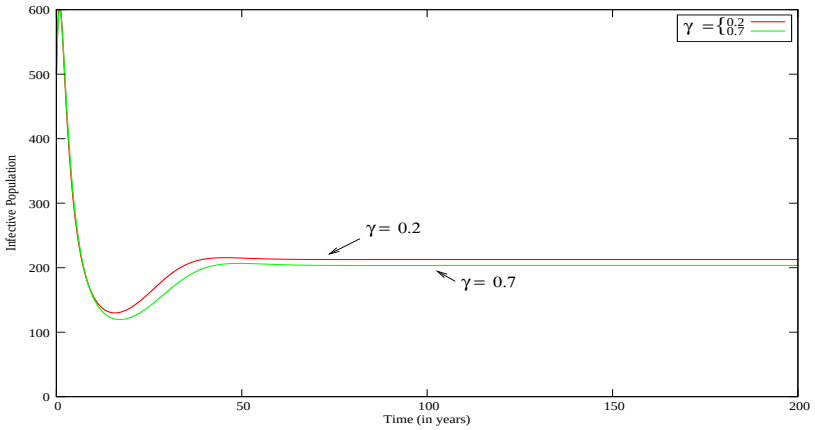

Figure 5.7: Variation of infective population with time for different values of γ, where $\Lambda = 100, \mu = 0.0545, \eta_1 = 0.57, \eta_2 = 0.57, \eta_3 = 4, \alpha = 0.7, \theta = 0.001, p = 0.75, \nu = 0.02, \epsilon = 0.15, \delta = 0.4, \beta = 0.672, \mu_1 = 0.1.$

demonstrates the effect of treatment whereas Figure 5.7. exhibits the role of screening of unaware infectives. It is clearly observed that increase in the parametric values of δ and γ lowers the number of infectives in the population under consideration.

5.6 Conclusion

In this chapter, we have formulated and analyzed a deterministic model for the transmission dynamics of TB by considering standard incidence type of interaction. The susceptible individuals either move to exposed class or directly to the infected class depending upon their levels of immunity, when they come into effective contact with an infective. This fact has been incorporated through fast or slow progression rate into the infected

class. The equilibria of model and the basic reproduction number R_0 have been computed and we observe that the disease-free equilibrium (E_0) is locally asymptotically stable when $R_0 < 1$. The present model undergoes a backward bifurcation, when the associated reproduction number $R_0 < 1$. The backward bifurcation gives rise to existence of more than one i.e. multiple endemic equilibria for $R_0 < 1$. This suggests that just $R_0 < 1$ is not sufficient to eradicate the disease from the population. In this case R_0 needs to be lowered much below one to confirm the global stability of disease-free equilibrium. An accurate estimation of parameters and the level of control measures are required to reduce the infection prevalence of TB in endemic region. We also noticed that the increase in the rate of case detection shifts the backward bifurcation diagram towards right which results in the increase in threshold value of R_0^c.

We have shown that the treatment is reducing the equilibrium level of infective population. Numerical simulations carried out in Section (5.5) support the analytic results. The present results are significantly important as they associate with the elimination and/or persistence of the TB disease in a community. This study illustrated a clear vision of the impact of treatment on the dynamics of TB and its association with case detection. Our study supports the need of sustained treatment strategy with improved case detection rate to control the spread of TB in human population.

Chapter 6

Mathematical Modelling of HIV/AIDS and Tuberculosis Co-infection: Effect of Screening and Treatment [1]

6.1 Introduction

The eradication of an infectious disease through appropriate treatments and control strategies is in itself a major public health concern. Most of the developing countries are fighting against number of infectious diseases among which TB and HIV continuously remain serious threat to the lives of human population. The situation becomes worse in case of co-epidemics. In these cases it becomes necessary to handle the problems more efficiently and sensitively, because sometimes the patient infected with one disease suffers mortality due to the absence of timely diagnosis and care/treatment of the other opportunistic infection. Among many of the co-epidemics HIV-TB is a deadly combination as these two are much more destructive together than either of the disease alone can be. HIV infection is characterized by the progressive decline of $CD4^+$ T cells. The immunity level of the patients diagnosed with HIV infection goes on decreasing due to reduction in the

[1]This work has been communicated in *Journal of Biological Systems*

count of $CD4^+$ T-cells and they become victim of other opportunistic infections. TB is a common illness and cause of death among people living with HIV by accounting one in five HIV related deaths. TB increases the rate of progression from HIV to AIDS and shortens the life span of patients living with HIV infection. The risk of developing TB is estimated to be between 21-34 times greater in HIV positive people than HIV-negative individuals [155]. The 2012, WHO fact sheet mentions that the largest number of new TB cases occurred in Asia which is accounted for approximately 60% of new TB cases globally. Whereas, sub-Saharan Africa carried the greatest proportion of new TB cases per population accounting over 255 cases per 1,00,000 population in 2012 [12].

The current statistical figures associated with the two diseases are frightening. The statistics show that all over the world around 35.3 million people are living with HIV and at least one-third these are infected with latent TB. Global data estimated that there were 1.1 million HIV positive new TB cases and around 75% of these infected individuals live in sub-Saharan Africa. In the same year around 3,20,000 people died of HIV-associated TB [9].

The objective of controlling the HIV-TB dual epidemic remains a major challenge for the countries with high HIV-TB prevalence rate. South Africa accounts the world's greatest burden of HIV and TB, although it is making great strides in addressing both diseases. There is no vaccine to protect and no treatment to cure an individual infected with HIV. The use of Anti-Retroviral drugs (ARVs), remarkably the Highly Active Anti-Retroviral Therapy (HAART), suppresses HIV viral replication, which reduces morbidity and mortality from the virus [96]. Unlike HIV, TB is curable by using DOTS (directly observed treatment short course), which cures TB in 95% of cases and the treatment is available and affordable in almost all parts of the world [135].

As mentioned above, TB poses a serious health threat and is a leading cause of morbidity and mortality among the people living with HIV [3; 10; 14; 24; 73; 155]. The epidemiological models are extensively used in evaluating policies to control and prevent

the spread of HIV and TB. In recent years, various analytic and conceptual studies, such as [24; 121; 124; 126; 144; 146; 159; 174; 175] have been carried out to analyze the transmission dynamics of HIV, TB and HIV-TB co-infections using mathematical models. In [68; 128; 166], authors have incorporated the effect of screening of HIV infective. Some authors have given a basic groundwork for modelling the complex HIV-TB interaction in population under consideration [37; 68; 113; 146]. In [126; 124], the authors have studied the co-epidemic by incorporating treatment of latent and active TB classes. From the available literature on modelling of HIV-TB co-infection it is observed that the researchers have been emphasizing the effect of screening of infectives and even some of these have studied the co-epidemic by sub-dividing the total number of infectives in aware and unaware classes.

The present work intends to identify and study the factors which robustly influence the spread of HIV-TB co-infection and would complement the aforementioned studies. Here, a non-linear mathematical model has been considered to study the dynamics of HIV-TB co-infection that integrate the essential epidemiological features of these two diseases incorporating screening and treatment of infectives. It is important to mention that TB is a bacterial disease where as HIV is a viral infection and even though both the diseases have different modes of transmission, yet they show a synergistic interaction and each infection stimulate the progression of the other one [24]. TB can be transmitted directly from air, if the susceptible individual inhales the bacilli present in air. The individuals of all ages (child, adult, old) are susceptible to TB and can become infected with the infection. Although, available data witnesses the presence of pediatric TB as a responsible factor in some countries, yet in the present study we have not included children in the compartment of individuals who are susceptible to TB. Heterosexual intercourse is the main mode of transmission of HIV infection, hence we concentrate only on sexually-active adult population susceptible to HIV in the model formulation. Rather, we consider sexually-active individuals only who can acquire or transmit HIV or TB.

This chapter is organized as follows: in Section (6.2), the HIV-TB mathematical has been described and formulated. Section (6.3), is divided into three subsections. In Subsection (6.3.1) reproduction number is computed and thereafter in Subsections (6.3.2) and (6.3.3) existences of various equilibria is discussed. Section (6.4), deals with the stability analysis of the various equilibria. In Section (6.5), numerical simulations intend to illustrate analytical findings to observe the effect of various parameters on the transmission dynamics of HIV. The chapter concludes with brief discussion in Section (6.6). In this section, we attempted to draw epidemiologically relevant conclusions from the analytical observations made from the present model. To an extent, the conclusion shall also projected ideas that could help and guide the course of future research in this area.

6.2 Mathematical model

The total sexually active population at time t, denoted by N(t) or N, is divided into five mutually-exclusive compartments: susceptible (S(t)), individuals infected with TB ($I_1(t)$) assumed to be infectious, asymptomatically infected individuals with HIV ($I_2(t)$), dually-infected individuals (infected with both the diseases) i.e. active TB and asymptotic stage of HIV infection ($I_3(t)$), and AIDS patients ($I_4(t)$) i.e. HIV patients showing symptoms of AIDS). So that

$$N(t) = S(t) + I_1(t) + I_2(t) + I_3(t) + I_4(t).$$

The proposed model is formulated based on certain facts and assumptions. We assume that a fraction of the total HIV infectives is screened and is aware of having this disease. Also, proper counseling is provided to this fraction of aware infectives with the target that they don't take part into transmission of HIV to others. We have assumed that screening is associated with proper counseling and the screened HIV infectives are not participating in the transmission of HIV. However, some screened HIV infectives may contribute in the transmission of HIV virus, but in this work we have ignored those

individuals as if they are not screened. Further, it has been considered that some fraction of HIV aware patients have received administered treatment using ARVs and due to which their progression rate to AIDS compartment is slow as compared to untreated HIV individuals. Similarly, a fraction of co-infected individuals who received treatment have a slow progression rate to AIDS compartment in comparison to untreated individuals. It is assumed that the co-infected individuals are too weak to transmit the infection and hence they do not contribute in the transmission of HIV or TB. Combining all the above mentioned assumptions a simple mathematical model governed by system of differential equations to study the dynamics of HIV-TB co-infection in a sexually-active population is formulated. The model intends to incorporate the essential epidemiological features of both the diseases (HIV and TB) in the presence of screening and treatment of infectives. The model is proposed as follows:

$$\begin{aligned}
\frac{dS}{dt} &= \Lambda - \beta_1 S I_1 - \beta_2(1-\alpha) S I_2 - \mu S + \gamma I_1, \\
\frac{dI_1}{dt} &= \beta_1 S I_1 - \beta_2(1-\alpha) I_1 I_2 - (\gamma+\mu) I_1 - \mu_1 I_1, \\
\frac{dI_2}{dt} &= \beta_2(1-\alpha) S I_2 - \beta_1 I_1 I_2 - \alpha\{\delta_1\nu + (1-\nu)\delta_2\} I_2 \\
&\quad -(1-\alpha)\delta_2 I_2 - (\mu+\mu_2) I_2, \qquad (6.1) \\
\frac{dI_3}{dt} &= \beta_1 I_1 I_2 + \beta_2(1-\alpha) I_1 I_2 - \alpha\{\delta_3\nu + (1-\nu)\delta_4\} I_3 - (1-\alpha)\delta_4 I_3 - (\mu+\mu_3) I_3, \\
\frac{dI_4}{dt} &= \alpha\{\delta_1\nu + \delta_2(1-\nu)\} I_2 + (1-\alpha)\delta_2 I_2 + \alpha\{\delta_3\nu + (1-\nu)\delta_4\} I_3 \\
&\quad +(1-\alpha)\delta_4 I_3 - (\mu_4+\mu) I_4,
\end{aligned}$$

Here

$S(0) > 0, I_1(0) \geq 0, I_2(0) \geq 0, I_3(0) \geq 0, I_4(0) \geq 0$, and $N(t) = S(t) + I_1(t) + I_2(t) + I_3(t) + I_4(t)$.

For further analysis the model system (6.1) can be simply rewritten as follows:

$$\begin{aligned}
\frac{dS}{dt} &= \Lambda - \beta_1 S I_1 - \beta_2(1-\alpha) S I_2 - \mu S + \gamma I_1, \\
\frac{dI_1}{dt} &= \beta_1 S I_1 - \beta_2(1-\alpha) I_1 I_2 - (\gamma+\mu) I_1 - \mu_1 I_1, \\
\frac{dI_2}{dt} &= \beta_2(1-\alpha) S I_2 - \beta_1 I_1 I_2 - (k_1+\mu+\mu_2) I_2, \\
\frac{dI_3}{dt} &= \beta_1 I_1 I_2 + \beta_2(1-\alpha) I_1 I_2 - (k_2+\mu+\mu_3) I_3, \\
\frac{dI_4}{dt} &= k_1 I_2 + k_2 I_3 - (\mu+\mu_4) I_4
\end{aligned} \tag{6.2}$$

where

$k_1 = \alpha\{\delta_1\nu + \delta_2(1-\nu)\} + (1-\alpha)\delta_2, k_2 = \alpha\{\delta_3\nu + (1-\nu)\delta_4\} + (1-\alpha)\delta_4$. Here, the variables and parameters considered in this model are non-negative. The biologically-feasible region of attraction of this model is given by

$$\mathcal{D} = \left\{ (S, I_1, I_2, I_3, I_4) \in \mathcal{R}_+^5 : N \leq \frac{\Lambda}{\mu} \right\}$$

is positively invariant and the solutions $S(t), I_1(t), I_2(t), I_3(t)$ and $I_4(t)$ of the model system (6.1) remain non-negative for all time $t > 0$.

The transfer diagram for the simplified model is shown in the Figure 6.1 whereas Figure 6.2 describes the flowchart which governs the movement of individuals from HIV class to AIDS class. Similar flowchart governing movement of individuals from co-infected class to AIDS class is easy to visualize.

The descriptions of all parameters considered in model formulation are summarized in Table 6.1. Notice that here $\delta_1 < \delta_2$ and $\delta_3 < \delta_4$.

Table 6.1: Description of parameters used in model system (6.1).

Parameter	Description
Λ	Recruitment rate into the population,
μ	Natural death rate,
α	Fraction of individuals under screening with proper counseling,
γ	Recovery rate of TB patient,
ν	Fraction of infectives under treatment,
δ_1 and δ_2	Progression rates of HIV infected treated, and untreated individuals to AIDS individuals, respectively,
β_1	Rate of TB transmission,
β_2	Rate of HIV transmission,
μ_1	TB related death rate,
μ_2	HIV related death rate,
μ_3	Disease-induced mortality for mixed-infections to the illness,
μ_4	Disease-induced mortality for AIDS,
δ_3 and δ_4	Progression rates of treated and untreated co-infected individuals to AIDS.

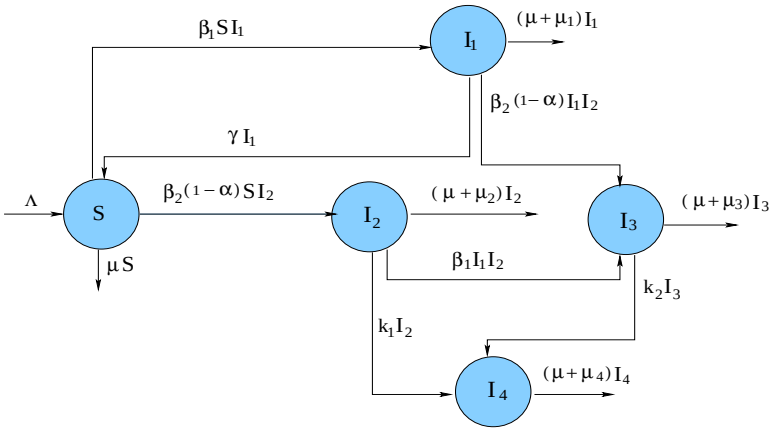

Figure 6.1: Transfer diagram of the model (6.2)

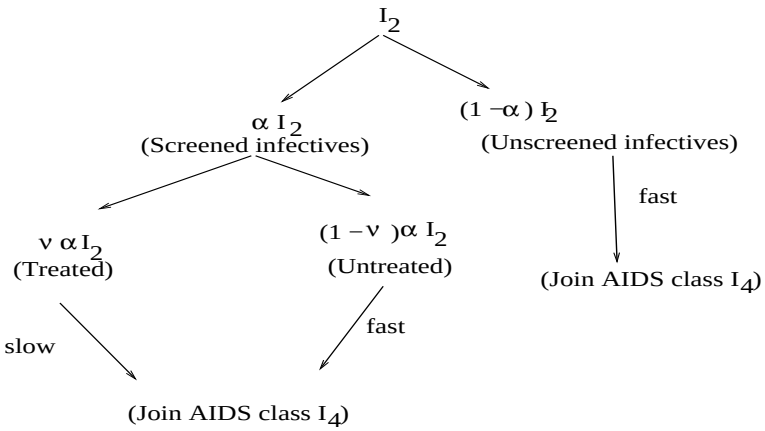

Figure 6.2: Flow chart for the movement of HIV infectives

6.3 Basic reproduction number and existence of equilibria

6.3.1 Basic reproduction number

The model has a disease-free equilibrium, obtained by setting the right-hand sides of the equations in the model (6.2) to zero,, given by $E_0 = (S_0, 0, 0, 0, 0)$ with $S_0 = \frac{\Lambda}{\mu}$. Using the next generation matrix method [168], the matrices $\mathcal{F}$ and $\mathcal{V}$, are obtained as follows:

$$\mathcal{F} = \begin{pmatrix} \beta_1 S I_1 \\ \beta_2(1-\alpha) S I_2 \\ \beta_1 S I_1 I_2 + \beta_2(1-\alpha) S I_1 I_2 \\ 0 \end{pmatrix}, \mathcal{V} = \begin{pmatrix} \beta_2(1-\alpha) I_1 I_2 + (\gamma + \mu + \mu_1) I_1 \\ \beta_1 I_1 I_2 + (k_1 + \mu + \mu_2) I_2 \\ (k_2 + \mu + \mu_3) I_3 \\ (\mu + \mu_4) I_4 - k_1 I_2 - k_2 I_3 \end{pmatrix}$$

Further

$$\text{F} = \text{Jacobian of } \mathcal{F} \text{ at } E_0 = \begin{pmatrix} \beta_1 S_0 & 0 & 0 & 0 \\ 0 & \beta_2(1-\alpha) S_0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{pmatrix}$$

and

$$\text{V} = \text{Jacobian of } \mathcal{V} \text{ at } E_0 = \begin{pmatrix} (\gamma + \mu + \mu_1) & 0 & 0 & 0 \\ 0 & (k_1 + \mu + \mu_2) & 0 & 0 \\ 0 & 0 & (k_2 + \mu + \mu_3) & 0 \\ 0 & -k_1 & -k_2 & (\mu + \mu_4) \end{pmatrix}$$

The spectral radius of the next generation operator FV^{-1} is denoted by R_0 where

$$FV^{-1} = \begin{pmatrix} \frac{\beta_1 S_0}{(\gamma+\mu+\mu_1)} & 0 & 0 & 0 \\ 0 & \frac{\beta_2(1-\alpha) S_0}{(k_1+\mu+\mu_2)} & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{pmatrix}$$

We obtain two non-zero eigenvalues from this matrix. It is easy to observe that one eigenvalue corresponds to TB and the other corresponds to HIV. The reproduction number corresponding to TB and HIV are respectively computed as

$$R_T = \frac{\Lambda\beta_1}{\mu(\gamma+\mu+\mu_1)} \quad \text{and} \quad R_H = \frac{\Lambda\beta_2(1-\alpha)}{\mu(k_1+\mu+\mu_2)}.$$

The associated reproduction number for HIV-TB dual infection is given by

$$R_0 = \max\{R_T, R_H\},$$

where, R_T and R_H are as defined before. i.e.

$$R_0 = max\left\{\frac{\beta_1\Lambda}{\mu(\gamma+\mu+\mu_1)}, \frac{\beta_2(1-\alpha)\Lambda}{\mu(k_1+\mu+\mu_2)}\right\}. \tag{6.3}$$

6.3.2 Equilibria of the model

The model system (6.1) has four equilibrium points defined as follows:

(i) Disease-free equilibrium denoted by E_0,

(ii) TB-only equilibrium E_1, for which TB is endemic in the population,

(iii) HIV-only equilibrium E_2, for which HIV is endemic in the population,

(iv) The co-infection equilibrium E_0 for which TB, HIV and HIV-TB dual infection are all endemic in the population.

The disease-free equilibrium is given by:

$$E_0 = \left(\frac{\Lambda}{\mu}, 0, 0, 0, 0\right). \tag{6.4}$$

TB-only equilibrium is obtained as :

$$\begin{aligned} E_1 &= (\bar{S}, \bar{I}_1, 0, 0, 0) \\ &= \left(\frac{\gamma+\mu+\mu_1}{\beta_1}, \frac{(\gamma+\mu+\mu_1)\mu}{\beta_1(\mu+\mu_1)}(R_T-1), 0, 0, 0\right). \end{aligned} \tag{6.5}$$

HIV-only equilibrium is obtained as:

$$\begin{aligned} E_2 &= (S^*, I_1^*, I_2^*, I_3^*, I_4^*) \\ &= \left(\frac{k_1+\mu+\mu_2}{\beta_2(1-\alpha)}, 0, I_2^*, 0, \frac{k_1 I_2^*}{(\mu+\mu_4)}\right), \end{aligned} \tag{6.6}$$

where
$I_2^* = \dfrac{\mu(R_H-1)}{\beta_2(1-\alpha)}$.

The co-infection equilibrium is denoted by $E_3(\hat{S}, \hat{I}_1, \hat{I}_2, \hat{I}_3, \hat{I}_4)$ and is derived in following subsection:

6.3.3 The existence and uniqueness of co-infection equilibrium

To find the co-infection equilibrium point E_3, we equate the right hand side of equations in system (6.2) to zero, we get

$$\hat{I}_1 = \frac{\beta_2(1-\alpha)\hat{S} - (k_1+\mu+\mu_2)}{\beta_1}, \tag{6.7}$$

$$\hat{I}_2 = \frac{\beta_1\hat{S} - (\gamma+\mu+\mu_1)}{\beta_2(1-\alpha)} \tag{6.8}$$

$$\hat{I}_3 = \frac{\{\beta_1 + \beta_2(1-\alpha)\}\hat{I}_1\hat{I}_2}{(k_2+\mu+\mu_3)}, \tag{6.9}$$

$$\hat{I}_4 = \frac{k_1\hat{I}_2 + k_2\hat{I}_3}{(\mu+\mu_4)}. \tag{6.10}$$

Here, $\hat{S}$ is the root of the following quadratic equation:

$$A\hat{S}^2 + B\hat{S} + C = 0. \tag{6.11}$$

where

$$A = \beta_2(1-\alpha) + \beta_1 > 0,$$

$$B = -\left(k_1+\mu+\mu_2+\gamma+\mu_1+\frac{\beta_2(1-\alpha)\gamma}{\beta_1}\right) < 0,$$

$$C = \frac{\gamma(k_1+\mu+\mu_2)}{\beta_1} - \Lambda,$$

and

$$\begin{aligned} B^2 - 4AC &= \left[((k_1+\mu+\mu_2) - \left\{\gamma+\mu_1+\frac{\beta_2(1-\alpha)\gamma}{\beta_1}\right\}\right]^2 \\ &\quad +4\mu_1(k_1+\mu+\mu_2) + 4\{\beta_2(1-\alpha)+\beta_1\}\Lambda > 0. \end{aligned}$$

Now, if $C > 0$, then we get two positive roots of the quadratic equation (6.12), but we need to verify that whether both the roots satisfy the conditions corresponding to $\hat{I}_1$ and $\hat{I}_2$ to be positive or not. For $\hat{I}_1$ and $\hat{I}_2$ to be positive the following condition needs to be true:

$$\hat{S} > \max\left\{\frac{k_1+\mu+\mu_2}{\beta_2(1-\alpha)}, \frac{\gamma+\mu+\mu_1}{\beta_1}\right\}. \tag{6.12}$$

Additionally, the smaller root of the quadratic equation will be less than $\dfrac{-B}{2A}$, which gives

$$\hat{S} < \frac{(k_1+\mu+\mu_2)+\gamma+\mu_1+\frac{\beta_2(1-\alpha)\gamma}{\beta_1}}{2\{\beta_1+\beta_2(1-\alpha)\}}$$

or

$$\hat{S} < \frac{(k_1+\mu+\mu_2)}{2\{\beta_1+\beta_2(1-\alpha)\}} + \frac{\gamma+\mu_1+\frac{\beta_2(1-\alpha)\gamma}{\beta_1}}{2\{\beta_1+\beta_2(1-\alpha)\}} \tag{6.13}$$

Now, the following two cases arise:

(i) when $(k_1+\mu+\mu_2) > \gamma+\mu_1+\dfrac{\beta_2(1-\alpha)\gamma}{\beta_1}$ we get $S < \dfrac{(k_1+\mu+\mu_2)}{\{\beta_1+\beta_2(1-\alpha)\}}$, which contradicts the condition stated in inequality (6.12), i.e., $S > \dfrac{k_1+\mu+\mu_2}{\beta_2(1-\alpha)}$. Hence in this case we do not have positive I_1 corresponding to the smaller root ($\hat{S}$) of the quadratic equation (6.11).

(ii) when $(k_1+\mu+\mu_2) < \gamma+\mu_1+\dfrac{\beta_2(1-\alpha)\gamma}{\beta_1}$, we get, $\hat{S} < \dfrac{\gamma+\mu_1+\frac{\beta_2(1-\alpha)\gamma}{\beta_1}}{\{\beta_1+\beta_2(1-\alpha)\}}$.

From the inequality (6.12), we want $\hat{S} > \dfrac{\gamma+\mu+\mu_1}{\beta_1}$.

Hence, we must have

$$\frac{\gamma+\mu+\mu_1}{\beta_1} < \frac{\gamma+\mu_1+\frac{\beta_2(1-\alpha)\gamma}{\beta_1}}{\{\beta_1+\beta_2(1-\alpha)\}}.$$

This gives, $\beta_1\mu+\beta_2(1-\alpha)(\mu+\mu_1) < 0$, which is false as all the parameters are positive and $\alpha < 1$. Thus, in this case I_2 becomes negative.

Finally, we conclude that smaller root of the quadratic equation never gives both $\hat{I}_1$ and $\hat{I}_2$ positive. Hence, for $C > 0$, we get unique co-infection equilibrium corresponding to the larger root of the quadratic equation provided the condition mentioned in the inequality (6.12) is satisfied.

And if C is negative i.e. $\dfrac{\Lambda\beta_1}{\gamma(k_1+\mu+\mu_2} > 1$, then we get unique positive root and corresponding to this we get unique co-infection equilibrium point provided condition mentioned in (6.13) is satisfied.

Additionally, the value of S corresponding to the co-infection equilibrium point must be less than the S corresponding to the disease-free equilibrium point, so we must have $S < \dfrac{\Lambda}{\mu}$. And by using the inequality (6.12) we get $R_T > 1$ and $R_H > 1$.

Thus, we have a unique endemic equilibrium $E_3(\hat{S}, \hat{I}_1, \hat{I}_2, \hat{I}_3, \hat{I}_4)$ under the condition stated in (6.12) irrespective of $C < 0$ or $C > 0$ whenever both $R_T > 1$ and $R_H > 1$.

6.4 Stability analysis

In this section we discuss the local and global stability of the equilibria obtained in Subsection (6.3.2).

6.4.1 Stability analysis of disease-free equilibrium

The local asymptotic stability of the disease-free equilibrium point E_0 is established by using Jacobian matrix and is stated in the following theorem.

Theorem 6.4.1: *If $R_T < 1$ and $R_H < 1$, the disease-free equilibrium E_0 is locally asymptotically stable and is unstable for $R_T > 1$ or $R_H > 1$.*

Proof. To study the stability of the disease-free equilibrium the Jacobian matrix M_0 of

the system corresponding to the disease-free equilibrium E_0 is obtained as

$$M_0 = \begin{pmatrix} -\mu & -\beta_1\frac{\Lambda}{\mu}+\gamma & -\beta_2(1-\alpha)\frac{\Lambda}{\mu} & 0 & 0 \\ 0 & m_{22} & 0 & 0 & 0 \\ 0 & 0 & m_{33} & 0 & 0 \\ 0 & 0 & 0 & -(k_2+\mu+\mu_3) & 0 \\ 0 & 0 & k_1 & k_2 & -(\mu+\mu_4), \end{pmatrix}$$

where

$m_{22} = \beta_1\frac{\Lambda}{\mu} - (\mu+\mu_1+\gamma),\ m_{33} = \beta_2(1-\alpha)\frac{\Lambda}{\mu} - (k_1+\mu+\mu_2).$

The eigenvalues of this the Jacobian matrix are $-\mu, \beta_1\frac{\Lambda}{\mu} - (\mu+\mu_1+\gamma), \beta_2(1-\alpha)\frac{\Lambda}{\mu} - (k_1+\mu+\mu_2), -(k_2+\mu+\mu_3) and -(\mu+\mu_4)$. Clearly, here two eigenvalues are positive for $R_T > 1$ and $R_H > 1$, which implies instability of disease-free equilibrium E_0. So the equilibrium is locally asymptotically stable provided $R_T < 1$ and $R_H < 1$. ∎

Theorem 6.4.2: *If $R_T < 1$ and $R_H < 1$, the disease-free equilibrium E_0 is globally stable in the region $\mathcal{D}$.*

Proof. Let us take the Lyapunov function as follows:

$$L = I_1 + I_2 + I_3.$$

which gives

$$\begin{aligned} \dot{L} &= \dot{I}_1 + \dot{I}_2 + \dot{I}_3 \\ &= \{\beta_1 I_1 + \beta_2(1-\alpha)I_2\}S - (\gamma+\mu+\mu_1)I_1 - (k_1+\mu+\mu_2)I_2 - (k_2+\mu+\mu_3)I_3 \\ &= \{\beta_1 S - (\gamma+\mu+\mu_1)\}I_1 + \{\beta_2(1-\alpha)S - (k_1+\mu+\mu_2)\}I_2 - (k_2+\mu+\mu_3)I_3 \\ &\leq \left\{\beta_1\frac{\Lambda}{\mu} - (\gamma+\mu+\mu_1)\right\}I_1 + \left\{\beta_2(1-\alpha)\frac{\Lambda}{\mu} - (k_1+\mu+\mu_2)\right\}I_2 - (k_2+\mu+\mu_3)I_3 \\ &= (\gamma+\mu+\mu_1)(R_T-1)I_1 + (k_1+\mu+\mu_2)(R_H-1)I_2 - (k_2+\mu+\mu_3)I_3 \qquad (6.14) \end{aligned}$$

Clearly, $\dot{L} \leq 0$ whenever both $R_T < 1$ and $R_H < 1$ and it is 0 only when $I_1 = 0 = I_2 = I_3$. Also for $R_T < 1$ and $R_H < 1$, from the second and third equations of the system (6.2),

we have

$$\lim_{t\to\infty} I_1 = 0, \quad \lim_{t\to\infty} I_2 = 0.$$

Now, for $I_1 = 0 = I_2$ using first and fourth equations of the system (6.2), we get

$$\lim_{t\to\infty} S = \frac{\Lambda}{\mu} \text{ and } \lim_{t\to\infty} I_3 = 0.$$

Therefore, the largest compact invariant set in $\{(S, I_1, I_2, I_3, I_4) \in \mathcal{D} : \dot{L} = 0\}$ is the singleton $\{E_0\}$ in $\mathcal{D}$, where E_0 is the disease-free equilibrium. LaSalle's invariant principle [106] implies that the disease-free equilibrium E_0 is globally asymptotically stable for $R_T < 1$ and $R_H < 1$. ∎

6.4.2 Stability analysis of endemic equilibrium

Theorem 6.4.3: *The TB only equilibrium E_1 is locally asymptotically stable provided $R_T > R^*$ and unstable otherwise. The expression for R^* is given in the proof of the theorem.*

Proof. To study the stability of TB only equilibrium the Jacobian matrix M_1 of the system corresponding to TB only equilibrium E_1 is obtained as follows:

$$M_1 = \begin{pmatrix} -\beta_1\bar{I}_1 - \mu & -\beta_1\bar{S} + \gamma & -\beta_2(1-\alpha)\bar{S} & 0 & 0 \\ \beta_1\bar{I}_1 & 0 & -\beta_2(1-\alpha)\bar{I}_1 & 0 & 0 \\ 0 & 0 & \bar{m}_{33} & 0 & 0 \\ 0 & 0 & \{\beta_1 + \beta_2(1-\alpha)\}\bar{I}_1 & -(k_2+\mu_3+\mu) & 0 \\ 0 & 0 & k_1 & k_2 & -(\mu+\mu_4) \end{pmatrix}$$

where

$\bar{m}_{33} = \beta_2(1-\alpha)\bar{S} - (k_1+\mu+\mu_2) - \beta_1\bar{I}_1$, and $\bar{S} = \dfrac{\gamma+\mu+\mu_1}{\beta_1}$,

$\bar{I}_1 = \dfrac{(\gamma+\mu+\mu_1)\mu}{(\mu+\mu_1)\beta_1}(R_T - 1)$.

Two eigenvalues of this matrix M_1 are $-(\mu+\mu_4)$ and $-(k_2+\mu+\mu_3)$, which are clearly negative, whereas the third eigenvalue is given by $\beta_2(1-\alpha)\bar{S} - \beta_1\bar{I}_1 - (k_1+\mu_1+\mu_2)$. Rest

of the two eigenvalues are the roots of the following quadratic equation:

$$\psi^2 + (\beta_1 \bar{I}_1 + \mu)\psi + \beta_1(\Lambda - \mu\bar{S}) = 0. \tag{6.15}$$

The above quadratic will have negative roots or will have roots with negative real parts as the constant term in the quadratic is positive for $R_T > 1$. Hence, four eigenvalues of the matrix M_1 are either negative or have negative real parts. Finally, the fifth eigenvalue will be negative provided $\beta_2(1-\alpha)\bar{S} - \beta_1\bar{I}_1 - (k_1 + \mu_1 + \mu_2) < 0$, which corresponds to $R_T > R^*$,

where $R^* = \left(\frac{\mu + \mu_1}{\mu}\right)\left\{\frac{\beta_2(1-\alpha)}{\beta_1} - \frac{(k_1 + \mu + \mu_2)}{(\gamma + \mu + \mu_1)}\right\} + 1 = R^*$, (say) ∎

In the following theorem, the local asymptotic stability of the equilibrium point E_2 is established by using the Jacobian matrix and is stated in the following theorem.

Theorem 6.4.4: *The HIV-only equilibrium E_2 is locally asymptotically stable provided $R_H > R^{**}$ otherwise it is unstable. The expression for R^{**} is given in the proof of this theorem.*

Proof. To study the stability of model system (6.2) at HIV-only equilibrium E_2, the Jacobian matrix M_2 of the system is given as follows

$$M_2 = \begin{pmatrix} -\beta_2(1-\alpha){I_2}^* - \mu & -\beta_1 S^* + \gamma & -\beta_2(1-\alpha)S^* & 0 & 0 \\ 0 & n_{22} & 0 & 0 & 0 \\ \beta_2(1-\alpha){I_2}^* & -\beta_1 {I_2}^* & 0 & 0 & 0 \\ 0 & \{\beta_1 + \beta_2(1-\alpha)\}{I_2}^* & 0 & -(k_2 + \mu_3 + \mu) & 0 \\ 0 & 0 & k_1 & k_2 & -(\mu + \mu_4) \end{pmatrix},$$

where

$n_{22} = \beta_1 S^* - \beta_2(1-\alpha){I_2}^* - (\mu + \mu_1 + \gamma), S^* = \dfrac{k_1 + \mu + \mu_2}{\beta_2(1-\alpha)}, \quad I_2^* = \dfrac{\mu(R_H - 1)}{\beta_2(1-\alpha)}.$

Three eigenvalues of this the Jacobian matrix are

$-(k_2 + \mu + \mu_3), -(\mu + \mu_4), \beta_1 S^* - \beta_2(1-\alpha){I_2}^* - (\gamma + \mu + \mu_1)$ and other two eigenvalues are roots of the following quadratic:

$$\psi^2 + \{\beta_2(1-\alpha){I_2}^* + \mu\}\psi + \beta_2^2(1-\alpha)^2 S^* {I_2}^* \;=\; 0. \tag{6.16}$$

Clearly, the roots of this quadratic equation are either negative or have negative real parts. The equilibrium E_2 will be locally asymptotically stable provided all the eigenvalues are negative or have negative real parts.

So we require

$$\beta_1 S^* - \beta_2(1-\alpha){I_2}^* - (\gamma+\mu+\mu_1) < 0,$$

which corresponds to

$$R_H > \frac{1}{\mu}\left\{\frac{\beta_1(k_1+\mu+\mu_2)}{\beta_2(1-\alpha)} - (\gamma+\mu+\mu_1)\right\} + 1 = R^{**}, \text{ (say)}.$$

∎

The local asymptotic stability of co-infection equilibrium point $E_3(\hat{S}, \hat{I}_1, \hat{I}_2, \hat{I}_3, \hat{I}_4)$, can be established by by using the Jacobian matrix and is stated in the following theorem.

Theorem 6.4.5: *The co-infection equilibrium point $E_3(\hat{S}, \hat{I}_1, \hat{I}_2, \hat{I}_3, \hat{I}_4)$, is unstable whenever it exists.*

Proof. The Jacobian matrix corresponding to co-infection equilibrium point $E_3(\hat{S}, \hat{I}_1, \hat{I}_2, \hat{I}_3, \hat{I}_4)$ is computed as follows:

$$M_3 = \begin{pmatrix} \hat{m}_{11} & -\beta_1\hat{S}+\gamma & -\beta_2(1-\alpha)\hat{S} & 0 & 0 \\ \beta_1 I_1 & \hat{m}_{22} & -\beta_2(1-\alpha)\hat{I}_1 & 0 & 0 \\ \beta_2(1-\alpha)\hat{I}_2 & -\beta_1\hat{I}_2 & \hat{m}_{33} & 0 & 0 \\ 0 & \{\beta_1+\beta_2(1-\alpha)\}\hat{I}_2 & \{\beta_1+\beta_2(1-\alpha)\}\hat{I}_1 & -(k_2+\mu+\mu_3) & 0 \\ 0 & 0 & k_1 & k_2 & -(\mu+\mu_4) \end{pmatrix},$$

where

$\hat{m}_{11} = -\{\beta_1\hat{I}_1 + \beta_2(1-\alpha)\hat{I}_2\} - \mu, \quad \hat{m}_{22} = \beta_1\hat{S} - \beta_2(1-\alpha)\hat{I}_2 - (\gamma+\mu+\mu_1) = 0,$

$\hat{m}_{33} = \beta_2(1-\alpha)\hat{S} - \beta_1\hat{I}_1 - (k_1+\mu+\mu_2) = 0.$

Clearly, two eigenvalues of this matrix are given by $-(\mu+\mu_4)$ and $-(k_2+\mu+\mu_3)$ and other three eigenvalues are the roots of the following cubic equation which is the characteristic

equation corresponding to principal minor of order 3 of the matrix M_3.

$$\psi^3 + A\psi^2 + B\psi + C \;=\; 0, \tag{6.17}$$

Here

A =-(Sum of roots of this cubic equation),

B = Sum of products of the roots taken in pairs and

C = -(products of the roots).

We know that the product of roots represents the determinant of the matrix. Here it is easy to see that

$$C = -\beta_1\beta_2(1-\alpha)\hat{I}_1\hat{I}_2\left[2\beta_1\hat{I}_1 + 2\beta_2(1-\alpha)\hat{I}_2 + \mu + (k_1+\mu+\mu_2) + (\mu+\mu_1) + \gamma\frac{(\beta_1-\beta_2)}{\beta_1} + \frac{\gamma\alpha}{\beta_1}\right] < 0,$$

Based on epidemiological pattern and nature of the diseases we know that rate of TB transmission β_1 must be greater than the rate of HIV transmission β_2. Hence the last cubic must have one root with positive sign, which implies that the Jacobian matrix M_3 has at least one positive eigenvalue. Thus, we can conclude that the co-infection equilibrium point is always unstable whenever it exists. ∎

6.5 Numerical simulation

The system (6.2) is simulated for various set of parameters using XPP [65]. The stability of disease-free equilibrium point E_0 is shown in Figures 6.3-6.4, where both the reproduction numbers R_T and R_H corresponding to TB and HIV, respectively are less than 1 and the parameter values are as follows:

$$\Lambda = 30, \mu = 0.067, \beta_1 = 0.002, \beta_2 = 0.0005, \gamma = 0.8, \mu_1 = 0.07, \mu_2 = 0.08,$$

$$\mu_3 = 0.09, \mu_4 = 0.1, \alpha = 0.3, \nu = 0.5, \delta_1 = 0.01, \delta_2 = 0.02, \delta_3 = 0.02, \delta_4 = 0.03.$$

For this set of parameter values, we get $R_T = 0.955, R_H = 0.947$ and the disease-free equilibrium point E_0 is

$$S_0 = 447.7612, I_0 = 0 = I_2 = I_3 = I_4.$$

The stability of TB-only equilibrium point is shown in Figures 6.5-6.6, for which $R_T > 1$

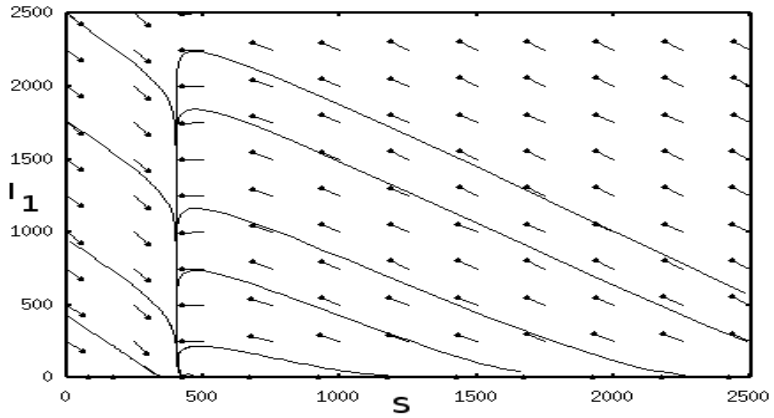

Figure 6.3: S-I_1 phase plane showing the stability of the disease-free equilibrium point E_0.

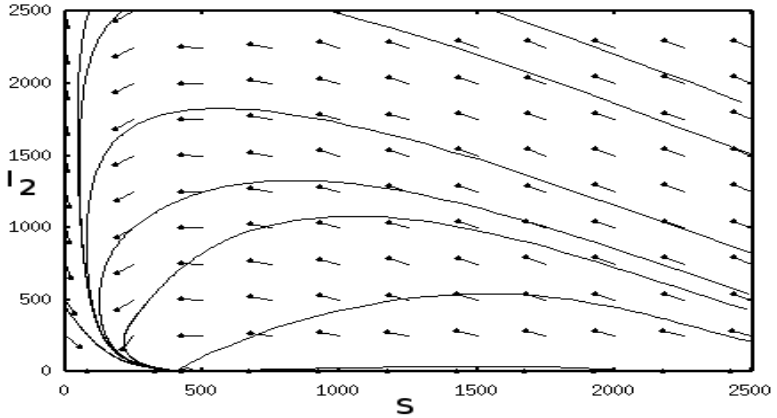

Figure 6.4: $S - I_2$ phase plane showing the stability of the disease-free equilibrium point E_0.

and $R_H < 1$. Simulation is carried for the following set of parameters:

$$\Lambda = 30, \mu = 0.067, \beta_1 = 0.002, \beta_2 = 0.0005, \gamma = 0.5, \mu_1 = 0.05, \mu_2 = 0.08,$$

$$\mu_3 = 0.09, \mu_4 = 0.1, \alpha = 0.6, \nu = 0.5, \delta_1 = 0.01, \delta_2 = 0.02, \delta_3 = 0.02, \delta_4 = 0.03.$$

For this set of parameters $R_T = 1.4514 > 1, R_H = 0.546 < 1$ and the equilibrium point E_1 is

$$\bar{S} = 308.50, \bar{I}_1 = 79.747, \bar{I}_2 = 0 = \bar{I}_3 = \bar{I}_4.$$

The equilibrium points E_2 and E_3 do not exist for this set of parameters. Similarly for

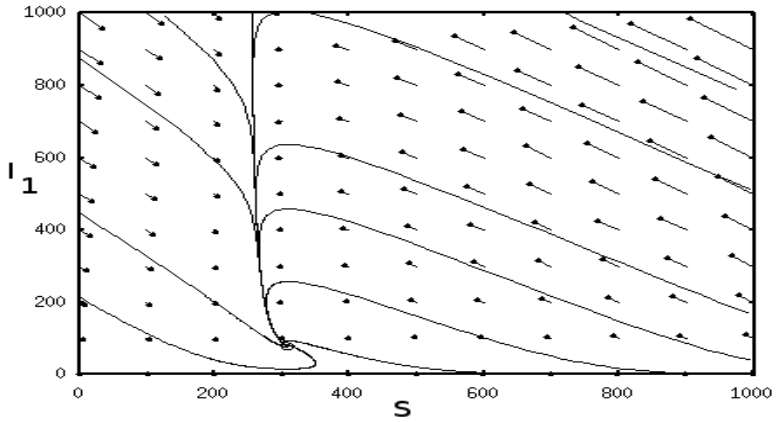

Figure 6.5: S-I_1 phase plane showing the stability of the TB-only equilibrium point E_1.

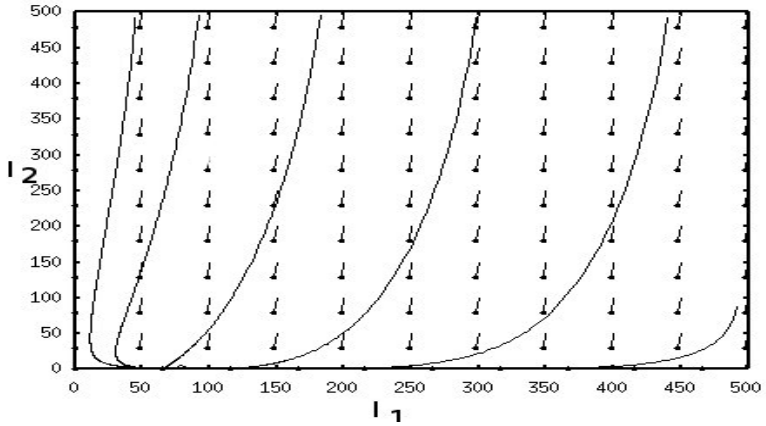

Figure 6.6: $I_1 - I_2$ phase plane showing the stability of the TB-only equilibrium point E_1.

$R_T < 1$ and $R_H > 1$, we get HIV-only equilibrium point E_2, which is locally asymptotically stable. This fact is demonstrated in Figures 6.7-6.8 for the following set of parameters:

$$\Lambda = 30, \mu = 0.067, \beta 1 = 0.002, \beta 2 = 0.001, \gamma = 0.8, \mu_1 = 0.07, \mu_2 = 0.08,$$

$$\mu_3 = 0.09, \mu_4 = 0.1, \alpha = 0.3, \nu = 0.5, \delta_1 = 0.01, \delta_2 = 0.02, \delta_3 = 0.02, \delta_4 = 0.03.$$

Here $R_T = 0.955, R_H = 1.893,\ E_2 = (236.428, 0, 85.554, 0, 9.477)$. The equilibria E_1 and E_3 do not exist and the disease-free equilibrium $E_0(447.76, 0, 0, 0, 0)$ is unstable. When R_T and R_H both are greater than 1, we have possibility to visualize the existence and stability of the equilibrium point E_3, which is demonstrated in Figures 6.9-6.10. Figure 6.9 is plotted using following set of parameters:

$$\Lambda = 40, \mu = 0.067, \beta_1 = 0.002, \beta_2 = 0.001, \gamma = 0.8, \mu_1 = 0.05, \mu_2 = 0.08,$$

$$\mu_3 = 0.09, \mu_4 = 0.1, \alpha = 0.6, \nu = 0.5 \delta_1 = 0.01, \delta_2 = 0.02, \delta_3 = 0.02, \delta_4 = 0.03.$$

Here $R_1 = 1.302, R_2 = 1.456,\ E_0 = (597.0149, 0, 0, 0, 0),\ E_1 = (458.50000, 79.32, 0, 0, 0)$, $E_2 = (410, 0, 76.402, 0, 7.777)$ and $E_3 = (466.29, 11.258, 38.955, 5.720, 4.89)$. The constant term C of the quadratic equation (6.11) is $25.6 > 0$. Figure 6.10 is demonstrating the

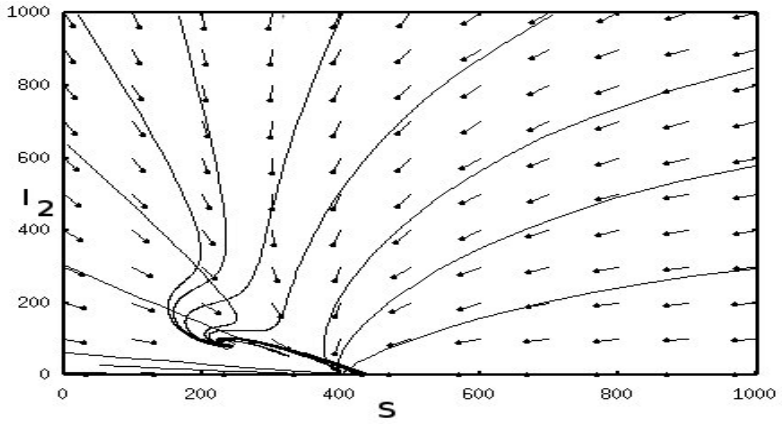

Figure 6.7: S-I_2 phase plane showing the stability of the HIV-only equilibrium point E_2.

same fact for the following set of parameters where $C = -0.866 < 0$,

$$\Lambda = 45, \mu = 0.067, \beta_1 = 0.003, \beta_2 = 0.002, \gamma = 0.8, \mu_1 = 0.07, \mu_2 = 0.08,$$

$$\mu_3 = 0.09, \mu_4 = 0.1, \alpha = 0.3, \nu = 0.5, \delta_1 = 0.01, \delta_2 = 0.02, \delta_3 = 0.02, \delta_4 = 0.03.$$

It is verified that the local stability conditions for the stability of E_1 and E_2 are satisfied, so they are stable but the equilibrium points E_0 and E_3 are unstable. As discussed already, the equilibria E_1 and E_2 are locally asymptotically stable under some conditions, so $R_T > 1$ and $R_H > 1$ do not guarantee the stability of these equilibria. This fact is

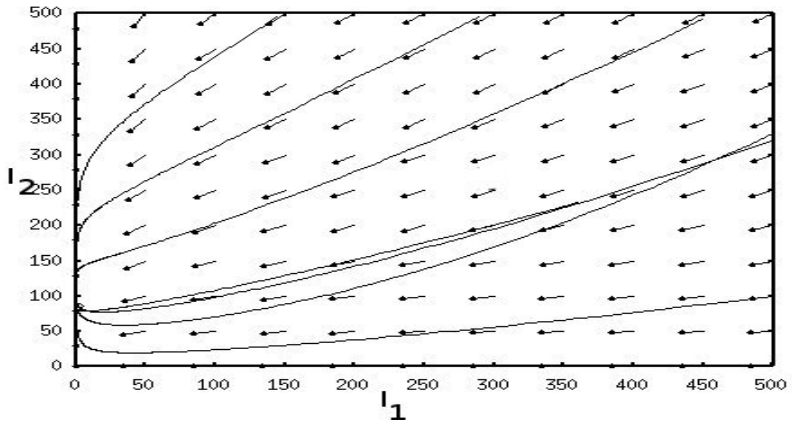

Figure 6.8: $I_1 - I_2$ phase plane showing the stability of the HIV-only equilibrium point E_2.

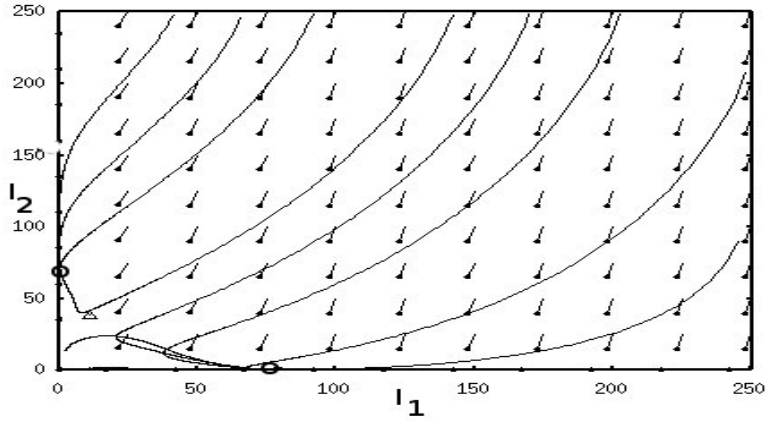

Figure 6.9: $I_1 - I_2$ phase plane showing the local stability of the equilibria E_1, E_2 and instability of the equilibrium point E_3 for $C > 0$.

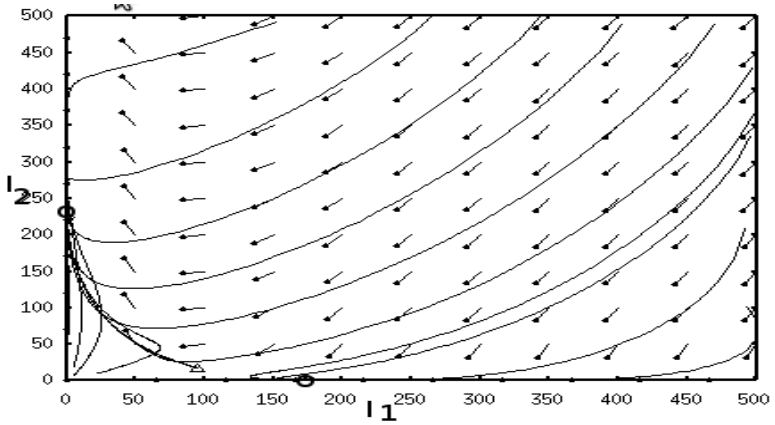

Figure 6.10: $I_1 - I_2$ phase plane showing the stability of the equilibria E_1 E_2 and instability of the equilibrium point E_3 for $C < 0$.

demonstrated in Figure 6.11, where $R_T > 1, R_H > 1$, E_1 is unstable, E_2 is stable and E_3

does not exist. Simulation is carried out for the following set of parameters

$$\Lambda = 40, \mu = 0.067, \beta_1 = 0.0016, \beta_2 = 0.001, \gamma = 0.8, \mu_1 = 0.05, \mu_2 = 0.08,$$

$$\mu_3 = 0.09, \mu_4 = 0.1, \alpha = 0.6, \nu = 0.5, \delta_1 = 0.01, \delta_2 = 0.02, \delta_3 = 0.02, \delta_4 = 0.03.$$

Here, $R_T = 1.04168, R_H = 1.456$, $E_0 = (597.0149, 0, 0, 0, 0)$, $E_1 = 573.125, 13.68, 0, 0, 0)$, $E_2 = (410, 0, 76.402, 0, 7.777)$. Figure 6.12 is demonstrating the same observation for the following set of parameters, where E_1 is stable and E_2 is unstable

$$\Lambda = 40, \mu = 0.067, \beta_1 = 0.002, \beta_2 = 0.001, \gamma = 0.4, \mu_1 = 0.06, \mu_2 = 0.08,$$

$$\mu_3 = 0.09, \mu_4 = 0.1, \alpha = 0.6, \nu = 0.5, \delta_1 = 0.01, \delta_2 = 0.02, \delta_3 = 0.02, \delta_4 = 0.03$$

For this set of parameters, we get $R_T = 2.265, R_H = 1.456$, $E_0 = (597.0149, 0, 0, 0, 0)$, $E_1 = (263.5, 175.948, 0, 0, 0)$ $E_2 = (410, 0, 76.4, 0, 7.777)$.

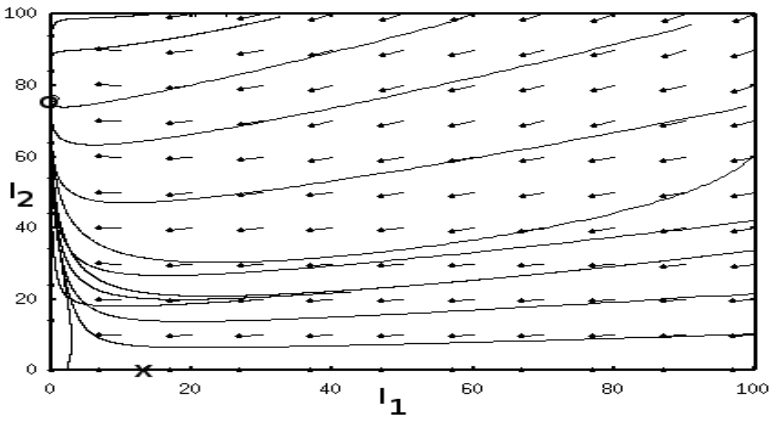

Figure 6.11: $I_1 - I_2$ phase plane showing the stability of the equilibrium E_2 and instability of the equilibria E_1 and E_3 for $R_T > 1,\ R_H > 1$.

To notice the effect of screening, we considered the case when both R_T and R_H are greater than one and both the equilibria E_1 and E_2 are locally asymptotically stable. It is observed that if our initial conditions are such that HIV-only equilibrium is locally asymptotically stable then with the increase in the fraction of screening parameter α, first the equilibrium level of HIV-infected population decreases and with further increase in this parameter makes this equilibrium E_2 unstable and in this case TB-only equilibrium

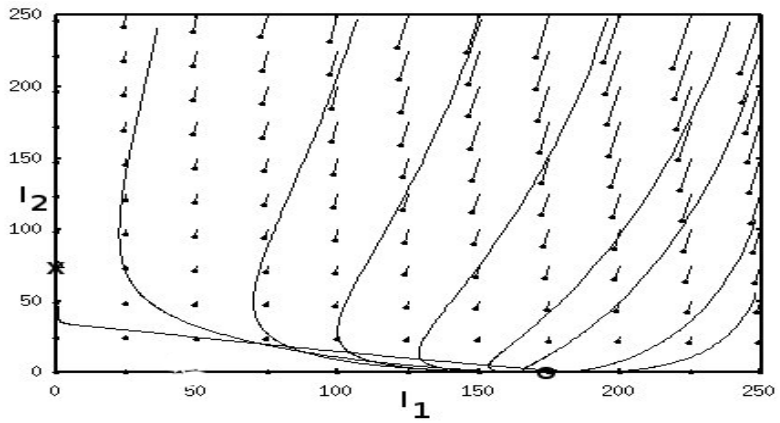

Figure 6.12: $I_1 - I_2$ phase plane showing the stability of the equilibrium E_1 and instability of the equilibria E_2 and E_3 for $R_T > 1,\ R_H > 1$.

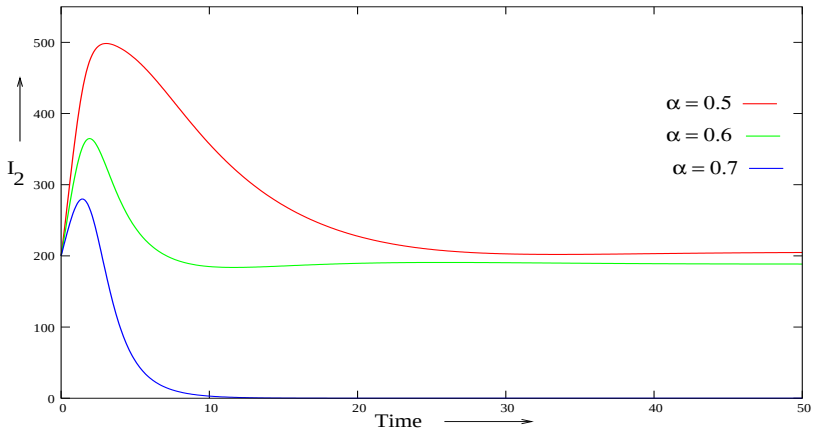

Figure 6.13: Variation of HIV infected population I_2 with time for different rates of screening α showing the effect of screening on the equilibrium level of HIV infected population.

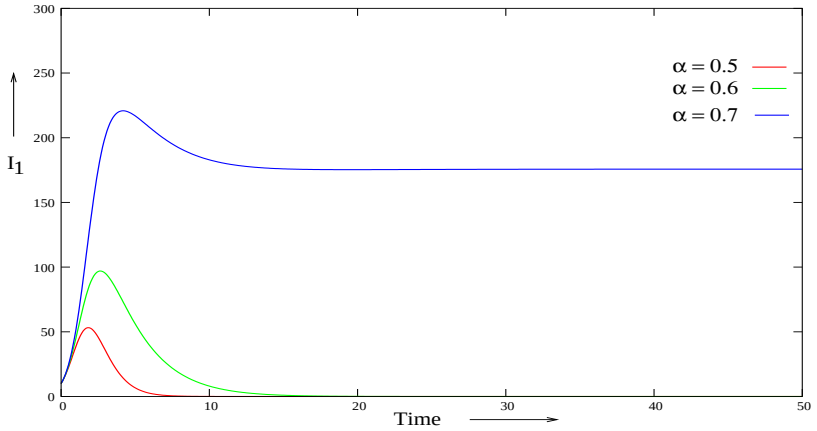

Figure 6.14: Variation of TB infected population I_1 with time for different rates of screening (α) showing the effect of screening on the equilibrium level of TB infected population.

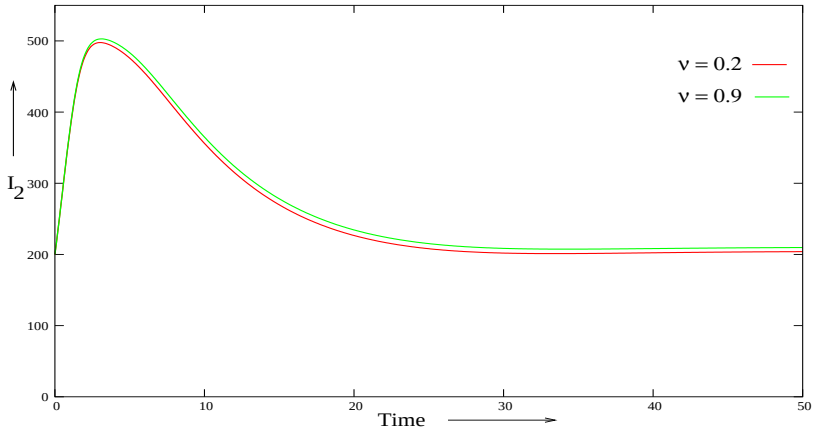

Figure 6.15: Variation of HIV infected population I_2 with time for different rates of treatment ν showing the effect of treatment on the equilibrium level of HIV infected population.

becomes stable.

This fact is demonstrated in the Figures 6.13-6.14, where variation of HIV infected population I_2 and TB infected population I_1 with time are shown for different values of α. The variation in fraction of infectives under treatment does not have much impact on the equilibrium level of HIV. The strong positive association between ART and the improved quality of life of patients living with HIV increase the waiting time of HIV infected individuals in HIV class. Hence, due to this the equilibrium level of HIV infectives increases with the increase in the fraction of infectives under treatment ν. Figure 6.15 is demonstrating this observation.

6.6 Conclusion

In this chapter, we have formulated and analyzed a five-dimensional nonlinear mathematical model for HIV/AIDS-TB co-infection with treatment and screening of HIV infectives. The reproduction numbers corresponding to TB (R_T) and HIV (R_H) have been obtained. The existence and stability of various equilibria have also been discussed. It is found that the system always tends to TB-only equilibrium point or to HIV-only equilibrium point if both R_T and R_H are greater than one. Further it has been found that the co-infection

equilibrium point is always unstable whenever it exists. Numerical simulation shows that the screening of HIV infected people plays a very prominent role in controlling the spread of this disease. Numerically, it is shown that with the increase in the fraction of screening, the system gets diverted from HIV-only equilibrium to TB-only equilibrium with same initial start. It is observed that the recovery rate of TB has positive impact on the reproduction number R_T corresponding to TB, i.e. with the increase in the recovery rate of TB infectives, the reproduction number R_T decreases.

Thus, it is concluded that with the increase of the recovery rate constant γ and the fraction of screening α, both R_T and R_H can be reduced below one, leading to disease-free equilibrium to be stable. The numerically performed analysis clearly indicates that the number of HIV infectives significantly decreases with increase in the fraction of screening of infectives. In fact, on the other part, the equilibrium level of HIV infected population increases with the increase in the fraction of infectives under treatment ν as it increases the waiting time of HIV positive individuals in HIV class. Overall at the end we can conclude that, in the countries with high HIV and TB prevalence, it is highly desirable to offer regular screening, counseling and testing for both the diseases to the natives. As the delay in the diagnosis and treatment of TB in people living with HIV is the strongest factor responsible to increase in the contacts among HIV and TB infectives and it also multiplies the risk for death [113]. For effective management of HIV-TB patients and to reduce and eradicate the dual infection from the population a strong coordination between the national level TB and the AIDS control programmes is required.

Chapter 7

The Role of Screening and Treatment in the Transmission Dynamics of HIV/AIDS and Tuberculosis Co-infection: A Mathematical Study [1]

7.1 Introduction

The main objectives of mathematical modeling of infectious diseases are to identify and study the factors which influence the spread of the disease and to predict the future dynamics of a particular disease or combination of diseases under consideration. The health of the patient who has dual infection deteriorates much faster than with a single infection. As discussed in chapter 6, TB and HIV are well known mortality and morbidity resulting diseases worldwide. As HIV infection causes decrease in the immunity level of individuals, so the people infected with HIV are more likely to get opportunistic infections. Tuberculosis is most common opportunistic infection for people living with HIV.

Various practices and initiatives have been conducted by various health organizations such as World Health Organization (WHO), the Joint United Nations Programme on

[1]This work has been published in *Journal of Biological Physics* 40(2) (2014) 139–166 **(SCI)**

HIV/AIDS (UNAIDS), the U.S. National Institutes of Health (NIH) etc. by appointing key investigators, public health experts, HIV-TB programme managers and civil society delegates to disseminate awareness regarding the available control measures. But the magnitude and seriousness of these infectious diseases remained high due to lack of coverage and access to prevention services to the individuals who can get benefit from the available control strategies [95].

Since, currently no cure exists for the HIV disease, only the prevention is effective in controlling its spread amongst the population. We believe that the detection of HIV infection and subsequent counseling can be treated as a control measure. In India, the HIV counseling and testing services started in 1997. Numbers of 'Integrated Counseling and Testing Center (ICTCs)'/'Prevention of Parent to Child Transmission (PPTCTs)', 'Surveillance Centres under NACO (National AIDS Control Organization)' are actively working in screening and providing counseling to HIV infectives. The Government of India has opened many 'Anti-retroviral Therapy (ART) Centres', to provide anti-retroviral therapy to the HIV/AIDS infected patients in the country. In addition to this several NGO's such as 'The Naz Foundation', 'Desire Society', and 'SAATHII', etc. are working towards bringing better awareness and knowledge regarding HIV, AIDS and TB in the population.

In recent years, the mathematical modeling of HIV, TB and HIV-TB co-infections have been reported by several researchers, (for details refer [36; 120; 121; 128; 144; 146; 175]). However, most of these models do not incorporate the effects of screening of infectives in the transmission dynamics of these diseases. In some of the studies [128; 166], authors have incorporated the effect of screening of HIV infectives, but did not incorporate and analyze the importance of treatment . Most of the researchers, who have incorporated the screening of infectives, have designed separate classes for aware and unaware infectives. Hence, the extension of these models for HIV-TB co-infection is very difficult as the number of variables in the mathematical model will increase and it will make analysis of

the model very complicated.

In this chapter, we consider a simple mathematical model using standard incidence for the dynamics of HIV-TB co-infection by incorporating both screening and treatment of infectives. We have kept our approach of model formulation simplified in such a manner that the incorporation of both the treatment and screening does not complicate the analysis of the model. It is assumed that the screening is associated with proper counseling. And, further it is assumed that the screened HIV infectives are not taking part in the transmission of HIV. However, some screened HIV infectives can contribute to the transmission of HIV virus, but in this work we have ignored those individuals as if they were not screened. We have considered only the adult sexually active population in the model formulation as majority of the HIV transmissions are due to heterosexual intercourse.

The chapter is organized as follows: Section (7.2) presents the mathematical model for HIV-TB co-infection, Section (7.3) is devoted to the analysis of the sub-models (HIV-only model and TB-only model) of the full model, Section (7.4) deals with the analysis (for the stability of the associated disease-free equilibrium) of the full model, Section (7.5) presents the numerical simulations to illustrate analytical findings and to see the effect of various parameters on the transmission dynamics of HIV, and Section (7.6) concludes the chapter with a brief discussion.

7.2 Mathematical model

We formulated a deterministic HIV/AIDS-TB co-infection model to investigate the effect of screening (with proper counseling) and treatment of infectives. The total sexually active human population $N(t)$ is divided into six sub-populations i.e. susceptible individuals (S), active TB individuals who are capable of transmitting the disease (I_1), HIV-infected individuals (I_2), individuals dually infected with HIV and TB (I_3), AIDS patients (I_4) and

AIDS individuals dually infected with TB (I_5). Hence the total sexually active human population N is given by

$$N = S + I_1 + I_2 + I_3 + I_4 + I_5.$$

It is assumed that the susceptibles is recruited into the population at a constant rate Λ. Susceptible individuals acquire HIV infection due to effective contact with HIV-infected individuals at a rate λ_H and acquire TB infection following effective contact with TB-infected individuals at a rate λ_T. The force of infection associated with TB infection, denoted by λ_T is given by

$$\lambda_T = \frac{\beta_T(I_1 + I_3 + I_5)}{N}, \tag{7.1}$$

In (7.1), β_T is the effective contact rate for TB infection. HIV-infected individuals and AIDS patients may acquire TB at rate β_T.

Similarly, the susceptible individuals will acquire HIV following effective contact with HIV infectives, HIV-TB dual infectives, AIDS patients and AIDS-TB dual infectives. The force of infection associated with HIV infection is denoted by λ_H and is given by

$$\lambda_H = \frac{\beta_H\{(1-\alpha_1)I_2 + (1-\alpha_2)\eta_1 I_3 + (1-\alpha_3)I_4 + (1-\alpha_4)\eta_2 I_5\}}{N}, \tag{7.2}$$

Where β_H is the effective contact rate for HIV infection. The parameters $\eta_1, \eta_2 \geq 1$ are the modification parameters that correspond to the assumption that the dually infected individuals transmit HIV infection with a higher rate as compared to HIV-only infectives. Similarly, $\phi_1, \phi_2 \geq 1$ are modification parameters that correspond to the fact that HIV or AIDS infected individuals are more prone to acquire TB infection than the susceptibles. It is assumed that TB patients may recover after treatment at a rate γ and will enter susceptible class. μ is the natural death rate, which is same for all the individuals in different subgroups. Further μ_i for $i = 1, 2, 3, 4, 5$ account for the disease related death rate in respective class. η is considered as the fraction of individuals who are screened for TB and it is assumed that the individuals who are screened of TB are keeping themselves away

from HIV infection. Here, α_i for $i = 1, 2, 3, 4$ are the fraction of screening for HIV, HIV-TB dually infected individuals, AIDS and AIDS-TB dually infected individuals respectively. The parameters δ_1 and δ_2 are the disease progression rates to AIDS by HIV treated and untreated individuals respectively. Similarly δ_3 and δ_4 are the disease progression rates to AIDS-TB dual infection by HIV-TB dually infected treated and untreated individuals respectively. The fraction of infectives who are under treatment for HIV is denoted by ν, under the assumption that the disease progression rate will be slow in the individuals who are taking treatment. Combining the different rates mentioned above τ_1 is considered as the progression rate to AIDS by HIV-infected individuals and τ_2 is the progression rate to AIDS-TB dually infected class by HIV-TB dually infected individuals. Here τ_1 and τ_2 are given by

$$\tau_1 = \alpha_1\{\delta_1\nu + \delta_2(1-\nu)\} + \delta_2(1-\alpha_1),$$

$$\tau_2 = \alpha_2\{\delta_3\nu + \delta_4(1-\nu)\} + \delta_4(1-\alpha_2).$$

Combining all the above mentioned assumptions and definitions, the mathematical model can be formulated as follows:

$$\begin{aligned}
\frac{dS}{dt} &= \Lambda - \lambda_T S - \lambda_H S - \mu S + \gamma\eta I_1 \\
\frac{dI_1}{dt} &= \lambda_T S - \lambda_H(1-\eta)I_1 - \mu I_1 - \mu_1 I_1 - \gamma\eta I_1 \\
\frac{dI_2}{dt} &= \lambda_H S - \phi_1\lambda_T I_2 + \alpha_2\gamma I_3 - (\mu + \mu_2 + \tau_1)I_2 \\
\frac{dI_3}{dt} &= \lambda_H(1-\eta)I_1 + \phi_1\lambda_T I_2 - \alpha_2\gamma I_3 - (\mu + \mu_3 + \tau_2)I_3 \\
\frac{dI_4}{dt} &= \tau_1 I_2 - \phi_2\lambda_T I_4 - (\mu + \mu_4)I_4 + \gamma\alpha_4 I_5 \\
\frac{dI_5}{dt} &= \phi_2\lambda_T I_4 + \tau_2 I_3 - (\mu + \mu_5)I_5 - \gamma\alpha_4 I_5
\end{aligned} \tag{7.3}$$

Here

$S > 0$, $I_1 \geq 0$, $I_2 \geq 0$, $I_3 \geq 0, I_4 \geq 0$, $I_5 \geq 0$ and $N(t) = S(t) + I_1(t) + I_2(t) + I_3(t) + I_4(t) + I_5(t)$.

The model system (7.3) governs human population, hence the variables and parameters

used in model formulation are non-negative.

7.2.1 Basic model properties

We consider a biologically-feasible region

$$\mathcal{D} = \left\{ (S, I_1, I_2, I_3, I_4, I_5) \in R_+^6 : N \leq \frac{\Lambda}{\mu} \right\}.$$

The following steps have been carried to show the positive invariance of $\mathcal{D}$ i.e. all the solutions of (7.3) which initiate in $\mathcal{D}$ remain in the region $\mathcal{D}$.

We have $N(t) = S(t) + I_1(t) + I_2(t) + I_3(t) + I_4(t) + I_5(t)$. The rate of change of total population by adding all the equations considered in (7.3) is

$$\frac{dN}{dt} = \Lambda - \mu N - \mu_1 I_1 - \mu_2 I_2 - \mu_3 I_3 - \mu_4 I_4 - \mu_5 I_5$$

Clearly, whenever $N > \frac{\Lambda}{\mu}$, then $\frac{dN}{dt} < 0$. Notice that $\frac{dN}{dt}$ is bounded by $\Lambda - \mu N$. By using standard comparison theorem [105], it can be shown that, $0 \leq N(t) \leq \frac{\Lambda}{\mu}(1 - e^{-\mu t}) + N(0)e^{-\mu t}$.

In particular, $N(t) \leq \frac{\Lambda}{\mu}$ if $N(0) \leq \frac{\Lambda}{\mu}$.

Hence, the region $\mathcal{D} = \left\{ (S, I_1, I_2, I_3, I_4, I_5) \in R_+^6 : N \leq \frac{\Lambda}{\mu} \right\}$ is positively invariant for the system (7.3).

Further it is also necessary to prove that all the variables of the model (7.3) are non-negative so that the solutions of the system with positive initial conditions remain positive for all $t > 0$. We prove following lemma to describe this result:

Lemma 7.2.1: *If $S(0) \geq 0, I_i(0) \geq 0$ for $i = 1, 2 \ldots 5$, the solutions $S(t), I_1(t), I_2(t), I_3(t), I_4(t), I_5(t)$ of the system (7.3) are positive for all $t > 0$.*

Proof. We shall prove this lemma using contradiction by assuming that the total population $N(t) \neq 0$ for all $t \geq 0$.

We assume that, there exists a first time t_1 such that

$$S(t_1) = 0, S'(t_1) < 0, I_1(t) \geq 0, I_2(t) \geq 0, I_3(t) \geq 0, I_4(t) \geq 0, I_5(t) \geq 0,\ 0 \leq t \leq t_1, \quad (7.4)$$

there exists a first time t_2 such that

$$I_1(t_2) = 0, I_1'(t_2) < 0, S(t) \geq 0, I_2(t) \geq 0, I_3(t) \geq 0, I_4(t) \geq 0, I_5(t) \geq 0,\ 0 \leq t \leq t_2, \quad (7.5)$$

there exists a first time t_3 such that

$$I_2(t_3) = 0, I_2'(t_3) < 0, S(t) \geq 0, I_1(t) \geq 0, I_3(t) \geq 0, I_4(t) \geq 0, I_5(t) \geq 0,\ 0 \leq t \leq t_3, \quad (7.6)$$

there exists a first time t_4 such that

$$I_3(t_4) = 0, I_3'(t_4) < 0, S(t) \geq 0, I_1(t) \geq 0, I_2(t) \geq 0, I_4(t) \geq 0, I_5(t) \geq 0,\ 0 \leq t \leq t_4, \quad (7.7)$$

there exists a first time t_5 such that

$$I_4(t_5) = 0, I_4'(t_5) < 0, S(t) \geq 0, I_1(t) \geq 0, I_2(t) \geq 0, I_3(t) \geq 0, I_5(t) \geq 0,\ 0 \leq t \leq t_5, \quad (7.8)$$

there exists a first time t_6 such that

$$I_5(t_6) = 0, I_5'(t_6) < 0, S(t) \geq 0, I_1(t) \geq 0, I_2(t) \geq 0, I_3(t) \geq 0, I_4(t) \geq 0,\ 0 \leq t \leq t_6. \quad (7.9)$$

From (7.4) $S'(t_1) = \Lambda + \gamma\eta I_1(t_1) > 0$, which is a contradiction meaning that $S(t) \geq 0, t \geq 0$. From (7.5), we get

$$I_1'(t_2) = \lambda_T|_{t=t_2} S(t_2) = \frac{\beta_T[I_1(t_2) + I_3(t_2) + I_5(t_2)]}{N(t_2)} S(t_2) \geq 0,$$

which again is a contradiction meaning that $I_1(t) \geq 0, t \geq 0$.

Again from (7.6), we get

$$\begin{aligned} I_2'(t_3) &= \lambda_H|_{t=t_3}\ S(t_3) + \alpha_2\gamma I_3(t_3) \\ &= \frac{(1-\alpha_2)\eta_1 I_3(t_3) + (1-\alpha_3) I_4(t_3) + (1-\alpha_4)\eta_2 I_5(t_3)}{N(t_3)} S(t_3) + \alpha_2\gamma I_3(t_3) \geq 0, \end{aligned}$$

which is a contradiction implying $I_2(t) \geq 0, t \geq 0$.

Similarly, using the assumptions in equations (7.7)-(7.9), we get following contradictions respectively,

$$\begin{aligned} I_3'(t_4) &= \lambda_H|_{t=t_4}\ (1-\eta)I_1(t_4) + \phi_1\lambda_T|_{t=t_4}\ I_2(t_4) \\ &= \frac{\beta_H\{(1-\alpha_1)I_2(t_4) + (1-\alpha_3)I_4(t) + (1-\alpha_4)\eta_2 I_5(t_4)\}}{N(t_4)}(1-\eta)I_1(t_4) \\ &\quad +\phi_1\frac{\beta_t I_1(t_4) + I_5(t_4)}{N(t_4)}I_2(t_4)\ \geq 0, \\ I_4'(t_5) &= \tau_1 I_2(t_5) + \gamma\alpha_4 I_5(t_5)\ \geq 0, \\ I_5'(t_6) &= \phi_2\lambda_T|_{t=t_6}I_4(t_6) + \tau_2 I_3(t_6) \\ &= \phi_2\beta_T\frac{I_1(t_6) + I_3(t_6)}{N(t_6)}I_4(t_6) + \tau_2 I_3(t_6)\ \geq 0, \end{aligned}$$

Hence, we conclude $I_3(t) \geq 0, I_4(t) \geq 0, I_5(t) \geq 0$, for $t \geq 0$. Thus, the solutions $S(t), I_i(t), i = 1, 2 \ldots 5$ of the system (7.3) remains positive for all $t > 0$. ∎

The schematic flow diagram in Figure 7.1, describes the flow of individuals from one to another compartment with the possibility of acquiring TB, HIV or HIV-TB co-infection. In the following section, first we will discuss the dynamics of models for TB only and HIV

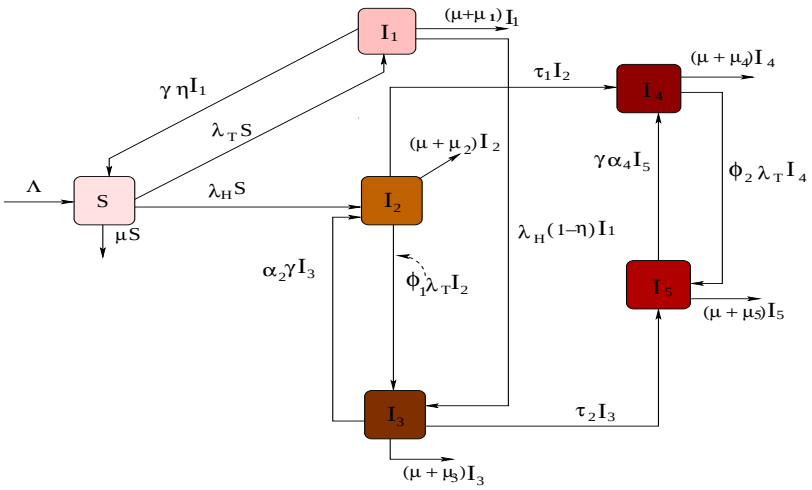

Figure 7.1: The schematic flow diagram of HIV-TB model system (7.3)

only diseases and there after we will investigate the HIV-TB co-infection full model (7.3).

7.3 Analysis of the sub-models

The analysis of the full model (7.3) will be followed by analyzing the dynamics of the sub-models with TB-only and HIV-only.

7.3.1 TB-only model

The TB-only model is obtained by setting $I_2 = I_3 = I_4 = 0 = I_5$ and is given by

$$\begin{aligned} \frac{dS}{dt} &= \Lambda - \lambda_T S - \mu S + \gamma\eta I_1, \\ \frac{dI_1}{dt} &= \lambda_T S - \mu I_1 - \mu_1 I_1 - \gamma\eta I_1. \end{aligned} \tag{7.10}$$

where

$\lambda_T = \dfrac{\beta_T I_1}{N}$ and $N = S + I_1$.

The basic reproduction number for above model is calculated as

$$R_T = \frac{\beta_T}{\mu + \mu_1 + \gamma\eta}. \tag{7.11}$$

The region of attraction for this sub-model is given by

$$\mathcal{D}_1 = \left\{ (S, I_1) \in R_+^2 : S + I_1 = N \leq \frac{\Lambda}{\mu} \right\}.$$

7.3.2 Stability of disease-free equilibrium

The model (7.10) has a disease-free equilibrium, obtained by setting the right-hand side of the equations in the model to zero and is given by

$$\mathcal{E}_{T0} = (S^0, I_1^0) = \left(\frac{\Lambda}{\mu}, 0 \right) \tag{7.12}$$

Theorem 7.3.1: *The disease-free equilibrium $\mathcal{E}_{T0}$ of the system (7.10) is locally asymptotically stable when $R_T < 1$.*

Proof. To study the stability of disease-free equilibrium, we have calculated the Jacobian matrix at $\mathcal{E}_{T0}$ given as

$$M = \begin{pmatrix} -\mu & -\beta_T + \gamma\eta \\ 0 & \beta_T - (\mu + \mu_1 + \gamma\eta) \end{pmatrix}$$

it gives two eigenvalues $-\mu$ and $-(1 - R_T)(\mu + \mu_1 + \gamma\eta)$ which are negative for $R_T < 1$ that ensures that the disease-free equilibrium $\mathcal{E}_{T0}$ is locally asymptotically stable. ∎

Theorem 7.3.2: *If $R_T < 1$, then the disease-free steady state $\mathcal{E}_{T0}$ of (7.10) is globally asymptotically stable in the region $\mathcal{D}_1$.*

Proof. Define the Lyapunov-LaSalle function $U : \{(S, I_1) \in \mathcal{D}_1 : S > 0\} \to \mathbb{R}$ by

$$U(S, I_1) = \frac{1}{2} I_1^2.$$

The time derivative of U computed along solutions of (7.10) is

$$\begin{aligned} U'(S, I_1) &= \left(\frac{\beta_T I_1 S}{S + I_1} - (\mu + \mu_1 + \gamma\eta) I_1 \right) I_1 \\ &= \frac{I_1^2}{(S + I_1)} \{\beta_T S - (\mu + \mu_1 + \gamma\eta)(S + I_1)\} \\ &= (\mu + \mu_1 + \gamma\eta) \frac{I_1^2}{(S + I_1)} \left\{ \left(\frac{\beta_T}{\mu + \mu_1 + \gamma\eta} - 1 \right) S - I_1 \right\} \\ &= -(\mu + \mu_1 + \gamma\eta) \frac{I_1^2}{(S + I_1)} \{(1 - R_T) S + I_1\} \end{aligned}$$

Since, all the model parameters are positive and variables are non-negative, it follows that $U'(S, I_1) \leq 0$ for $R_T \leq 1$ with $U'(S, I_1) = 0$ if and only if $I_1 = 0$. Hence the largest invariant set contained in $\{(S, I_1) \in \mathcal{D}_1, U' = 0\}$ is the singleton $\{\mathcal{E}_{T0}\}$.

Thus the global asymptotic stability of $\mathcal{E}_{T0}$ for $R_T < 1$ follows from the LaSalle's invariance Principle [35]. ∎

7.3.3 Existence and stability of endemic equilibrium point

The unique endemic equilibrium point of the system (7.10) is given by

$$\mathcal{E}_1 = (S^*, I_1^*) = \left(\frac{\Lambda}{(\mu+\mu_1)(R_T-1)+\mu}, \frac{\Lambda(R_T-1)}{(\mu+\mu_1)(R_T-1)+\mu} \right), \tag{7.13}$$

which exists whenever $R_T > 1$. The local stability of this equilibrium point is summarized in the following theorem:

Theorem 7.3.3: *The TB-only endemic equilibrium $\mathcal{E}_1$ of the system (7.10) is locally asymptotically stable if $R_T > 1$.*

Proof. The Jacobian matrix of the system (7.10) evaluated at the equilibrium point ($\mathcal{E}_1$) is given by

$$J(\mathcal{E}_1) = \begin{pmatrix} -\mu - \dfrac{\beta_T (I_1^*)^2}{(S^*+I_1^*)^2} & -\dfrac{\beta_T (S^*)^2}{(S^*+I_1^*)^2} + \gamma\eta \\ \dfrac{\beta_T (I_1^*)^2}{(S^*+I_1^*)^2} & \dfrac{\beta_T (S^*)^2}{(S^*+I_1^*)^2} - (\mu+\mu_1+\gamma\eta) \end{pmatrix}$$

Using steady state of the model system (7.10), we take into account the following identity

$$\gamma\eta + \mu_1 + \mu = \frac{\beta_T S^*}{S^* + I_1^*}$$

and the above Jacobian matrix can be rewritten as

$$J(\mathcal{E}_1) = \begin{pmatrix} -\mu - \dfrac{\beta_T (I_1^*)^2}{(S^*+I_1^*)^2} & \dfrac{\beta_T S^* I_1^*}{(S^*+I_1^*)^2} - (\mu+\mu_1) \\ \dfrac{\beta_T (I_1^*)^2}{(S^*+I_1^*)^2} & -\dfrac{\beta_T S^* I_1^*}{(S^*+I_1^*)^2} \end{pmatrix}$$

The trace of $J(\mathcal{E}_1)$ is

$$tr(J(\mathcal{E}_1)) = -\left\{ \mu + \frac{\beta_T I_1^*}{(S^*+I_1^*)} \right\} < 0.$$

Further,

$$det(J(\mathcal{E}_1)) = \frac{\mu\beta_T S^* I_1^*}{(S^*+I_1^*)^2} + \frac{(\mu+\mu_1)\beta_T I_1^{*2}}{(S^*+I_1^*)^2} > 0.$$

Hence, the eigenvalues of the Jacobian matrix $J(\mathcal{E}_1)$ have negative real parts. Thus the endemic equilibrium is locally asymptotically stable whenever it exists. ∎

The global stability of TB-only endemic equilibrium $\mathcal{E}_1$ is proved by using the method of Lyapunov and is stated in the following theorem.

Theorem 7.3.4: *If $R_T > 1$, then the unique TB-only endemic equilibrium $\mathcal{E}_1$ of (7.10) is globally asymptotically stable.*

Proof. Define $L : \{(S, I_1) \in \mathcal{D}_1 : S, I_1 > 0\} \to \mathbb{R}$ by

$$\begin{aligned} L(S, I_1) &= \left[(S - S^*) + (I_1 - I_1^*) - (S^* + I_1^*) \ln\left(\frac{S + I_1}{S^* + I_1*}\right)\right] \\ &\quad + \frac{(2\mu + \mu_1)(S^* + I_1^*)}{\beta_T}\left(\ln\frac{I_1}{I_1^*} + \frac{I_1^*}{I_1} - 1\right). \end{aligned}$$

Here, L is C^1 on the interior of $\mathcal{D}_1$, $\mathcal{E}_1$ is the global minimum of L on $\mathcal{D}_1$, and $L(S^*, I_1^*) = 0$. Computing the time derivative of above function along the solutions of (7.10) , we get

$$\begin{aligned} L'(S, I_1) &= \frac{[(S - S^*) + (I_1 - I_1^*)]}{S + I_1}\frac{d(S + I_1)}{dt} + \frac{(2\mu + \mu_1)(S^* + I_1^*)}{\beta_T}\frac{(I_1 - I_1^*)}{I^2}\frac{dI_1}{dt}, \\ &= \frac{[(S - S^*) + (I_1 - I_1^*)]}{S + I_1}(\Lambda - \mu(S + I_1) - \mu_1 I_1) \\ &\quad + \frac{(2\mu + \mu_1)(S^* + I_1^*)}{\beta_T}\frac{(I - I^*)}{I_1^2}\left(\frac{\beta_T S I_1}{S + I_1} - (\mu + \mu_1 + \gamma\eta)I_1\right), \\ &= \frac{[(S - S^*) + (I_1 - I_1^*)]}{S + I_1}\{-\mu(S - S^*) - (\mu + \mu_1)(I_1 - I_1^*)\} \\ &\quad + (2\mu + \mu_1)(S^* + I_1^*)\frac{(I_1 - I_1^*)}{I_1}\left(\frac{S}{S + I_1} - \frac{S^*}{S^* + I_1^*}\right), \end{aligned}$$

Using

$$\frac{S}{S + I_1} - \frac{S^*}{S^* + I_1^*} = \frac{I_1(S - S^*) - S(I_1 - I_1^*)}{(S + I_1)(S^* + I_1^*)}$$

$$L'(S, I_1) = -\mu\frac{(S - S^*)^2}{S + I_1} - \left\{(\mu + \mu_1) + (2\mu + \mu_1)\frac{S}{I_1}\right\}\frac{(I_1 - I_1^*)^2}{(S + I_1)}.$$

Clearly, $L'(S, I_1) < 0$ always holds except at the TB-only endemic equilibrium, $\mathcal{E}_1$. Also, $L(S, I_1) \to \infty$ as $S \to \infty$ and $L(S, I_1) \to \infty$ as $I_1 \to 0$ or $I_1 \to \infty$. Therefore, we may conclude that function $L(S, I_1)$ is a Lyapunov function for system (7.10), and that, by

the Lyapunov asymptotic stability theorem [110], the endemic steady state is globally asymptotically stable in the interior of $\mathcal{D}_1$, when it exists. ∎

Now, the dynamics of HIV-only model is explored as below.

7.3.4 HIV-only model

The HIV-only model is obtained by setting $I_1 = I_3 = 0 = I_5$ in model system (7.3) and is given by

$$\begin{aligned} \frac{dS}{dt} &= \Lambda - \lambda_H S - \mu S, \\ \frac{dI_2}{dt} &= \lambda_H S - (\mu + \mu_2 + \tau_1) I_2, \\ \frac{dI_4}{dt} &= \tau_1 I_2 - (\mu + \mu_4) I_4. \end{aligned} \tag{7.14}$$

where
$\lambda_H = \dfrac{\beta_H\{(1-\alpha_1)I_2 + (1-\alpha_3)I_4\}}{N}$ and $N = S + I_2 + I_4$.

7.3.5 Local stability of disease-free equilibrium

The HIV-only model (7.14) has a disease-free equilibrium given by

$$\mathcal{E}_{H0} = (S^0, I_2^0, I_4^0) = \left(\frac{\Lambda}{\mu}, 0, 0\right) \tag{7.15}$$

The linear stability of $\mathcal{E}_{H0}$ is carried out by the basic reproduction number R_H. The stability of the equilibrium is further investigated using the next generation matrix operator [168]. The F and V matrices corresponding to new infection terms and remaining transfer terms are respectively given as follows:

$$F = \begin{pmatrix} \beta_H(1-\alpha_1) & \beta_H(1-\alpha_3) \\ 0 & 0 \end{pmatrix}, \quad V = \begin{pmatrix} (\mu + \mu_2 + \tau_1) & 0 \\ -\tau_1 & (\mu + \mu_4) \end{pmatrix}$$

Thus

$$R_H = \rho(FV^{-1}) = \frac{\beta_H \{(1-\alpha_1)(\mu+\mu_4)+\tau_1(1-\alpha_3)\}}{(\mu+\mu_2+\tau_1)(\mu+\mu_4)}. \tag{7.16}$$

(Note that $S^* = N^*$ at the disease-free equilibrium $\mathcal{E}_{H0}$.) Now, using Theorem 2 of [168], the following result is established:

Theorem 7.3.5: *The disease-free equilibrium of the model (7.14) given by $\mathcal{E}_{H0}$, is locally asymptotically stable if $R_H < 1$, and unstable if $R_H > 1$.*

Proof. The local stability analysis can also be viewed by evaluating the Jacobian matrix $J(\mathcal{E}_{H0})$ at the disease-free equilibrium point $\mathcal{E}_{H0}$ given as

$$J(\mathcal{E}_{H0}) = \begin{pmatrix} -\mu & -\beta_H(1-\alpha_1) & -\beta_H(1-\alpha_3) \\ 0 & \beta_H(1-\alpha_1)-(\mu+\mu_2+\tau_1) & \beta_H(1-\alpha_3) \\ 0 & \tau_1 & -(\mu+\mu_4) \end{pmatrix}$$

One eigenvalue of the Jacobian matrix $J(\mathcal{E}_{H0})$ is evaluated as $-\mu$ and other two eigenvalues are the roots of the following quadratic equation:

$$\lambda^2 + \{(\mu+\mu_2+\tau_1)+(\mu+\mu_4)-(\beta_H(1-\alpha_1))\}\lambda + (\mu+\mu_2+\tau_1)(\mu+\mu_4)(1-R_H) = 0.$$

Clearly, for $R_H < 1$, the constant term as well as the coefficient of λ is positive implying the local stability of the disease-free equilibrium point $\mathcal{E}_{H0}$. Also, it is noted that one of the eigenvalue will be zero for $R_H = 1$. ∎

The non-trivial equilibrium $\mathcal{E}_2 = (S^*, I_2^*, I_4^*)$ of the system (7.14), is given by

$$\begin{aligned} S^* &= \frac{(\mu+\mu_2+\tau_1)N^*}{\beta_H\left\{(1-\alpha_1)+(1-\alpha_3)\frac{\tau_1}{\mu+\mu_4}\right\}}, \\ I_2^* &= \frac{(\mu+\mu_4)}{\mu+\mu_4+\tau_1}\left[1-\frac{(\mu+\mu_2+\tau_1)}{\beta_H\left\{(1-\alpha_1)+(1-\alpha_3)\frac{\tau_1}{\mu+\mu_4}\right\}}\right]N^*, \\ I_4^* &= \frac{\tau_1}{(\mu+\mu_4)}I_2^*, \\ N^* &= \frac{\Lambda\beta_H\left\{(1-\alpha_1)+(1-\alpha_3)\frac{\tau_1}{\mu+\mu_4}\right\}}{\left(\frac{(\mu+\mu_4)}{\mu+\mu_4+\tau_1}\left[\beta_H\left\{(1-\alpha_1)+(1-\alpha_3)\frac{\tau_1}{\mu+\mu_4}\right\}-(\mu+\mu_2+\tau_1)\right]+\mu\right)(\mu+\mu_2+\tau_1)}. \end{aligned} \tag{7.17}$$

It is clear that the nontrivial equilibrium point $\mathcal{E}_2$ exists only when $R_H > 1$ and this corresponds to existence of a unique positive equilibrium point associated with HIV-only model.

7.3.6 Stability and bifurcation analysis for endemic equilibrium point

In this section the local stability of endemic equilibrium is investigated. For this purpose we employ center manifold theory [50] as explained in Theorem 4.1 of [56]. Let us make following change in the variables $S = x_1, I_2 = x_2$ and $I_4 = x_3$, so that $N = x_1 + x_2 + x_3$. Using vector notation $X = (x_1, x_2, x_3, x_4, x_5)^T$, the model (7.14) is re-written in the form $\frac{dX}{dt} = F = (f_1, f_2, f_3, f_4, f_5)^T$, such that

$$\begin{aligned} \frac{dx_1}{dt} &= f_1 = \Lambda - \lambda_H x_1 - \mu x_1, \\ \frac{dx_2}{dt} &= f_2 = \lambda_H x_1 - (\mu+\mu_2+\tau_1)x_2, \\ \frac{dx_3}{dt} &= f_3 = \tau_1 x_2 - (\mu+\mu_4)x_3. \end{aligned} \tag{7.18}$$

where

$$\lambda_H = \frac{\beta_H\{(1-\alpha_1)x_2 + (1-\alpha_3)x_3\}}{(x_1+x_2+x_3)}$$

The Jacobian of the system (7.18), at disease-free equilibrium ($\mathcal{E}_{H0}$) is given by

$$J(\mathcal{E}_{H0}) = J^*_\beta = \begin{pmatrix} -\mu & -\beta_H(1-\alpha_1) & -\beta_H(1-\alpha_3) \\ 0 & \beta_H(1-\alpha_1) - (\mu+\mu_2+\tau_1) & \beta_H(1-\alpha_3) \\ 0 & \tau_1 & -(\mu+\mu_4) \end{pmatrix}$$

Let us choose β_H as bifurcation parameter. Considering the case $R_H = 1$ and solving the expression of R_H (as given in equation (7.16)) for β_H, gives

$$\beta_H = \beta^* = \frac{(\mu+\mu_2+\tau_1)(\mu+\mu_4)}{(1-\alpha_1)(\mu+\mu_4)+\tau_1(1-\alpha_3)}. \tag{7.19}$$

It is to be noticed that the above linearized system of transformed system (7.18) with $\beta_H = \beta^*$, has a zero eigenvalue which is simple. Therefore, the center manifold theory is used to analyze the dynamics of (7.18) near $\beta_H = \beta^*$.

Eigenvectors of $J(\mathcal{E}_{H0})|_{\beta_H=\beta^*}$

The Jacobian matrix of system (7.18) at $\beta_H = \beta^*$ (denoted by J_{β^*}) has a right eigenvector (associated with the zero eigenvalue) given by $w = [w_1, w_2, w_3]^T$, where

$w_1 = -\dfrac{(\beta^*[(1-\alpha_1)(\mu+\mu_4)+(1-\alpha_3)\tau_1])w_2}{\mu(\mu+\mu_4)}$, $w_2 = w_2 > 0$, and $w_3 = \dfrac{\tau_1}{\mu+\mu_4}w_2$.

Further, J_{β^*} has a left eigenvector $v = [v_1, v_2, v_3]$ (associated with the zero eigenvalue), where

$v_1 = 0, v_2 = v_2 > 0, v_3 = \dfrac{\beta^*(1-\alpha_3)}{(\mu+\mu_4)}v_2$.

Now further calculations are performed to determine the signs of a and b.

Computation of a and b:

For the system (7.14), the associated non-zero partial derivatives of f (at the disease-free equilibrium) are given by

$\dfrac{\partial^2 f_2}{\partial x_2 \partial x_3} = -\dfrac{\beta^*[(1-\alpha_1)+(1-\alpha_3)]\mu}{\Lambda}$, $\dfrac{\partial^2 f_2}{\partial x_2^2} = -\dfrac{2\beta^*(1-\alpha_1)\mu}{\Lambda}$, $\dfrac{\partial^2 f_2}{\partial x_3^2} = -\dfrac{2\beta^*(1-\alpha_3)\mu}{\Lambda}$,

$\dfrac{\partial^2 f_2}{\partial x_2 \partial \beta^*} = (1-\alpha_1)$, $\dfrac{\partial^2 f_2}{\partial x_3 \partial \beta^*} = (1-\alpha_3)$.

From the above expression, we obtain:

$$\begin{aligned} a &= v_2 \sum_{k,j,i=1}^{3} w_i w_j \frac{\partial^2 f_k}{\partial x_i \partial x_j}(0,0), \\ &= -2v_2 \left(\frac{w_2 w_3 \mu}{\Lambda}[\beta^*(1-\alpha_1) + \beta^*(1-\alpha_3)] + w_2^2 \frac{\beta^*(1-\alpha_1)\mu}{\Lambda} + w_3^2 \frac{\beta^*(1-\alpha_3)\mu}{\Lambda} \right) < 0 \end{aligned}$$

and

$$\begin{aligned} b &= v_2 \sum_{k,i=1}^{3} w_i \frac{\partial^2 f_k}{\partial x_i \partial \phi}(0,0), \\ &= v_2[(1-\alpha_1)w_2 + (1-\alpha_3)\frac{\tau_1}{(\mu+\mu_4)}w_2] > 0. \end{aligned}$$

Thus $a < 0$ and $b > 0$. From **(iv)** of the Theorem 4.1 of [56] (also refer Theorem 1.7.1 given in Chapter 1 of this thesis) it implies that the unique equilibrium point of the model system (7.18) which exists whenever $R_H > 1$ will be locally asymptotically stable when $R_H > 1$ and $\beta^* < \beta_H$ with β_H close to β^*. Hence we establish the following theorem.

Theorem 7.3.6: *The unique endemic equilibrium $\mathcal{E}_2$ is locally asymptotically stable for $R_H > 1$.*

7.4 Analysis of full model

The full HIV-TB co-infection model has four equilibria, namely, Disease-free equilibrium $\mathcal{E}_0$, TB-only equilibrium $\hat{\mathcal{E}}$, HIV-equilibrium $\mathcal{E}^*$ and endemic equilibrium point $\mathcal{E}^{**}$ (associated with the existence of co-epidemics).

(i) The TB-only equilibrium point $\hat{\mathcal{E}} = (\hat{S}, \hat{I}_1, 0, 0, 0, 0)$ is obtained by setting $I_2 = I_3 = I_4 = 0 = I_5$ and is given by

$$\begin{aligned} \hat{\mathcal{E}} &= (\hat{S}, \hat{I}_1, 0, 0, 0, 0) \\ &= \left(\frac{\Lambda}{(\mu+\mu_1)(R_T-1)+\mu}, \frac{\Lambda(R_T-1)}{(\mu+\mu_1)(R_T-1)+\mu}, 0, 0, 0, 0 \right). \end{aligned} \tag{7.20}$$

(ii) The HIV-only equilibrium point $\mathcal{E}^* = (S^*, 0, I_2^*, 0, I_4^*, 0)$, is obtained by setting $I_1 = I_3 = 0 = I_5$, where

$$\begin{aligned}
S^* &= \frac{(\mu+\mu_2+\tau_1)N^*}{\beta_H\left\{(1-\alpha_1)+(1-\alpha_3)\frac{\tau_1}{\mu+\mu_4}\right\}},\\
I_2^* &= \frac{(\mu+\mu_4)}{\mu+\mu_4+\tau_1}\left[1-\frac{(\mu+\mu_2+\tau)}{\beta_H\left\{(1-\alpha_1)+(1-\alpha_3)\frac{\tau_1}{\mu+\mu_4}\right\}}\right]N^*, \qquad (7.21)\\
I_4{}^* &= \frac{\tau_1}{(\mu+\mu_4)}I_2{}^*,\\
N^* &= \frac{\Lambda\beta_H\left\{(1-\alpha_1)+(1-\alpha_3)\frac{\tau_1}{\mu+\mu_4}\right\}}{\frac{(\mu+\mu_4)}{\mu+\mu_4+\tau_1}\left[\beta_H\left\{(1-\alpha_1)+(1-\alpha_3)\frac{\tau_1}{\mu+\mu_4}\right\}-(\mu+\mu_2+\tau_1)\right]+\mu(\mu+\mu_2+\tau_1)}.
\end{aligned}$$

The system (7.3) has co-existence equilibrium $\mathcal{E}^{**} = (S^{**}, I_1^{**}, I_2^{**}, I_3^{**}, I_4^{**}, I_5^{**})$, where

$$\begin{aligned}
S^{**} &= \frac{\{\lambda_H(1-\eta)+\mu+\mu_1+\gamma\eta\}\Lambda}{(\lambda_T+\lambda_H+\mu)\{\lambda_H(1-\eta)+\mu+\mu_1\}+(\lambda_H+\mu)\gamma\eta},\\
I_1^{**} &= \frac{\lambda_T\Lambda}{(\lambda_T+\lambda_H+\mu)\{\lambda_H(1-\eta)+\mu+\mu_1\}+(\lambda_H+\mu)\gamma\eta},\\
I_2^{**} &= \frac{\lambda_H(\alpha_2\gamma+\mu+\mu_3+\tau_2)S^{**}+\alpha_2\gamma\lambda_H(1-\eta)I_1^{**}}{(\phi_1\lambda_T+\mu+\mu_2+\tau_1)(\mu+\mu_3+\tau_2)+(\mu+\mu_2+\tau_1)\alpha_2\gamma}, \qquad (7.22)\\
I_3^{**} &= \frac{\lambda_H(1-\eta)I_1^{**}+\phi_1\lambda_T I_2^{**}}{\alpha_2\gamma+\mu+\mu_3+\tau_2},\\
I_4^{**} &= \frac{(\mu+\mu_5+\gamma\alpha_4)\tau_1 I_2^{**}+\gamma\alpha_4\tau_2 I_3^{**}}{(\mu+\mu_5+\gamma\alpha_4)(\mu+\mu_4)+(\mu+\mu_5)\phi_2\lambda_T},\\
I_5^{**} &= \frac{\tau_2 I_3^{**}+\phi_2\lambda_T I_4^{**}}{\mu+\mu_5+\gamma\alpha_4}.
\end{aligned}$$

From above expressions it is clear that all the variables $S^{**}, I_1^{**}, I_2^{**}, I_3^{**}, I_4^{**}, I_5^{**}$ can be written in terms of λ_T and λ_H. Now, using the expressions for λ_T and λ_H, following two equations give the system of two non-linear equations in λ_T and λ_H, which can be solved for λ_T and λ_H:

$$\lambda_T(S^{**}+I_1^{**}+I_2^{**}+I_3^{**}+I_4^{**}+I_5^{**}) = \beta_T(I_1^{**}+I_3^{**}+I_5^{**}),$$

$$\lambda_H\beta_T(I_1^{**}+I_3^{**}+I_5^{**}) = \lambda_T\beta_H\{(1-\alpha_1)I_2^{**}+(1-\alpha_2)\eta_1 I_3^{**}+(1-\alpha_3)I_4^{**}+(1-\alpha_4)\eta_2 I_5^{**}\}.$$

Once we know λ_T and λ_H, our co-infection equilibrium $\mathcal{E}^{**} = (S^{**}, I_1^{**}, I_2^{**}, I_3^{**}, I_4^{**}, I_5^{**})$, is completely known.

7.4.1 Local stability of disease-free equilibrium

The model (7.3) has a disease-free equilibrium given by $\mathcal{E}_0 = (S^0, 0, 0, 0, 0, 0) = \left(\frac{\Lambda}{\mu}, 0, 0, 0, 0, 0\right)$. By using next generation matrix method, the reproduction number R_{HT} has been calculated for which associated F and V matrices are given as

$$F = \begin{pmatrix} \beta_T & 0 & \beta_T & 0 & \beta_T \\ 0 & \beta_H(1-\alpha_1) & \beta_H(1-\alpha_2)\eta_1 & \beta_H(1-\alpha_3) & \beta_H(1-\alpha_4)\eta_2 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \end{pmatrix}$$

$$V = \begin{pmatrix} (\mu+\mu_1+\gamma\eta) & 0 & 0 & 0 & 0 \\ 0 & (\mu+\mu_2+\tau_1) & -\alpha_2\gamma & 0 & 0 \\ 0 & 0 & \alpha_2\gamma+(\mu+\mu_3+\tau_2) & 0 & 0 \\ 0 & -\tau_1 & 0 & (\mu+\mu_4) & -\gamma\alpha_4 \\ 0 & 0 & -\tau_2 & 0 & (\mu+\mu_5)+\gamma\alpha_4 \end{pmatrix}$$

Here, the associated reproduction number R_{HT} is given by

$$R_{HT} = \max\{R_T, R_H\}. \tag{7.23}$$

Again, using Theorem 2 in [168], the following result is established:

Theorem 7.4.1: *The disease-free equilibrium of the full HIV-TB model (7.3), given by $\mathcal{E}_0$, is locally asymptotically stable if $R_{HT} < 1$, and unstable if $R_{HT} > 1$.*

7.4.2 Local stability of TB-only and HIV-only equilibrium points

The Jacobian matrix corresponding to the system (7.3) at the TB-only equilibrium point is given by

$$M_1 = \begin{pmatrix} m_{11} & m_{12} & m_{13} & m_{14} & m_{15} & m_{16} \\ m_{21} & m_{22} & m_{23} & m_{24} & m_{25} & m_{26} \\ 0 & 0 & m_{33} & m_{34} & m_{35} & m_{36} \\ 0 & 0 & m_{43} & m_{44} & m_{45} & m_{46} \\ 0 & 0 & \tau_1 & 0 & m_{55} & m_{56} \\ 0 & 0 & 0 & \tau_2 & m_{65} & m_{66} \end{pmatrix}$$

where

$$m_{11} = -\left(\frac{\beta_T \hat{I}_1}{\hat{N}} + \mu\right) + \frac{\beta_T \hat{S}\hat{I}_1}{\hat{N}^2} = -\left(\frac{\beta_T \hat{I}_1^2}{\hat{N}^2} + \mu\right),$$

$$m_{12} = -\left(\frac{\beta_T \hat{S}^2}{\hat{N}^2}\right) + \gamma\eta,\ m_{13} = \frac{\beta_T \hat{I}_1 \hat{S}}{\hat{N}^2} - \frac{\beta_H(1-\alpha_1)\hat{S}}{\hat{N}},$$

$$m_{14} = -\left(\frac{\beta_T \hat{S}^2}{\hat{N}^2}\right) - \frac{\beta_H(1-\alpha_2)\eta_1 \hat{S}}{\hat{N}},\ m_{15} = \frac{\beta_T \hat{I}_1 \hat{S}}{\hat{N}^2} - \frac{\beta_H(1-\alpha_3)\hat{S}}{\hat{N}},$$

$$m_{16} = \frac{\beta_T \hat{I}_1 \hat{S}}{\hat{N}^2} - \frac{\beta_H(1-\alpha_4)\eta_2 \hat{S}}{\hat{N}},$$

$$m_{21} = \frac{\beta_T \hat{I}_1^2}{\hat{N}^2}, m_{22} = -\frac{\beta_T \hat{I}_1 \hat{S}}{\hat{N}^2},$$

$$m_{23} = -\frac{\beta_T \hat{S}\hat{I}_1}{\hat{N}^2} - \frac{(1-\eta)\beta_H(1-\alpha_1)\hat{I}_1}{\hat{N}}, m_{24} = \frac{\beta_T \hat{S}^2}{\hat{N}^2},$$

$$m_{25} = -\frac{\beta_T \hat{S}\hat{I}_1}{\hat{N}^2} - \frac{(1-\eta)(1-\alpha_3)\beta_H \hat{I}_1}{\hat{N}}, m_{26} = \frac{\beta_T \hat{S}^2}{\hat{N}^2} - \frac{\beta_H(1-\eta)(1-\alpha_4)\eta_2 \hat{I}_1}{\hat{N}},$$

$$m_{33} = \frac{\hat{S}\beta_H(1-\alpha_1)}{\hat{N}} - \frac{\phi_1 \beta_T \hat{I}_1}{\hat{N}} - (\mu + \mu_2 + \tau_1), m_{34} = \frac{\hat{S}\beta_H(1-\alpha_2)\eta_1}{\hat{N}} + \alpha_2\gamma,$$

$$m_{35} = \frac{\hat{S}\beta_H(1-\alpha_3)}{\hat{N}},\ m_{36} = \frac{\hat{S}\beta_H(1-\alpha_4)\eta_2}{\hat{N}},$$

$$m_{43} = \frac{(1-\eta)\beta_H(1-\alpha_1)\hat{I}_1}{\hat{N}} + \frac{\phi_1 \beta_T \hat{I}_1}{\hat{N}},\ m_{44} = \frac{(1-\eta)\beta_H(1-\alpha_2)\eta_1 \hat{I}_1}{\hat{N}} - (\mu + \mu_3 + \tau_2 + \alpha_2\gamma),$$

$$m_{45} = \frac{(1-\eta)\beta_H(1-\alpha_3)\hat{I}_1}{\hat{N}},\ m_{46} = \frac{(1-\eta)(1-\alpha_4)\eta_2 \hat{I}_1}{\hat{N}},$$

$$m_{55} = -\frac{\phi_2 \beta_T \hat{I}_1}{\hat{N}} - (\mu + \mu_4),\ m_{56} = \gamma\alpha_4,$$

$$m_{65} = \frac{\phi_2 \beta_T \hat{I}_1}{\hat{N}}, m_{66} = -(\mu + \mu_5 + \gamma\alpha_4).$$

It is easy to observe that the eigenvalues of this Jacobian matrix are the roots of the following polynomials:

$$\psi^2 - (m_{11} + m_{22})\psi + (m_{11}m_{22} - m_{12}m_{21}) = 0, \tag{7.24}$$

and

$$\psi^4 + a_3\psi^3 + a_2\psi^2 + a_1\psi + a_0 = 0. \tag{7.25}$$

where

$$\begin{aligned}
a_3 &= -(m_{33} + m_{44} + m_{55} + m_{66}) \\
a_2 &= m_{33}(m_{44} + m_{55} + m_{66}) + m_{55}m_{66} - m_{65}m_{56} + m_{44}(m_{55} + m_{66}) - \tau_2 m_{46} - m_{43}m_{13} \\
&\quad -\tau_1 m_{35} \\
a_1 &= -m_{33}\{m_{55}m_{66} - m_{65}m_{56} + m_{44}(m_{55} + m_{66}) - \tau_2 m_{46}\} \\
&\quad -m_{44}(m_{55}m_{66} - m_{65}m_{56}) - \tau_2(m_{46}m_{56} - m_{46}m_{55}) \\
&\quad +m_{43}m_{13}(m_{55} + m_{66}) - \tau_2 m_{36} - \tau_1 m_{34}m_{45} + m_{35}(m_{44} + m_{66})\tau_1 - \tau_1 m_{36}m_{65}, \\
a_0 &= m_{33}\{m_{44}(m_{55}m_{66} - m_{65}m_{56}) + \tau_2(m_{45}m_{56} - m_{46}m_{55})\} \\
&\quad -m_{43}m_{13}(m_{55}m_{66} - m_{56}m_{65}) - m_{43}\tau_2(m_{35}m_{56} - m_{36}m_{55}) \\
&\quad +\tau_1 m_{34}(m_{45}m_{66} - m_{46}m_{65}) + \tau_1\tau_2 m_{35}m_{46} \\
&\quad -\tau_1 m_{35}m_{44}m_{66} + \tau_1 m_{36}(m_{44}m_{65} - \tau_2 m_{45}).
\end{aligned}$$

It is clearly observed that the co-efficient of ψ and the constant term in the first quadratic equation is positive, which implies roots of this quadratic are either negative or have negative real parts. Now using Routh-Hurwitz criteria, the biquadratic equation will have roots with negative real part provided $a_3 > 0$ and $a_1a_2a_3 - a_1^2 - a_0a_3^2 > 0$. Hence, the equilibrium point $\hat{\mathcal{E}}$ is locally asymptotically stable provided $a_3 > 0$ and $a_1a_2a_3 - a_1^2 - a_0a_3^2 > 0$. The Jacobian matrix corresponding to the system (7.3) at the HIV-only

equilibrium point $\mathcal{E}^*$is given by

$$M_2 = \begin{pmatrix} n_{11} & n_{12} & n_{13} & n_{14} & n_{15} & n_{16} \\ 0 & n_{22} & 0 & n_{24} & 0 & m_{26} \\ n_{31} & n_{32} & n_{33} & n_{34} & n_{35} & n_{36} \\ 0 & n_{42} & 0 & n_{44} & 0 & n_{46} \\ 0 & n_{52} & n_{53} & n_{54} & n_{55} & n_{56} \\ 0 & n_{62} & 0 & n_{64} & 0 & n_{66} \end{pmatrix}$$

where

$$\begin{aligned}
n_{11} &= -[\beta_H\{(1-\alpha_1)I_2^* + (1-\alpha_3)I_4^*\} + \mu] + \frac{\beta_H\{(1-\alpha_1)I_2^* + (1-\alpha_3)I_4^*\}}{N^{*2}} \\
n_{12} &= \frac{S^*\beta_T}{N^*} + \frac{\beta_H\{(1-\alpha_1)I_2^* + (1-\alpha_3)I_4^*\}}{N^{*2}} + \gamma\eta \\
n_{13} &= \frac{-\beta_H(1-\alpha_1)S^*}{N^*} + \frac{\beta_H\{(1-\alpha_1)I_2^* + (1-\alpha_3)I_4^*\}S^*}{N^{*2}} \\
n_{14} &= \frac{-\beta_T S^*}{N^*} - \frac{\beta_H(1-\alpha_2)\eta_1 S^*}{N^*} + \frac{\beta_H\{(1-\alpha_1)I_2^* + (1-\alpha_3)I_4^*\}S^*}{N^{*2}} \\
n_{15} &= \frac{\beta_H(1-\alpha_3)S^*}{N^*} + \frac{\beta_H\{(1-\alpha_1)I_2^* + (1-\alpha_3)I_4^*\}S^*}{N^{*2}} \\
n_{16} &= \frac{\beta_H(1-\alpha_4)\eta_2 S^*}{N^*} + \frac{\beta_H\{(1-\alpha_1)I_2^* + (1-\alpha_3)I_4^*\}S^*}{N^{*2}} \\
n_{22} &= \frac{\beta_T S^*}{N^*} - \left[\frac{\beta_H\{(1-\alpha_1)I_2^* + (1-\alpha_3)I_4^*\}}{N^*}(1-\eta) + \mu + \mu_1 + \gamma\eta\right] \\
n_{24} &= \frac{\beta_T S^*}{N^*} \\
n_{26} &= \frac{\beta_T S^*}{N^*} \\
n_{31} &= \frac{\beta_H\{(1-\alpha_1)I_2^* + (1-\alpha_3)I_4^*\}}{N^*} - \frac{S^*\beta_H\{(1-\alpha_1)I_2^* + (1-\alpha_3)I_4^*\}}{N^{*2}} \\
n_{32} &= \frac{S^*\beta_H\{(1-\alpha_1)I_2^* + (1-\alpha_3)I_4^*\}}{N^{*2}} - \frac{\phi_1 I_2^*\beta_T}{N^*} \\
n_{33} &= \frac{S^*\beta_H(1-\alpha_1)}{N^*} - \frac{S^*\beta_H\{(1-\alpha_1)I_2^* + (1-\alpha_3)I_4^*\}}{N^{*2}} + \alpha_2\gamma - \frac{\phi_1 I_2^*\beta_T}{N^*} \\
n_{34} &= \frac{S^*\beta_H(1-\alpha_2)\eta_1}{N^*} - \frac{S^*\beta_H\{(1-\alpha_1)I_2^* + (1-\alpha_3)I_4^*\}}{N^{*2}} \\
n_{35} &= \frac{S^*\beta_H(1-\alpha_3)}{N^*} - \frac{S^*\beta_H\{(1-\alpha_1)I_2^* + (1-\alpha_3)I_4^*\}}{N^{*2}} \\
n_{36} &= \frac{S^*\beta_H(1-\alpha_4)\eta_2}{N^*} - \frac{S^*\beta_H\{(1-\alpha_1)I_2^* + (1-\alpha_3)I_4^*\}}{N^{*2}} - \frac{\phi_1 I_2^*\beta_T}{N^*} \\
n_{42} &= \frac{\beta_H\{(1-\alpha_1)I_2^* + (1-\alpha_3)I_4^*\}(1-\eta)}{N^*} + \frac{\phi_1 I_2^*\beta_T}{N^*} \\
n_{44} &= \frac{\phi_1 I_2^*\beta_T}{N^*} - (\mu + \mu_3 + \tau_2 + \alpha_2\gamma)
\end{aligned}$$

$$
\begin{aligned}
n_{46} &= \frac{\phi_1 I_2^* \beta_T}{N^*} \\
n_{52} &= -\frac{\phi_2 I_4^* \beta_T}{N^*} \\
n_{53} &= \tau_1 \\
n_{54} &= -\frac{\phi_2 I_4^* \beta_T}{N^*} \\
n_{55} &= -(\mu + \mu_4) \\
n_{56} &= -\frac{\phi_2 I_4^* \beta_T}{N^*} + \gamma\alpha_4 \\
n_{62} &= \frac{\phi_2 I_4^* \beta_T}{N^*} \\
n_{64} &= \frac{\phi_2 I_4^* \beta_T}{N^*} + \tau_2 \\
n_{66} &= -(\mu + \mu_5 + \gamma\alpha_4).
\end{aligned}
$$

The eigenvalues of this Jacobian matrix are the roots of following two cubic equations:

$$\psi^3 + g_1\psi^2 + g_2\psi + g_3 = 0, \tag{7.26}$$

$$\psi^3 + f_1\psi^2 + f_2\psi + f_3 = 0. \tag{7.27}$$

where

$$
\begin{aligned}
g_1 &= -(n_{22} + n_{44} + n_{66}) \\
g_2 &= n_{44}n_{66} + n_{22}(n_{44} + n_{66}) - n_{64}n_{46} - n_{24}n_{42} \\
g_3 &= n_{22}n_{64}n_{46} + n_{24}n_{42}n_{66} - n_{24}n_{62}n_{46} - n_{22}n_{44}n_{66} \\
f_1 &= -(n_{11} + n_{33} + n_{55}) \\
f_2 &= n_{33}n_{55} + n_{11}(n_{33} + n_{55}) - n_{13}n_{31} - n_{35}n_{53} \\
f_3 &= n_{31}n_{13}n_{55} + n_{11}n_{35}n_{53} - n_{11}n_{33}n_{55} - n_{31}n_{15}n_{53}.
\end{aligned}
$$

Using Routh-Hurwitz's criteria, this equilibrium is locally asymptotically stable provided $g_1 > 0, f_1 > 0, g_1g_2 - g_3 > 0$ and $f_1f_2 - f_3 > 0$. Hence we conclude that when both the reproduction numbers are greater than one, then the local asymptotic stability of any boundary equilibrium i.e. TB-only or HIV-only equilibrium point is not guaranteed. They are locally asymptotic stable only under some restriction on parameters.

7.4.3 Local stability analysis the endemic equilibrium of full HIV-TB model

Consider $S = x_1, I_1 = x_2, I_2 = x_3, I_3 = x_4, I_4 = x_5, I_5 = x_6$ and $N = S+I_1+I_2+I_3+I_4+I_5$. The model system (7.3) can be re-written in the following form:

$$\begin{aligned}
\frac{dx_1}{dt} &= f_1 = \Lambda - \lambda_T x_1 - \lambda_H x_1 - \mu x_1 + \gamma\eta x_2 \\
\frac{dx_2}{dt} &= f_2 = \lambda_T x_1 - \lambda_H(1-\eta)x_2 - \mu x_2 - \mu_1 x_2 - \gamma\eta x_2 \\
\frac{dx_3}{dt} &= f_3 = \lambda_H x_1 - \phi_1\lambda_T x_3 - \alpha_2\gamma x_4 - (\mu + \mu_2 + \tau_1)x_3 \\
\frac{dx_4}{dt} &= f_4 = \lambda_H(1-\eta)x_2 + \phi_1\lambda_T x_3 - \alpha_2\gamma x_4 - (\mu + \mu_3 + \tau_2)x_4 \\
\frac{dx_5}{dt} &= f_5 = \tau_1 x_3 - \phi_2\lambda_T x_5 - (\mu + \mu_4)x_5 - \gamma\alpha_4 x_6 \\
\frac{dx_6}{dt} &= f_6 = \phi_2\lambda_T I_4 + \tau_2 x_4 - (\mu + \mu_5 + \gamma\alpha_4)x_6
\end{aligned} \tag{7.28}$$

To analyze the dynamics of full model (7.3), we compute the Jacobian matrix of (7.28) at the disease-free equilibrium $\mathcal{E}_0$ denoted by $J(\mathcal{E}_0)$.

$$J(\mathcal{E}_0) = J^*_\beta = \begin{pmatrix}
-\mu & -\beta_T + \gamma\eta & -\beta_H(1-\alpha_1) & K_1 & -\beta_H(1-\alpha_3) & K_2 \\
0 & \beta_T - (\mu + \mu_1 + \gamma\eta) & 0 & \beta_T & 0 & \beta_T \\
0 & 0 & K_3 & \beta_H(1-\alpha_2)\eta_1 + \alpha_2\gamma & \beta_H(1-\alpha_3) & K_4 \\
0 & 0 & 0 & -\alpha_2\gamma - (\mu + \mu_3 + \tau_2) & 0 & 0 \\
0 & 0 & \tau_1 & 0 & -(\mu + \mu_4) & \gamma\alpha_4 \\
0 & 0 & 0 & \tau_2 & 0 & K_5
\end{pmatrix}$$

here

$K_1 = -\beta_T - \beta_H\eta_1(1-\alpha_2), K_2 = -\beta_T - \beta_H(1-\alpha_4)\eta_2, K_3 = \beta_H(1-\alpha_1) - (\mu + \mu_2 + \tau_1)$,

$K_4 = \beta_H(1-\alpha_4)\eta_2, K_5 = -(\mu + \mu_5) - \gamma\alpha_4$.

The four eigenvalues of this matrix are

$-[\alpha_2\gamma + (\mu + \mu_3 + \tau_2)], -\mu, \beta_T - (\mu + \mu_1 + \gamma\eta), -(\mu + \mu_5 + \gamma\alpha_4)$ and other eigenvalues are the roots of the following quadratic equation

$\lambda^2 - [\beta_H(1-\alpha) - (\mu + \mu_2 + \tau_1) - (\mu + \mu_4)]\lambda + (\mu + \mu_2 + \tau_1)(\mu + \mu_4)(1 - R_H) = 0$

which has zero eigenvalue for $R_H = 1$.

Now consider the case when $R_H > R_T$ i.e. $R_{HT} = R_H$ and $R_{HT} = 1$. Choose $\beta_H = \beta^*$ as the bifurcation parameter.

Eigenvectors of J^*_β :

For the case when $R_{HT} = 1$, it is shown that the Jacobian of (7.28) at $\beta_H = \beta^*$ has a right eigenvector and left eigenvector given by $\mathbf{w} = [w_1, w_2, w_3, w_4, w_5, w_6]^T$ and $\mathbf{v} = [v_1, v_2, v_3, v_4, v_5, v_6]$, respectively, where

$$\begin{aligned} w_1 &= -\frac{\beta^*\{(1-\alpha_1)w_3 + (1-\alpha_3)w_5\}}{\mu}, \\ w_2 &= 0 = w_4 = w_6, \\ w_5 &> 0, \\ w_3 &= \frac{(\mu+\mu_4)w_5}{\tau_1}. \end{aligned}$$

J^*_β has left eigenvector $\mathbf{v} = [v_1, v_2, v_3, v_4, v_5, v_6]$, where

$$\begin{aligned} v_1 &= 0 = v_2, \\ v_5 &= v_5 > 0, \\ v_3 &= \frac{(\mu+\mu_4)v_5}{\beta^*(1-\alpha_3)}, \\ v_4 &= \frac{(\beta^*(1-\alpha_2)\eta_1 + \alpha_2\gamma)v_3 + \tau_2 v_6}{\alpha_2\gamma + (\mu+\mu_3) + \tau_2}, \\ v_6 &= \frac{\gamma\alpha_4 v_5 + \beta^*(1-\alpha_4)\eta_2 v_3}{(\mu+\mu_5+\gamma\alpha_4)}. \end{aligned}$$

Computation of a and b:

Computing the non-zero partial derivatives associated with F at disease-free equilibrium and the expressions for a and b are given as :

$$\frac{\partial^2 f_3}{\partial x_3^2} = -\frac{2\beta^*(1-\alpha_1)\mu}{\Lambda}, \quad \frac{\partial^2 f_3}{\partial x_3 \partial x_5} = -\frac{\beta^*[(1-\alpha_1)+(1-\alpha_3)]\mu}{\Lambda}, \quad \frac{\partial^2 f_3}{\partial x_5^2} = -\frac{2\beta^*(1-\alpha_3)\mu}{\Lambda},$$

$$\frac{\partial^2 f_3}{\partial x_3 \partial \beta^*} = (1-\alpha_1), \quad \frac{\partial^2 f_3}{\partial x_5 \partial \beta^*} = (1-\alpha_3).$$

From the above expression, we obtain:

$$\begin{aligned} a &= -2v_3\beta^* \left(\frac{w_3^2(1-\alpha_1)\Lambda}{\mu} + \frac{w_3 w_5[(1-\alpha_1)+(1-\alpha_3)]\Lambda}{\mu} + \frac{w_5^2(1-\alpha_3)\Lambda}{\mu} \right) < 0, \\ b &= v_3(w_3(1-\alpha_1) + w_5(1-\alpha_3)) > 0. \end{aligned}$$

Again we get, $a < 0$ and $b > 0$. From **(iv)** of the Theorem 1.7.1 given in Chapter 1 (also refer [56] for details), it is clear that the unique nontrivial equilibrium point of the model system (7.3) which exists whenever $R_H > 1$ will be locally asymptotically stable when $R_H > R_T > 1$ and $\beta^* < \beta_H$ with β_H close to β^*. This establishes the following theorem:

Theorem 7.4.2: *The unique endemic equilibrium $\mathcal{E}^{**}$ is locally asymptotically stable for $R_H > R_T > 1$.*

7.4.4 Global stability of disease-free equilibrium

Here, we list two conditions which should be satisfied to guarantee the global asymptotic stability of the disease-free state. Following Castillo-Chavez et al. [56], we rewrite model system (7.3) as follows:

$$\begin{cases} X'(t) = F(X,Y), \\ Y'(t) = G(X,Y), \quad G(X,0) = 0. \end{cases} \tag{7.29}$$

where $X = S$ and $Y = (I_1, I_2, I_3, I_4, I_5)^T$ with $X \in \mathbb{R}_+$ denoting the number of uninfected individuals and $Y \in \mathbb{R}_+^5$ denoting number of infected and co-infected individuals. The disease-free equilibrium is denoted here by $E_0 = (X_0, 0) = \left(\frac{\Lambda}{\mu}, 0, 0, 0, 0, 0\right)$

The conditions (H_1) and (H_2) below must be met to guarantee global asymptotic stability.

H_1: For $X'(t) = F(X_0, 0)$, X_0 is globally asymptotically stable ($g.a.s.$),

H_2: $G(X,Y) = AY - \widehat{G}(X,Y), \widehat{G}(X,Y) \geq 0$ for $(X,Y) \in \mathcal{D}$.

Here $A = D_Y G(X_0, 0)$ is an M-matrix (the off diagonal elements of A are non-negative) and $\mathcal{D}$ is the region where the model makes biological sense. If model system (7.29)

satisfies the conditions H_1 and H_2, the result stated in following theorem (7.4.3) holds.

Theorem 7.4.3: *The fixed point $E_0 = (X_0, 0)$ is globally asymptotically stable equilibrium of system (7.3), provided $R_{HT} < 1$ and the conditions stated in H_1 and H_2 are satisfied.*

Proof. In subsection 7.4.1, we have proved that for $R_{HT} < 1$, $\mathcal{E}_0$ is locally asymptotically stable.

Consider

$F(X, 0) = \Lambda - \mu S$, $G(X, Y) = AY - \widehat{G}(X, Y)$,

where

$$A = \begin{pmatrix} r_{11} & 0 & r_{13} & 0 & r_{15} \\ 0 & r_{22} & r_{23} & r_{24} & r_{25} \\ 0 & 0 & r_{33} & 0 & 0 \\ 0 & r_{42} & 0 & r_{44} & r_{45} \\ 0 & 0 & r_{53} & 0 & r_{55} \end{pmatrix}$$

here

$r_{11} = \beta_T - (\mu + \mu_1 + \gamma\eta)$, $r_{13} = \beta_T$, $r_{15} = \beta_T$, $r_{22} = \beta_H(1 - \alpha_1) - (\mu + \mu_2 + \tau_1)$, $r_{23} = \beta_H(1 - \alpha_2)\eta_1 + \alpha_2\gamma$, $r_{24} = \beta_H(1 - \alpha_3)$, $r_{25} = \beta_H(1 - \alpha_4)\eta_2$,

$r_{33} = -\alpha_2\gamma - (\mu + \mu_3 + \tau_2)$, $r_{42} = \tau_1$, $r_{44} = -(\mu + \mu_4), r_{45} = \gamma\alpha_4$, $r_{53} = \tau_2$, $r_{55} = -(\mu + \mu_5) - \gamma\alpha_4$.

then

$$\widehat{G}(X, Y) = \begin{pmatrix} \widehat{G_1}(X, Y) \\ \widehat{G_2}(X, Y) \\ \widehat{G_3}(X, Y) \\ \widehat{G_4}(X, Y) \\ \widehat{G_5}(X, Y) \end{pmatrix} = \begin{pmatrix} \beta_T(I_1 + I_3 + I_5)\left(1 - \frac{S}{N}\right) + \lambda_H(1 - \eta)I_1 \\ \beta_H\left[(1 - \alpha_1)I_2 + (1 - \alpha_2)\eta_1 I_3 + (1 - \alpha_3)I_4 + (1 - \alpha_4)\eta_2 I_5\right]\left(1 - \frac{S}{N}\right) + \lambda_T\phi_1 I_2 \\ -(\lambda_H(1 - \eta)I_1 + \lambda_T\phi_1 I_2) \\ \phi_2\lambda_T I_4 \\ -\phi_2\lambda_T I_4 \end{pmatrix}$$

Notice that the matrix A is an M-Matrix since all its off-diagonal elements are non-negative, whereas to establish the result of global stability of $\mathcal{E}_0$, we need to prove

$\widehat{G}(X,Y) \geq 0$ but here $\widehat{G_3}(X,Y) < 0$ and $\widehat{G_5}(X,Y) < 0$. This implies that the disease-free equilibrium ($\mathcal{E}_0$) is not globally stable. ∎

7.5 Numerical simulation

To visualize the dynamics of the HIV-TB full model (7.3), numerical simulations are carried out in XPP [65] by using various set of parameters. Figures 7.2-7.3 are demonstrating the stability of disease-free equilibrium $\mathcal{E}_0 = \left(\frac{\Lambda}{\mu}, 0, 0, 0, 0, 0\right)$ for the set of parameters described in Table 7.1. Here all the parameters are in yr^{-1}. The basic reproduction numbers corresponding to TB and HIV are $R_T = 0.8888$ and $R_H = 0.9077$ for this set of parameter values and $\mathcal{E}_0 = (12500, 0, 0, 0, 0, 0)$. That means the two diseases are eradicated from the population. The stability of TB-only equilibrium point is demonstrated in Figures 7.4-7.5, where the parameter $\beta_T = 0.1$ and all other parameters are same as listed in Table 7.1. Here $R_T = 1.1111$ and $R_H = 0.9077$ and the TB-only equilibrium point $\hat{\mathcal{E}}$ is given by

$$\hat{S} = 9782.609, \hat{I}_1 = 1086.957, \hat{I}_2 = 0 = \hat{I}_3 = \hat{I}_4 = \hat{I}_5.$$

In this case the disease-free equilibrium is unstable and HIV-only and co-infection equilib-

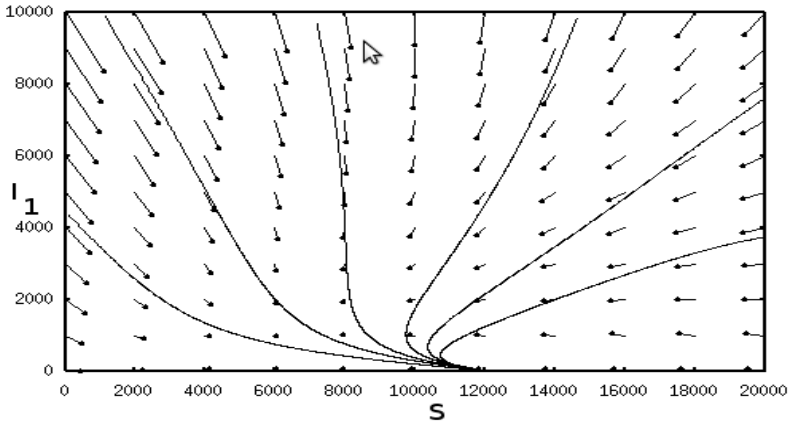

Figure 7.2: $S - I_1$ phase plane showing the stability of the disease-free equilibrium point $\mathcal{E}_0$ when $R_T = 0.8888889, R_H = 0.9077159$.

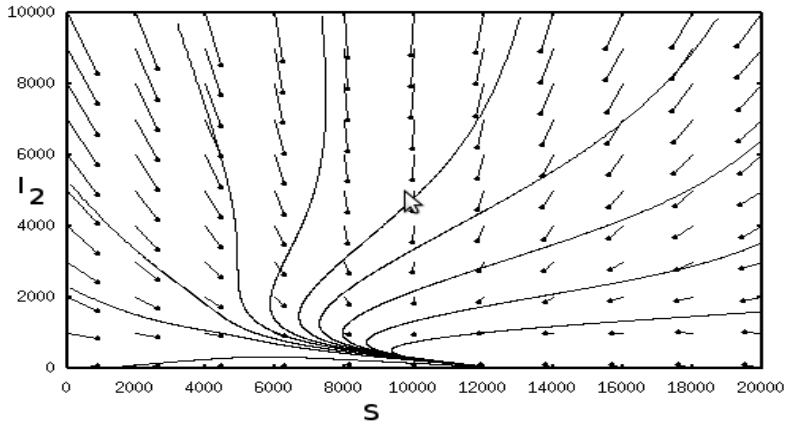

Figure 7.3: $S - I_2$ phase plane showing the stability of the disease-free equilibrium point $\mathcal{E}_0$ when $R_T = 0.8888889, R_H = 0.9077159$.

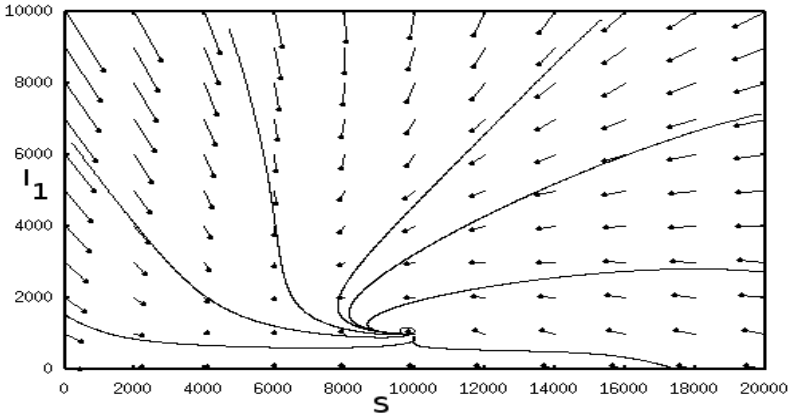

Figure 7.4: $S - I_1$ phase plane showing the stability of the TB-only equilibrium point $\hat{\mathcal{E}}$ when $R_T = 1.111111, R_H = 0.9077159$.

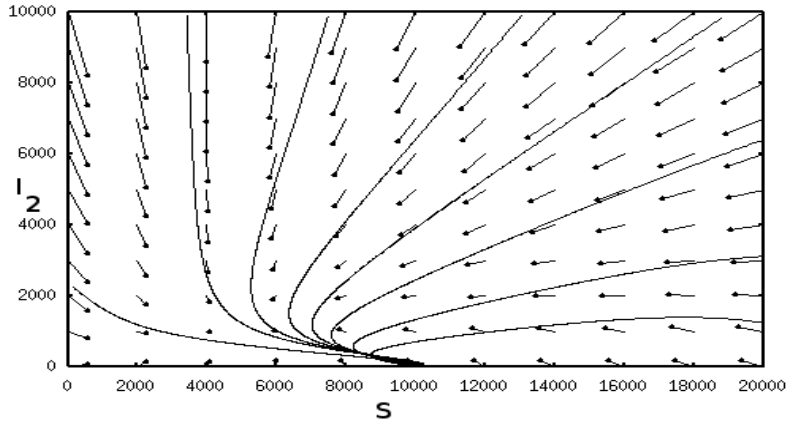

Figure 7.5: $S - I_2$ phase plane showing the stability of the TB-only equilibrium point $\hat{\mathcal{E}}$ when $R_T = 1.111111, R_H = 0.9077159$.

rium do not exist. Now the system (7.3) is again simulated by changing the parameter β_H as 0.12 and keeping all other parameters as listed in Table 7.1. For this set of parameters $R_T = 0.8888889$ and $R_H = 1.210288$. Here TB-only and co-infection equilibrium do not exist and the disease-free equilibrium point is unstable. Figures 7.6-7.7 are demonstrating the stability of HIV-only equilibrium point $\mathcal{E}^*$ which is given as

$$S^* = 7581.92, I_1^* = 0, I_2^* = 1167.57, I_3^* = 0, I_4^* = 426.81, I_5^* = 0.$$

When both the reproduction numbers R_T and R_H are greater than one then there is a possibility of stability of co-infection equilibrium $\mathcal{E}^{**}$ which is demonstrated in Figure 7.8 for the parameter values described in Table 7.1, except $\beta_T = 0.15, \beta_H = 0.12$. For this set of parameters, $R_T = 1.666667, R_H = 1.210288$. The TB-only equilibrium $\hat{\mathcal{E}}$, the HIV-only equilibrium $\mathcal{E}^*$ and the co-infection equilibrium $\mathcal{E}^{**}$ are given by $(4687.5, 3125.0, 0, 0, 0)$, $(7581.92, 0, 1167.574, 0, 426.8125, 0)$ and $(4067.9, 2166.5, 451.85, 223.72, 148.2, 113.17)$ respectively. It is observed that the co-infection equilibrium $\mathcal{E}^*$ whenever exists is locally asymptotically stable and in this case the other equilibria becomes unstable.

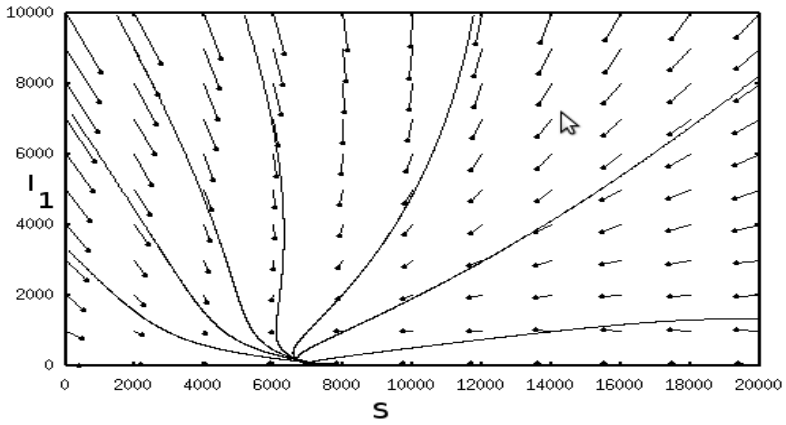

Figure 7.6: $S - I_1$ phase plane showing the stability of the HIV-only equilibrium point $\mathcal{E}^*$ when $R_T = 0.8888889, R_H = 1.210288$.

That means for $R_H > 1$ and $R_T > 1$, both the diseases will co-exist. In Figure 7.9, the effect of screening of TB patients is shown, which shows significant decrease in the number of TB-infectives with increase in fraction of individuals who are under screening. Similarly, the effect of screening in HIV patients is also significant as the number of HIV

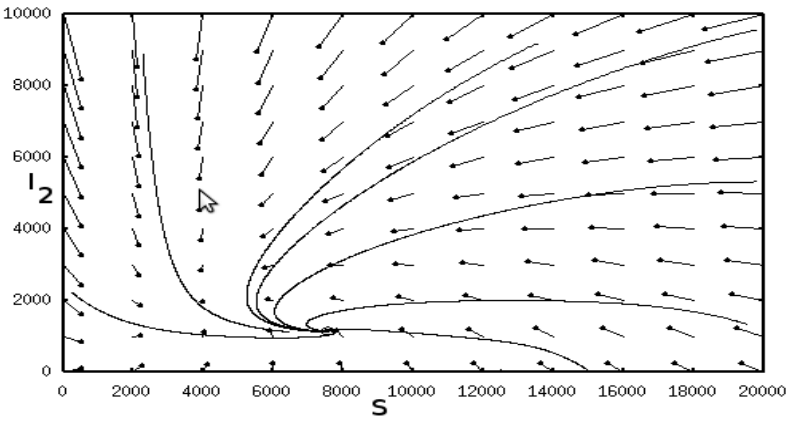

Figure 7.7: $S - I_2$ phase plane showing the stability of the HIV-only equilibrium point $\mathcal{E}^*$ when $R_T = 0.8888889, R_H = 1.210288$.

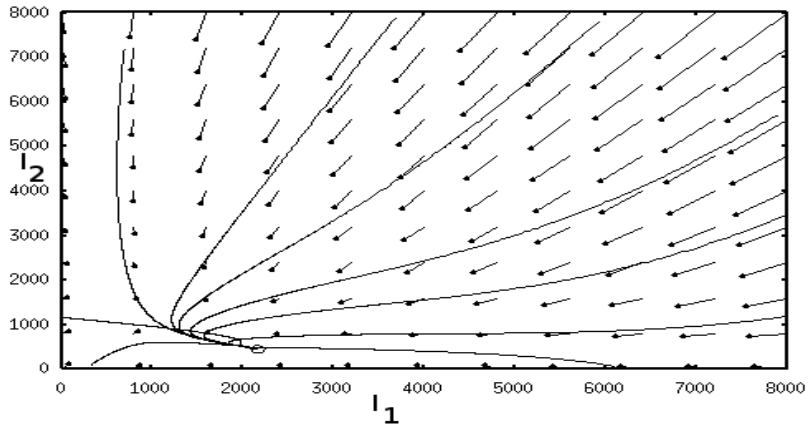

Figure 7.8: $I_1 - I_2$ phase plane showing the stability of the co-infection equilibrium point $\mathcal{E}^{**}$ when $R_T = 1.666667, R_H = 1.210288$.

infectives also decreases with the increase in the fraction of screened individuals. This fact is demonstrated in Figure 7.10.

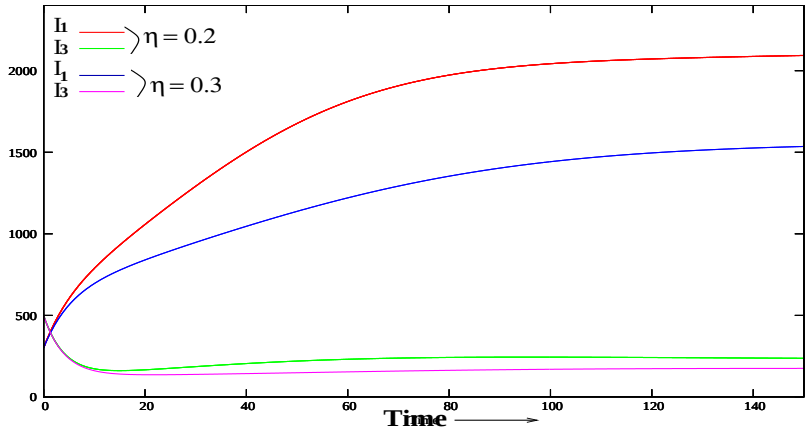

Figure 7.9: Variation of I_1 and I_3 with time showing the effect of fraction of individuals screened for TB where all other parameters are as stated for co-infection equilibrium point $\mathcal{E}^{**}$.

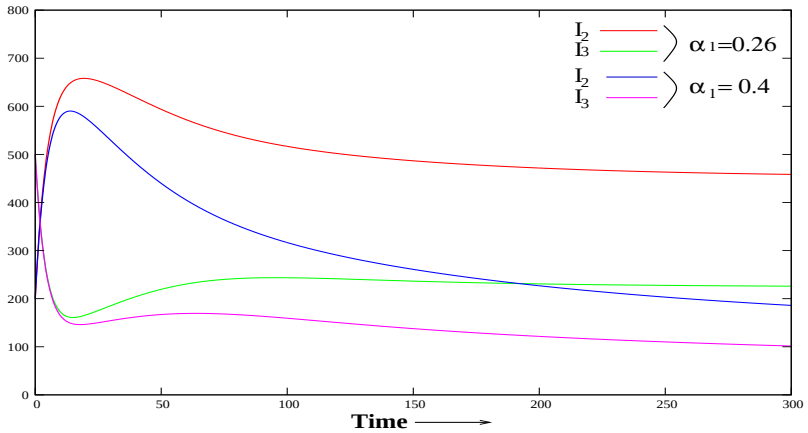

Figure 7.10: Variation of I_2 and I_3 with time showing the effect of fraction of individuals screened for HIV where all other parameters are as stated for co-infection equilibrium point $\mathcal{E}^{**}$.

The combined effect of rates of the screening of TB and HIV is demonstrated in Figure 7.11, where both the TB and HIV infectives decrease significantly with the increase in the rates of screening of TB and HIV. The effects of rate of transmission of TB is demonstrated in Figures 7.12, where it is observed that with the increase in this parameter, the equilibrium levels of the TB infectives and the co-infected population increase. Similarly with the increase in the rate of transmission of HIV, the equilibrium level of HIV infectives

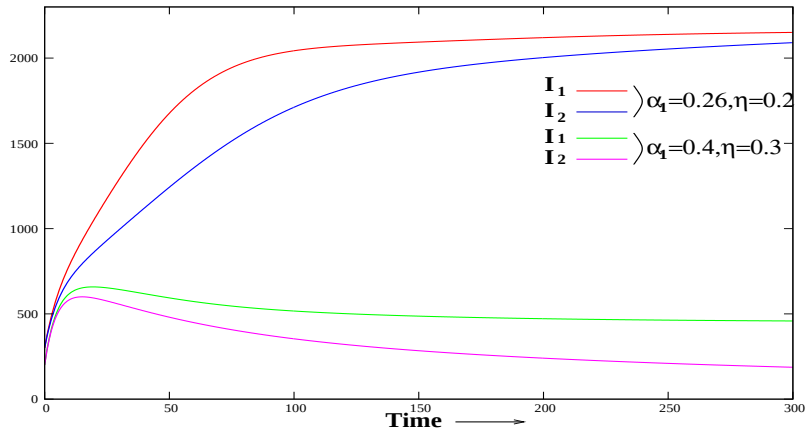

Figure 7.11: Variation of I_1 and I_2 with time showing the combined effect of fraction of individuals screened for both TB and HIV where all other parameters are as stated for co-infection equilibrium point $\mathcal{E}^{**}$.

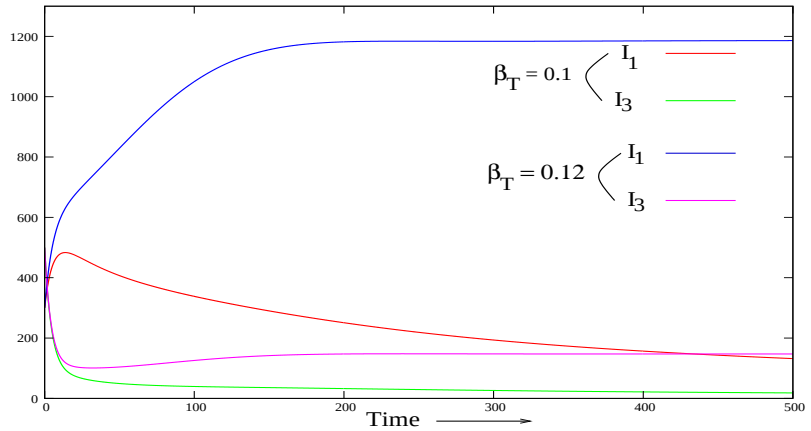

Figure 7.12: Variation of I_1 and I_3 with time for different β_T showing the effect of rate of transmission of TB where all other parameters are as stated for co-infection equilibrium point $\mathcal{E}^{**}$.

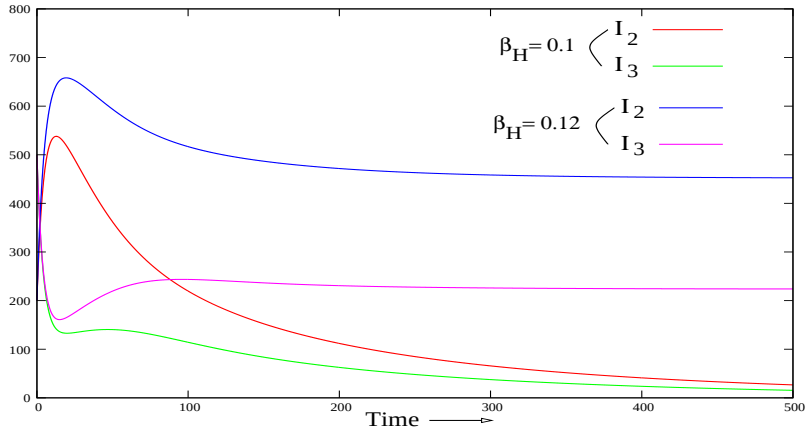

Figure 7.13: Variation of I_2 and I_3 with time for different β_H showing the effect of rate of transmission of HIV where all other parameters are as stated for co-infection equilibrium point $\mathcal{E}^{**}$.

and the co-infected population increase, which is demonstrated in Figure 7.13.

Table 7.1: Description of parameters used in HIV-TB co-infection model system (7.3).

Parameter	Description	Estimate (Range)	Source
Λ	Recruitment rate	250	Variable
μ	Natural mortality rate	0.02	[155]
$\mu_1, \mu_2, \mu_3, \mu_4, \mu_5$	Disease induced mortality rate due to TB, HIV, HIV-TB AIDS and AIDS-TB	0.03, 0.035, 0.04, 0.06, 0.07	Assumed
γ	Recovery rate for TB	0.2	Assumed
β_T	Probability of being infected with TB	0.08	Variable
β_H	Probability of being infected with HIV	0.09	Variable
η	Fraction of individuals screened for TB	0.2	Variable
$\alpha_1, \alpha_2, \alpha_3, \alpha_4$	Fraction of individuals screened for HIV, HIV-TB co-infected individuals, AIDS and AIDS-TB co-infected individuals	0.26, 0.54, 0.7, 0.42	Variable
δ_1, δ_2	Progression rates to AIDS by HIV treated and untreated individuals, respectively	0.01, 0.0303	Assumed [155]
δ_3, δ_4	Progression rates to AIDS-TB by HIV-TB treated and untreated individuals, respectively	0.035, 0.04	Assumed
ϕ_1, ϕ_2	Modification parameters	1.2, 1.4	[155]
η_1, η_2	Modification parameters	1.4, 1.5	Assumed
ν	Fraction of HIV infectives under treatment	0.2	Assumed.

7.6 Conclusion

In this chapter, we have formulated and analyzed a mathematical model for the HIV/AIDS-TB co-infection with screening and treatment of both the HIV and TB infectives. The reproduction numbers corresponding to both TB and HIV have been computed. The existence and stability of various equilibria have also been discussed. We found that the system always tends to disease-free equilibrium if the basic reproduction numbers R_T and

R_H corresponding to TB and HIV respectively are less than one. We have shown that the co-infection equilibrium point is locally asymptotically stable whenever it exists. Our numerical simulation showed that the screening of HIV infected people plays notable role in controlling the spread of this disease. From our presented results, it can be easily seen that the screening of TB has positive impact in the 'Reproduction Number (R_T)' corresponding to TB, i.e. with the increase in the fraction of screening of TB infectives, the reproduction number R_T decreases.

Thus we conclude that with the increase in the fraction of screening of TB i.e. η, the number of TB-infectives decreases which is reflected in numerical simulation too. Also it is easy to observe that both the reproduction numbers R_T and R_H can be reduced below one by increasing the fraction of screening for the TB and HIV, leading to disease free equilibrium to be stable. Also numerical simulation suggests that the rates of transmission of both TB and HIV should be decreased as increase in this causes increase in the number of infectives at equilibrium level.

Future Work

In future, the results reported in this thesis will be explored for further extension by incorporating and studying the following aspects:

- The role of migration of individuals from one patch to another on the spread of HIV, e.g. two patch models.
- To develop age-structured model for the HIV infection.
- To explore the optimal control model for the HIV, TB and other infectious diseases.
- To investigate the delay differential equation models for the HIV and TB.
- To develop and analyze sex-structured model for the HIV and TB.

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