Modelling the impact of different health care systems and dropouts on the dynamics of HIV/AIDS

by

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Thesis presented in partial fulfilment of the requirements for the degree of Master of Science in Mathematics in the Faculty of Science at Stellenbosch University

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Declaration

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Date: March 2020 .....

Abstract

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Side effects from antiretroviral drugs (ARVs) over time, present a major challenge to individuals on treatment and is a major cause of dropouts from treatment programs. The provision of treatment for the infected varies depending on their levels of affordability in many developing countries. In this thesis, we formulate a mathematical model to determine the impact of dropouts on the dynamics of HIV/AIDS which depends on different health care systems. We categorize the health care systems into two, private and public with the dropout rates being dependent on the health care system. The model's steady states are determined and their stabilities presented in terms of the reproduction number, $\mathfrak{R}_o$. Numerical simulations are carried out and the results suggest that the management of dropouts is significant to the dynamics and management of HIV/AIDS. The role of essential parameters is also investigated through sensitivity analysis that employs the Latin Hypercube Sampling technique. The results have implications to the management and policy designs with regards to health care systems, dropouts and disease progression.

Uittreksel

Modelling the impact of different health care systems and dropouts on the dynamics of HIV/AIDS

(" Modelling the impact of different health care systems and dropouts on the dynamics of HIV/AIDS")

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Newe-effekte van antiretrovirale medisyne (ARV's) met verloop van tyd, is 'n groot uitdaging vir individue wat op behandeling is en is die grootste oorsaak van die uitval van behandelingsprogramme. Die verskaffing van behandeling vir besmette wissel afhangend van hul bekostigbaarheidsvlakke in baie ontwikkelende lande. In hierdie tesis formuleer ons 'n wiskundige model om die impak van uitvalle op die dinamika van MIV / VIGS te bepaal wat afhang van verskillende gesondheidsorgstelsels. Ons kategoriseer die gesondheidsorgstelsels in twee, privaat en publiek, en die uitvalkoers is afhanklik van die gesondheidsorgstelsel. Die standvastoestande van die model word bepaal en hul stabiliteit word aangebied in terme van die reproduksienommer, $\mathfrak{R}_o$. Numeriese simulasies word uitgevoer en die resultate dui daarop dat die bestuur van uitvalle belangrik is vir die dinamika en hantering van MIV / VIGS. Die rol van essensiÃ«le parameters word ook ondersoek deur middel van sensitiwiteitsanalise wat gebruik maak van die Latynse Hypercube Monsternemingstegniek. Die resultate het gevolge vir

die bestuur en beleidsontwerpe ten opsigte van gesondheidsorgstelsels, uitvalle en progressie van siektes.

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Dedications

To my lovely husband, Dennis and son Toluwanimi.

Publication

The following publication is the expected publication that will arise from the thesis.

- Modelling the potential impact of different health care systems and dropouts on the dynamics of HIV/AIDS. Publication in review.

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Chapter 1

Introduction

1.1 HIV/AIDS: General overview

The Human Immunodeficiency Virus (HIV) is a virus that causes an infection that can progress to Acquire Immunodeficiency Syndrome (AIDS) if the infected are not treated [89]. HIV is different from some other viruses because once an individual is infected with the virus, they have it for a lifetime. This is because there is currently no cure for HIV, but with adequate medical attention and care, it can be managed. HIV is a virus that spread through body fluids and attacks the body's immune system. Specifically, HIV attacks the $CD4^+$ T cells (types of white blood cells that move throughout the body to fight and destroy viruses, germs, bacteria, etc), macrophages and dendritic cells. It destroys many of these cells and the cells will be unable to fight against any disease or infections [26]. A normal $CD4^+$ T cell count is between $500 - 1400$ cells per cubic millimetre of blood in humans. HIV infection leads to a reduction in the count of $CD4^+$ T cell. And when the $CD4^+$ T cells decrease to a particular level (< 200 cells per cubic millimetre of blood), the immune system will no longer function properly and this causes the body to be susceptible to other infections and diseases, which eventually leads to the development of AIDS.

HIV is a member of the genus Lentivirus, which is part of the family of retroviruses [63]. Lentiviruses have properties that are common biologically. They are responsible for illnesses that have a long duration and with a long incubation period. HIV structure is roughly spherical and the diame-

ter is about 120nm which is about 60 times smaller than a red blood cell [63].

There are two main types of HIV: HIV-1 and HIV-2 [22]. HIV-1 is the virus that was first discovered and widely known worldwide as the cause of HIV infections globally. It is called Lymphadenopathy Associated Virus (LAV) and Human T-lymphotropic Virus 3 (HTLV-III). HIV-1 has a greater chance of damaging the host and it is more infectious than HIV-2. Generally, HIV-1 is believed to have originated from Southern Cameroon [2]. On the other hand, HIV-2 is common in West Africa [29]. The viral load of HIV-2 is lower to that of HIV-1 which results in a lower rate of transmission of the virus[69].

Generally, the belief is that HIV originated from animals in Africa. Scientific studies concluded that this happened as a result of the transfer of a virus named Simian Immunodeficiency Virus (SIV) from Chimpanzees or apes to human beings [2]. Studies also show that the version of the Immunodeficiency Virus (SIV) might have been transmitted to humans from contacts with monkey blood while hunting for meat to eat [39], and metamorphosed to HIV in humans.

HIV is transmitted or spread by body fluids of infected individuals such as semen, vagina fluids, blood, rectal fluids, breast milk and from an infected mother to the fetus while pregnant, a process commonly known as vertical transmission. There are three main sources of contracting HIV. A person can contract HIV by

(i) Having unprotected sex with an HIV infected individual (either by anal or sometimes oral sex).

(ii) Sharing needles that are already contaminated.

(iii) Through vertical transmission.

1.2 HIV/AIDS control strategies

Controlling HIV/AIDS is a major challenge that the world is facing at the present moment. The challenges include a lack of medical equipment, illiteracy, poverty, poor health care systems, etc. A significant number of people

have HIV infection but do not know their status. On the other hand, some know their status but find it difficult to seek treatment and access other available disease management services [46]. The mode of controlling the disease presently is by; total abstinence, the use of condoms, screening of blood before transfusion and treatment of people that are already infected [65]. Since there is no cure for HIV presently, it is important to make sure that infected individuals are pre-informed about the available control measures or precautions so as not to spread the disease. Similarly, individuals at risk should be educated on HIV infection, so that they avoid getting infected. Currently, with adequate control measures and interventions, HIV can be managed over a long period.

1.2.1 Treatment for HIV/AIDS

Even though presently there is no cure or vaccine for HIV/AIDS, there is treatment that can help to reduce the viral load. Antiretroviral (ARV) drugs are drugs available to people that are infected with HIV and for those that have not been infected. Pre-exposure Prophylaxis (PrEP) is an ARV drug that has been found to be useful in preventing infections for people that have a high chance of being infected with HIV and are usually prescribed. PrEP, should be taken daily for it to be effective in preventing HIV from sex or injection drug use. Post-exposure Prophylaxis (PrEP) is an ARV drug that is approved for individuals that are potentially exposed to HIV, to prevent becoming infected. PrEP must start within 72hours after a possible exposure to the virus. The very first ARV drug to be permitted for use against HIV is called zidovudine, which was available for use in the year 1987 [87]. This also helped to reduce the risk of transmitting HIV. Recently, Highly Active Antiretroviral Therapy (HAART) was introduced in 1996 [67]. HAART consists of three drugs belonging to at least two types of antiretroviral agents that help to reduce the viral particles in the body, increase the number of immune cells (CD4+ T cells), slows down progression to AIDS, reduce the rate of transmission and prevents the virus from multiplying in the blood. For ARV drugs to be effective, they must be taken at the right time and as prescribed. The only way to prevent people from being infected with HIV is to make sure they are not exposed to the virus.

1.2.2 UNAIDS 90-90-90 treatment target

In 2014, the Joint United Nations Programme on HIV / AIDS (UNAIDS) came up with an ambitious target to end the AIDS epidemic. According to UNAIDS, it will be very difficult to bring the epidemic to an end if HIV treatment is not provided to everybody who is infected with the virus. UNAIDS has an ambitious $90-90-90$ target. The target is as follows:

- 90% of all individuals that are living with HIV will know their status by 2020.
- 90% of all individuals that have been diagnosed with HIV infection will receive sustained ARV drugs by 2020.
- 90% of all individuals receiving ARV drugs will have viral suppression.

The above target will have a result such that 81% of all individuals living with HIV infection will be on treatment and 73% of all individuals living with HIV achieve viral suppression. This will, in turn, enable the world to end the AIDS epidemic by 2030 [30]. Although the target is ambitious, scientists believe that it is achievable [77]. The target is a commitment to make available and improve access to ARVs to HIV infected individuals as a life-saving treatment and to prevent transmission to uninfected individuals [48].

For the target to be achieved, adequate and efficient delivery of medical care for HIV infected is needed. These include;

- Series of diagnostic tests: This can be achieved by making sure that there are awareness and adequate information for people to know their status.
- Treatment delivery: This also can be achieved by making available ARV drugs to infected individuals as soon as their status is known.
- Monitoring, giving support and care to infected individuals.
- Adequate Assessments on how the UNAIDS $90-90-90$ ambitious targets are being carried out.

Even though HIV treatment is advocated for the ending of the AIDS epidemic, it is not the only method that can help to end the epidemic. Taking precautionary measures to minimize the spread of the disease is also important. When individuals are aware of their status, they are enlightened about prevention strategies and those that are HIV negative are equally protected. The prevention strategies that are common for a disease such as HIV/AIDS are detailed below:

- Condoms: They play an important role in fighting or reducing the spread of HIV/AIDS because of their ability to prevent sexually transmitted HIV. Therefore, UNIADS target is currently on condom programming (male and female condom) to ensure that individuals that are at risk of contracting HIV are encouraged to use condoms. Condoms access and their consistent use are pivotal. The supply of and demand for condoms is also addressed, making sure condoms are available and accessible at no cost.

- PrEP: Sexually exposed individuals are encouraged to use PrEP ARV drugs to reduce the risk of being infected with HIV.

- Male circumcision: Research has shown that male circumcision done by well-trained health experts in properly equipped settings is very safe [90]. It has also shown that circumcising male reduces the risk of HIV infection in men by approximately 60%. Since male circumcision reduces the rate of HIV infection among men, this indirectly reduces the risk of exposure of the infection to women [27]. Furthermore, research has shown that male circumcision provides a degree of protection which is equivalent to what a highly effective vaccine would have achieved [9]. Therefore, UNAIDS recommended that male circumcision should be considered as an intervention for preventing HIV in countries that have heterosexual HIV transmission, high HIV prevalence, and low male circumcision.

- Elimination of mother-to-child transmission (MTCT): The aims of MTCT include: making sure that all expectant mothers know their status, up to 90% of infected mothers to receive ARV drug, up to 90% of infants that are breastfeeding receive ARV drug and adequate provision of

care, treatment and support measures for women and children that are living with HIV and also for their family members [2].

- Reduction in the harm caused by health professionals who inject drugs and transfuse blood include the screening of blood before transfusion and adequate sterilization of equipment before use.

Finally, UNAIDS aims to be consistent with the target, and also plan to make a routine report to track the progress towards the 90-90-90 target [30]. Sensitizing people via media and other awareness channels is also put in place to eliminate stigma, social exclusion, and discrimination towards HIV positive individuals. Countries around the world and scientists are working relentlessly towards achieving this ambitious target of UNAIDS and quite interesting results are being achieved [10, 36, 47, 48, 51, 56, 77].

1.3 Health care systems

Health care systems can be defined as organizations of people, institutions, and resources that make available health care services to meet the health needs of target populations. Health care systems can be categorized into two, the private and public health care system in many of the developing countries. Private health care is provided by institutions other than the government to meet the health needs of the people that prefer private health care and can afford it, while the public health care system is provided or funded by the government [11]. Public health care, apart from the fact that the services rendered to people are free or almost free in most countries, it has a lot of disadvantages. People who go for public health care experience long waiting periods before they are attended to, the facilities are sometimes old and poorly managed, the quality of care is poor and there is poor disease control and prevention [94]. This is not so with private health care, where there are short wait times, appointments are not rushed, better facilities, good care, and better disease control and prevention [94]. Therefore, the majority of people who can afford prefer to turn to private health care because of its accessibility, availability, and convenience of services [43, 50].

1.4 Attrition from HIV treatment

Advancement in the treatment of HIV over time has enabled many individuals that are infected to enjoy good health, live longer and also have hope for the future. Despite the improvement in the treatment of HIV, several infected individuals that are enrolled in treatment still dropout from treatment one way or the other [76]. This could be either because infected individuals do not use the ARV drugs as prescribed or refuse to go for outpatient health care services due to hostility and public humiliation by health care staff. Dropouts could also be a result of the side effects they experience from the ARV drugs. If HIV infected individuals skip doses of ARV drugs, the virus will, in turn, start replicating once again in their bodies. This can also make the virus to be resistant to the available drugs. Due to the high burden of HIV that the world is facing, it implies that the number of people on ARV drugs has increased resulting in health systems having a lot of patients to deal with. Due to the larger population of infected individuals, the waiting period for patients to receive services is usually longer and the quality of services is generally poor. This often results in patients being discouraged and often leads to attrition from ARV treatment [44]. Most of the cases of attrition are as a result of loss to follow up of HIV infected individuals [8]. Not having a personal desire and self-desire to continue can also contribute to attrition from ARV treatment [73]. This will affect the patients because the risk of drug-resistance to HIV will increase enormously and viral-load in patients will increase [49]. Care is very essential regarding individuals living with HIV/AIDS, but when the care is limited, it can contribute to individuals dropping out of treatment for those under treatment. Generally, private health care has fewer dropouts when compared with public health care systems.

1.4.1 Side effects of antiretroviral drugs

The side effects of ARV drugs are an important consideration in managing individuals that are infected with HIV. HIV infection is a disease that is chronic and as a result, many drugs are used by HIV infected persons for a long period [16]. Therefore, if there is no proper adherence to the way the drugs are administered, it could then lead to side effects as a result of the use of the medication [7]. Physicians noted that the reason that is com-

mon for HIV infected patients to refuse to continue treatment is due to fear of side effects, the actual side effects, and complications of the treatment [12]. The fact remains that it is still very difficult for HIV infected individuals to adhere to the treatment plan because they have to take these drugs for the rest of their lives. Side effects from ARV drugs could be so serious at times that they make infected individuals stop treatment. HIV infected individuals also have a higher chance of having secondary infections and the medications for those infections could cause side effects when they are taken concurrently with ARV drugs. Listed below are some of the severe and life-threatening side effects caused by ARV drugs [1, 34, 75].

- They cause hypersensitivity or allergic reactions (such as rash, swellings in the eyes, tongue, lips, hands, etc).
- They cause heart disease.
- They lead to kidney, liver or pancreas damage.
- High blood sugar and diabetes.
- Pain in the feet or hands as a result of nerve problems.
- They might also make some people have trouble sleeping.
- Feeling nausea and vomiting.
- They cause depression, anxiety and leads to changes in mood.
- They cause lipodystrophy (gaining or losing fat in certain areas of the body).
- They cause diarrhoea.
- They lead to loss of appetite.
- They also cause fatigue.

Therefore side effects to ARV drugs are a serious challenge the world is facing regarding the HIV/AIDS epidemic.

1.5 Mathematical modelling of HIV/AIDS

Mathematical models have been used as a tool to study the dynamics of HIV/AIDS. Mathematical models have enabled us to have a better understanding of the long and short term dynamics of the disease [18]. There are two types of models that are used for modelling HIV/AIDS. These are:

- **Stochastic models:** These are models based on individual simulations. In these models, each individual in a population is considered as a discrete entity and the simulations are carried out by random processes [37]. In stochastic models, a probabilistic approach is used to predict future events.

- **Deterministic models:** These are models that are based on population averages. In these models, it is assumed that all the individuals in the population have the same characteristics. Also, unique solutions are generated when solving models. Furthermore, the outcomes are determined precisely through known relationships among events and states. These models do not consider random variations [17]. Populations in these models are divided into different compartments depending on their infection status [40]. Differential equations are used to describe the changes in each compartment, which helps to determine the dynamics of each of the compartments. Deterministic models also enable us to determine variables and parameters that can be used in case of the inclusion of control variables when modelling disease control.

The use of either stochastic models or deterministic models is determined by the epidemiology of the infection, the population size and the assumptions built in the models.

1.6 Motivation

HIV/AIDS remains a global problem. Researchers are working tirelessly on how to put an end to the AIDS epidemic [82]. To date, there is no vaccine or cure for this disease except for ARV drugs that are used to suppress the viral load. Likewise, issues of dropouts from HIV treatment are also a great challenge. Therefore, it is important to determine the impact of dropouts on

the dynamics of the disease.

A number of HIV/AIDS models have been developed, analyzed and simulated but many of them do not include or consider side effects of ARV drugs, which is the driving force for why people dropout from treatment. Although, [78] considered dropout as a result of the loss of follow up from the health care setting, the differences in health care services were not considered. Poor health care services are a propelling factor that leads people to drop out of treatment. Some people might decide to make use of the private health care system and some, public health care system due to the different levels of affordability. This is crucial to consider when developing a mathematical model for HIV/AIDS.

Since dropping out from HIV treatment has a great impact on the dynamics of HIV/AIDS, the questions are;

(i) What will be the long-term dynamics of the disease if people keep dropping out of treatment?

(ii) How will the side effects of ARV drugs drive individuals to drop out of HIV treatment?

(iii) What is the potential impact of having two types of health care systems to the HIV/AIDS epidemic?

In [19] a model for HIV/AIDS of the SIT type (Susceptible-Infected-Treated) models dropouts by including a parameter from the treatment compartment back to the infected compartment. In this project, the model is extended by including a class of those that drop out of treatment and different health care systems. Models of HIV/AIDS that do not consider the effects of dropout from ARV drugs may not include the full dynamics of HIV/AIDS in the population, considering the current challenges around treatment and side effects.

1.7 Objectives

The main objective of this thesis is to study the potential impact of different health care systems and dropouts on the dynamics of HIV/AIDS, in which

side effects to ARV drugs are a propelling force that causes the dropouts. The specific objectives are listed below:

- To develop a deterministic mathematical model that describes the dynamics of HIV/AIDS within a population.
- To analyze the model by carrying out a stability analysis of steady states.
- To determine the reproduction number which enables us to determine the threshold conditions for disease persistence.
- To carry out the numerical simulations of the model system and also the sensitivity analysis of the formulated model.
- To fit the model to data from Warren Park, Zimbabwe drawn out from [19].
- To discuss the effects of dropouts on the dynamics of HIV/AIDS from the analysis done and make general conclusions.

1.8 Composition of the thesis

This project is structured as follows: Chapter 1 contains the general overview of HIV/AIDS, control strategies, attrition from HIV treatment and mathematical modelling of HIV/AIDS. The chapter also contains the thesis motivation, objectives, and overview of the thesis. Chapter 2 consists of the literature reviews of mathematical models of HIV/AIDS. In Chapter 3, the model to study the potential impact of different health care systems and dropouts on the dynamics of HIV/AIDS is formulated. Analysis of the model (steady states, stability, and reproduction number) is also done in the chapter. Numerical simulations were performed. The fourth chapter contains the discussion and conclusions. Some suggestions on how to improve the model are also given.

Chapter 2

Literature review

Mathematical modelling of epidemics is used to describe or demonstrate the dynamics of infectious diseases in a population. Daniel Bernoulli in the year 1766 was the first to carry out the mathematical modelling of the spread of diseases that are infectious [35]. The author used the model to make future predictions with regards to the infectious disease. The origins of modern-day mathematical modelling of diseases started with Kermack and McKendrick [40]. They constructed a simple deterministic (compartmental) model. The model was a success because it helped in predicting the behaviour of outbreaks which is similar to what is observed in many epidemics that have been recorded [15].

Several mathematical models have been used to study HIV/AIDS epidemics. These models have enabled us to have a better understanding of HIV/AIDS dynamics. These include knowing the short and long term impact of the disease in any given population [18]. These models enable us to know how changes in behaviour and preventive measures can affect transmission dynamics. The models also enable us to know how the disease is impacted by different population structures.

Dominik and Martin [92] described how mathematical models can be used to generate new hypotheses regarding the mechanism of disease progression and the principles underlying immunological control of HIV. One such control is immunotherapy, which helps to improve the immune responses against HIV and also helps in the control of the virus. These insights were applied to guide therapy regimes aimed at the long term control of HIV.

2.1 Earlier models for HIV/AIDS

The early models for HIV/AIDS do not incorporate the policy of treatment as prevention (TasP). The simplest HIV model has two compartments; susceptibles $S(t)$, i.e. individuals at risk of getting the infection, and infected individuals $I(t)$, popularly known as the SI epidemic model with disease-induced mortality. In the SI models, the assumption is that, once individuals are infected with HIV, they experience an increase in the mortality rate. This is probably the most basic model that can be constructed for HIV transmission and survival [38, 52]. The SI models are based on population averages with no random variations. Differential equations are used and analytical solutions obtained and with no curve fitting of the model to data.

The SI models were further improved because a simple SI model has an exponentially distributed time spent in the infectious stage, that is, the probability of surviving in the stage declines exponentially. This is not very realistic for HIV, where the duration of infectivity is long and the duration is subject to significant variation [52].

Maia [52] proposed a model to fit the world HIV/AIDS prevalence data. The SI model was improved by dividing the infected class, $I(t)$, into four subclasses: $I_1(t), I_2(t), I_3(t)$, and $I_4(t)$ in which individuals in all the four subclasses can infect the susceptible individuals. The disease-induced mortality is from the I_4 class only. The model was fitted to the HIV/AIDS prevalence data and the results show that the time spent in each of the infectious classes is approximately 3 years. The flowchart for the model is shown in Figure 2.1.

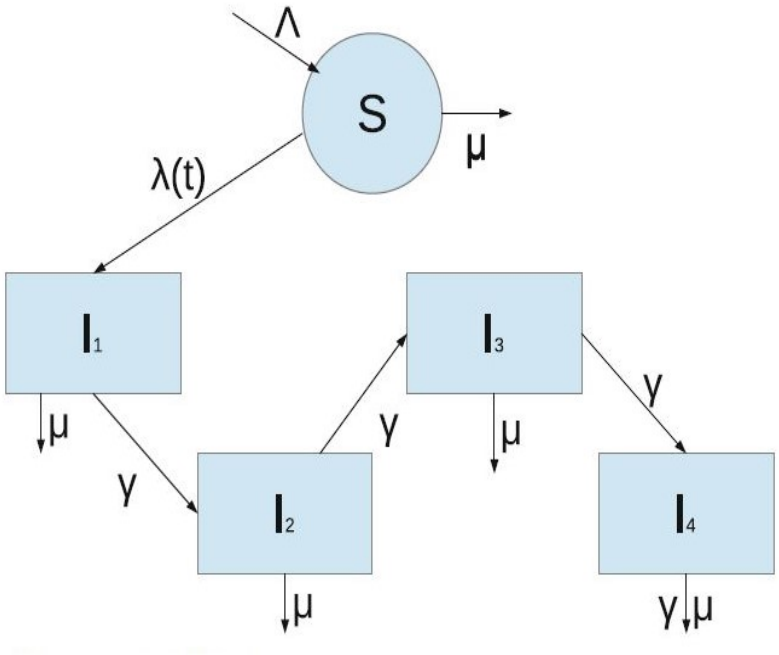


Figure 2.1: Flowchart of the HIV model. Source: [52].

Anulekha and Koushik [80] formulated a mathematical model that describes the spread of HIV. The model is divided into five classes: Susceptibles $S(t)$, infected $I(t)$, population initially not infected by HIV but going for unsafe sex $P_1(t)$, HIV infected population going for unsafe sex $P_2(t)$, population initially not infected but getting infected with HIV due to transfusion of contaminated blood, blood products or by sharing of contaminated needles $P_3(t)$. This model enables a better understanding of how HIV can escalate or increase in a population.

2.2 HIV/AIDS models driven by policy (test and treat)

Treatment as Prevention (TasP) can be described as HIV prevention programs, such as the use of ARV drugs to decrease the risk of HIV transmission. The Test and Treat strategy is a strategy in which the population that is at risk are screened for HIV infection and individuals that are diagnosed with HIV infection receive treatment immediately. According to Williams et al. [91], TasP has an important role to play in reducing HIV transmission

which will eventually help in bringing the HIV/AIDS epidemic to an end. Although, they also concluded that a lot of things still need to be learned, some obstacles to overcome still remain.

Several mathematical models have been used to study the dynamics of the HIV/AIDS epidemic with treatments. These models have enabled us to have a better understanding of the effects of treatment on infected individuals. We describe a few of the models relevant to this study below.

The first test and treat model was proposed by Granich et al. [31] in which they investigated the conditions under which the HIV epidemic could be driven towards elimination by universal voluntary HIV testing and immediate treatment with antiretroviral drugs. They used a stochastic model to determine the effect test and treat strategy on the reproductive number. They also used a deterministic model to determine the long-term dynamics of the HIV/AIDS epidemic, using South Africa as their case study for the generalized epidemic. They assumed that all HIV transmission was heterosexual. The population that was used was aged 15 years and older. As soon as they are diagnosed with HIV, individuals start antiretroviral treatment immediately. They concluded that universal voluntary HIV testing and immediate antiretroviral treatment, combined with present prevention approaches, could have a major effect on the severity of the HIV/AIDS epidemic. They also concluded that this approach merits further mathematical modelling, research, and broad consultation.

Nyabadza [61], proposed a model for the transmission of HIV with the inclusion of prevention strategies, such as the use of a condom, ARV drug treatment, and voluntary counselling and testing. The model was used to predict the potential impact of the strategies that are currently being used to control HIV/AIDS. The model was divided into four compartments: susceptible $S(t)$, infected $I(t)$, individuals under treatment $T(t)$ and those with AIDS $A(t)$. The study shows that multiple strategies can be useful in the control of the spread of the HIV epidemic. The model also shows that a reduction in the number of sexual contacts and the use of condoms has a significant impact in reducing the transmission of the disease.

Bhunu et al. [13] developed a two strain HIV/AIDS model with treatment which allows AIDS patients with sensitive HIV-strain to improve after treatment. This was presented as a system of non-linear ordinary differential equations. The model they developed classified the population that is sexually active into five classes, which are: susceptible (S), antiretroviral sensitive HIV infected (I_1), AIDS individuals with antiretroviral sensitive HIV (A_1), antiretroviral resistant HIV infected (I_2) and AIDS individuals with antiretroviral resistant HIV (A_2). The numerical solutions of the model show that the two strains co-exist when the reproduction number is more than 1. Furthermore, treatment may increase the total number of infective individuals but results in a decrease in the number of AIDS patients. Finally, the reproduction number analysis showed that as the use of antiretroviral increases, antiretroviral resistance will also increase.

Rahman et al. [70] developed an in-host model ($CD4^+$ T cell count based) mathematical model to study the impact of early treatment programs on HIV epidemic and the overall community-level immunity. The model is divided into seven classes: Susceptible $S(t)$; infected individuals with $CD4^+$ T cell count > 500 cells/mm^3, $I_1(t)$; infected individuals with $CD4^+$ T cell count between $350 - 500$ cells/mm^3, $I_2(t)$; infected individuals with $CD4^+$ T cell count < 350 cells/mm^3, $I_3(t)$; treated individuals with $CD4^+$ T cell count > 500 cells/mm^3, $T_1(t)$; treated individuals with $CD4^+$ T cell count between $350 - 500$ cells/mm^3, $T_2(t)$, treated individuals with $CD4^+$ T cell count < 350 cells/mm^3, $T_3(t)$.This model predicts that the early treatment of HIV reduces the new infections significantly and increases the community-level immunity. Although the treatment alone may not be enough to eliminate HIV epidemics, these findings, including community-level immunity, might provide helpful information for the proper implementation of HIV treatment programs.

Montaner et al. [54] also studied HIV treatment as prevention. They fitted two Poisson regression models over the study period in order to relate estimated HIV incidence and the number of individuals on HAART and the percentage of infected individuals that had viral suppression. They used population-level longitudinal data from province-wide (in Canada) registries including plasma viral load, CD4 count, drug resistance, HAART

use, HIV diagnoses, AIDS incidence, and HIV-related mortality. Their models suggested that for each increase of 100 individuals on HAART, the estimated HIV incidence decreased by 1.2% and also for every 1% increase in the number of individuals suppressed on HAART, the estimated HIV incidence also decreased by 1%. Their results also show that HAART expansion was associated with a decrease in morbidity, mortality and HIV transmission. Their findings suggest and agree with long-term effectiveness and sustainability of HIV treatment as prevention within an adequately resourced environment with no financial barriers to diagnosis, medical care or ARV drugs.

Nah et al. [57] proposed a simple mathematical model to understand how testing and treating have an influence on the population dynamics of HIV/AIDS. They divided the population into five compartments: susceptible, undiagnosed infected individuals without AIDS H_u, diagnosed infected individuals H_d, undiagnosed AIDS individuals A_u and diagnosed AIDS individuals A_d. They assumed that all diagnosed individuals are all under antiretroviral treatment. According to their findings, a decrease in HIV prevalence is associated with certain diagnosis coverage, care, and continued treatment. Their results also suggest for further research because sometimes HIV prevalence is not necessarily decreased because the test and treat strategy requires long-term, costly use of antiretroviral therapy.

Rufu et al. [74] studied the implementation of the test and treat policy for newly diagnosed people living with HIV in Zimbabwe in 2017. They used data gotten from sixteen mission hospitals in Zimbabwe that were implementing the test and treat program for people living with HIV. They analyzed the data using multivariate analysis. According to their study, it was the first from Zimbabwe to report on preliminary results of the test and treat approach at sixteen mission hospitals in four provinces of the country. Their findings were encouraging. Firstly, the 94% of people newly diagnosed with HIV were enrolled in care, and nearly 80% were initiated on antiretroviral treatment. They were unable to obtain reasons as to why some people did not enrol in HIV care. They concluded that the test and treat strategy was successful and feasible, not only in getting newly HIV-infected individuals initiated on antiretroviral treatment but also initiating the treatment on the

same day as being HIV tested. They also concluded that further research needs to be done to better understand the processes involved, benefits of the test and treat strategy and the potential risks involved in starting treatment and not adhering or attrition.

Narasimhamurthy and Leelavathy [58] proposed a non-linear mathematical model to study the transmission of HIV/AIDS in a population of varying size with treatment and vertical transmission under the assumption that due to sexual interaction of susceptibles and infectives, the infected babies are born and increase the growth of the infected population directly. The model is divided into five classes: susceptible $S(t)$, infected $I(t)$, pre-AIDS patients $p(t)$, treated class $T(t)$ and AIDS patients $A(t)$. They assumed that patients in pre-AIDS and AIDS classes are not able to produce children. According to their results, an increase in the rate of vertical transmission leads to an increase in the population of infectives which in turn increases the pre-AIDS and AIDS population.

Waziri et al. [88], also proposed a nonlinear deterministic model to study the dynamics of HIV/AIDS with treatment and vertical transmission. They divided the population into five compartments: susceptible $S(t)$, infectives $I(t)$, pre-AIDS patients $P(t)$ (this depends on their viral count), treated class $T(t)$ and AIDS patients $A(t)$. They assumed that the susceptibles become HIV infected as a result of sexual contact with the infectives which may also lead to the birth of infected children. A fraction of the newborn children contract HIV during birth and hence are recruited directly into the infectives class. Their results suggest that when the rate of vertical transmission is controlled, there will be a significant reduction in the spread of the disease.

2.3 HIV/AIDS models with dropouts

Despite the fact that a significant amount of research on the importance of enrolling in treatment for HIV infected individuals and also retaining in treatment has been done, infected individuals still drop out of treatment for one reason or the other and have negative effects on the disease dynamics. According to [31, 57, 91] the test and treat strategy only can not make the AIDS epidemic come to an end. The success of TasP is highly depen-

dent on infected individuals adhering to treatment. It is widely agreed that once antiretroviral treatment is started, it should not be interrupted. Incomplete viral suppression can cause the more sensitive strains of HIV to be resistant, which are harder to treat [66]. Therefore, it is important to do research on how individuals that drop out of ARV drugs affect the dynamics of HIV/AIDS.

The study by Schilkowsky et al. [76], was aimed at identifying factors that are associated with the health care of patients with HIV/AIDS who dropout. This study was developed in a specialized health care unit of a University hospital in Rio de Janeiro, Brazil, considering a stratified sample of adult patients including all dropout cases (155) and 44.0% of 790 cases under regular follow-up. They used Bivariate analysis to identify associations that are between health care dropout, demographic, socioeconomic and clinical variables. Logistic and Cox regression models were also used to identify the independent effects of the explanatory variables on risk for dropping out, in the latter by incorporating information on the outcome over time.

Ballot et al. [44], examined attrition from HIV treatment programs as a result of the relationship between patient volume, human resource levels, and patient characteristics. They used Cox proportional hazards models (regression model) to assess the association of patient volume, clinical staff burden, and pharmacy staff burden with attrition while adjusting for patient characteristics. After adjusting for patient characteristics, their results show that patients attending clinics with medium pharmacy staff burden and high pharmacy staff burden tend to have a higher risk of attrition. Likewise, patients that are attending clinics with higher clinical staff burden have a lower risk of attrition. Also, patients attending clinics with medium patient volume levels and high patient volume levels had a higher risk of attrition. They concluded that patients attending clinics with higher pharmacy staff burden had a higher risk of attrition. These results highlight a potential area within the health system where interventions could be applied to improve the retention of these patient population.

Chikomo in [19] modelled retention and attrition of HIV positive patients on ARV drugs for Warren Park Poly Clinic, Harare Province in the presence

of a test and treat strategy. An HIV mathematical model with a treatment option in the form of antiretroviral therapy for those infected with HIV was proposed. The population is divided into three compartments namely: $S(t)$ which represents the population that is susceptible or at risk of contracting the HIV virus at any time t, $I(t)$ represents those infected with the HIV virus and $T(t)$ represents those who accept to take treatment in the form of antiretroviral therapy. Infected individuals who, when initiated into treatment continue to take treatment as being retained in care. Therefore, $T(t)$ compartment can also be called the retention compartment. Also, individuals that drop out of treatment move back to the infected compartment. Therefore dropout is considered as a parameter in the proposed model. The model was fitted to data. According to the findings over the period from $2003 - 2017$, a total of 3236 infected individuals had been initiated for ART, 2519 of these were still retained in care and were regularly attending clinic visits and finally, 716 had dropped out of the care system. The model diagram is shown below;

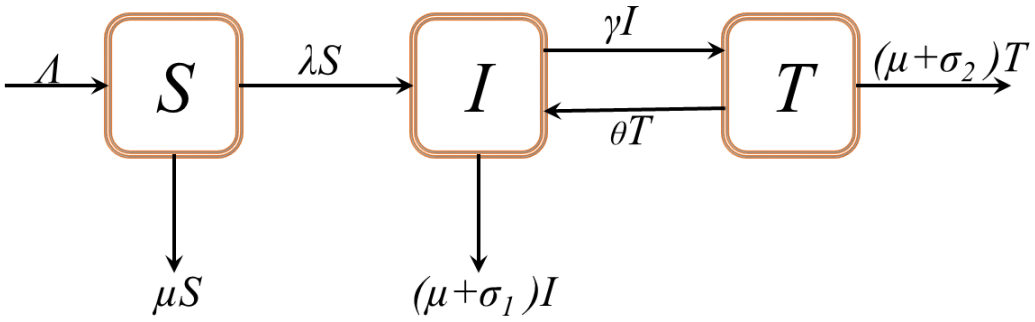


Figure 2.2: The model extended in this thesis.

In this research work, the model developed will focus on the potential impact of health care systems and dropouts on the dynamics of HIV/AIDS. The driving force for the drop out is driven by the side effects of the ARV

drugs. This work is innovative in proposing a function that describes how the level of side effects impacts the dropping rate for the infected on treatment. The effects of dropouts on the disease dynamics are studied in the following Chapter 3.

Chapter 3

Modelling the impact of different health care systems and dropouts on the dynamics of HIV/AIDS

3.1 Introduction

The world as a whole is faced with a diverse number of health problems in which the human immunodeficiency syndrome (HIV/AIDS) is one of the leading global health problems [6, 83]. The rate at which HIV infection has been spreading and the mortality due to the disease over the years have led to immense medical and scientific research [81]. According to the global HIV statistics, 76.1 million [65.2 – 88.0 million] people have become infected with HIV and 35.0 million [28.9 – 41.5 million] people have died from AIDS-related illnesses since the start of the epidemic. As of 2016, 36.7 million [30.8 – 42.9 million] people were living with HIV, 1.8 million [1.6 – 42.1 million] people became newly infected with HIV and 1 million [830 000 – 1.2 million] people died from AIDS-related illnesses [84]. Due to the mortality caused by HIV/AIDS, a significant amount of research has been done and still ongoing so as to provide effective prevention techniques and find a possible cure. However, to date, no HIV cure is available which implies that the only fight against the disease remains its management [3]. National Institute of Allergy and Infectious Diseases (NIAID) has helped in fostering and promoting the development of highly active antiretroviral therapy (HAART) that has led HIV infection from being fatal to a chronic condition

that can be managed [20, 59]. As a result of this, an HIV infected person can live a near-normal lifespan if they start the antiretroviral treatment early regardless of the CD4 count [42, 79]. The use of antiretroviral treatment will slow down the progression of HIV to AIDS [23, 32, 71]. Globally, 20.9 million people are on antiretroviral therapy as of 2017 and AIDS-related deaths have fallen by 48% since it had its pick in 2005 [84]. Likewise, infected individuals can go for antiretroviral treatment in either the private health care system or the public health care system due to affordability.

Despite the fact that there are advances in the treatment of HIV/AIDS, it is still very difficult to guarantee that patients that are diagnosed with HIV/AIDS will continue with the necessary treatment. This is not only for the patient to use ARV drugs appropriately and effectively but also for them to always be available for outpatient health care services [76]. Various factors can lead to patients dropping out of ARV treatment programs. The primary causes of patient dropouts are the drug side effects, poor adherence, and poor health care services [25].

The importance of staying on ARV treatment has been highlighted by many researchers, see for instance [25, 41]. Despite the advocacy and media campaigns on the need to stay on treatment once one has started, a number of dropouts are still being seen especially in resource-constrained communities. Mathematical models to investigate HIV treatment and associated challenges have been presented. Schilkowsky et al. [76] investigated factors associated with HIV/AIDS treatment dropouts considering the CD4 count. Su et al. [78] also considered dropout as a result of the loss of treatment follow-up from the health care system. Chikomo [19] also considered dropout as a result of death and loss of follow-up from the health care system for Warren Park Poly Clinic in Harare, Zimbabwe.

We consider the side effects of the ARV drugs as the driving force behind dropouts. Side effects of ARV drugs can arise as a result of taking drugs for a longer period of time, other medications interacting with HIV drugs and non-adherence to ARV treatment plans. Some of the common side effects of ARV drugs are as follows; loss of appetite, Lipodystrophy (this is a condition that makes people lose or gain fat in a certain area of the body), di-

arrhoea, fatigue, allergic reactions, nausea and vomiting, trouble sleeping, etc [16, 53]. Therefore, we assume that dropouts from private and public health care systems respectively are influenced by the side effects of the antiretroviral drugs. The most important aspect of side effects is the dosage or amount of exposure to the drugs.

3.2 Model formulation

The human population, $N(t)$, is partitioned into seven classes or compartments. The susceptibles, $S(t)$, which are those that are at risk of getting infected at any time t; the infectives, $I(t)$, that is those that have been infected with the HIV virus; $T_1(t)$, those that are on antiretroviral therapy and in a private health care system; $T_2(t)$, those that are on antiretroviral therapy but in the public health care system; $D_1(t)$, those that dropout from antiretroviral therapy in the private health care system; $D_2(t)$, those that dropout from antiretroviral therapy in the public health care system; and $A(t)$, those with full-blown AIDS, whom we assume, once they are in that class the health care system to which they came from is immaterial.

Thus, at any time $t \geq 0$, the total population is given by

$$N(t) = S(t) + I(t) + T_1(t) + T_2(t) + D_1(t) + D_2(t) + A(t). \tag{3.1}$$

Susceptible individuals $S(t)$ are recruited at a rate π, through births and immigration. We do not consider the direct recruitment of infected individuals. Individuals in all classes die naturally at a rate μ. Susceptible individuals acquire HIV infection at a rate λ, referred to as the force of infection, so that

$$\lambda = \frac{\beta(I(t) + \eta_1 T_1(t) + \eta_2 T_2(t) + \eta_3 D_1(t) + \eta_4 D_2(t) + \eta_5 A(t))}{N}, \tag{3.2}$$

where η_i, $i = 1, 2, 3, 4, 5$, are modification parameters due to infectiousness of all the other classes relative to I. The parameter β is the effective contact rate i.e the contact that results in infection per unit time. We shall assume that $\eta_1, \eta_2 \in (0, 1]$ due to the effect of treatment in reducing the spread of HIV while $\eta_3, \eta_4, \eta_5 > 1$ due to increased viral loads as a result of dropping

out from treatment programs and development of AIDS. The rate at which infected individuals are absorbed into treatment is γ with a proportion ρ moving into private health care and the remainder move into public health care. Those that are not screened for the disease will eventually progress to the AIDS class at a rate α_1. Individuals in both treatment classes can drop out of treatment as a result of the side effects of ARV drugs.

Functional responses have been used to model human behaviour, see for instance [33, 60]. An example is a functional relationship proposed by Njagarah [60], which was used to model person-to-person contact in cholera transmission dynamics. The author proposed a contact rate function that is dependent on the proportion of the population that practices proper hygiene of the form

$$f(H) = \frac{\beta_h^{max}}{1 + Ae^{\eta H}}. \tag{3.3}$$

where the constant A is the scale parameter, η the shape parameter, β_h^{max} is the rate of spread of the pathogen through person-to-person contact and H is the level of hygiene. From equation 3.3, the effective contact rate will reduce with increased level of hygiene, H.

Therefore, in this thesis, we propose a functional relationship $f(\xi)$ which is driven by the side effects to ARV drugs. It is plausible to believe that the dropout rate will increase with increased levels of side effects. We assume that individuals that drop out, return to treatment in their respective categories in relation to the health care system they can afford. We also assume that individuals do not change health care systems. We argue that individuals access the type of health care, especially HIV treatment, depending on their level of affordability. In this model, we propose a dropout function that is dependent on the side effects of antiretroviral drugs. We suggest a sigmoidal function of the form (3.4). The function has a similar curve to that of the logistic growth function.

$$f(\xi_i) = \frac{\omega_0 + \omega_{max}\xi_i^q}{k + \xi_i^q}, \tag{3.4}$$

where q is the shape parameter, k is the half saturated constant, ω_0 is the minimum dropout rate, ω_{max} is the maximum dropout rate, ξ_i, $i = 1, 2$

denotes the side effects level of the antiretroviral drugs. We assume that $f(\xi_1) < f(\xi_2)$ given there are likely to be more dropouts from the public health care system.

A typical example of a curve that depicts the change in the dropout rate is shown in Figure 3.1.

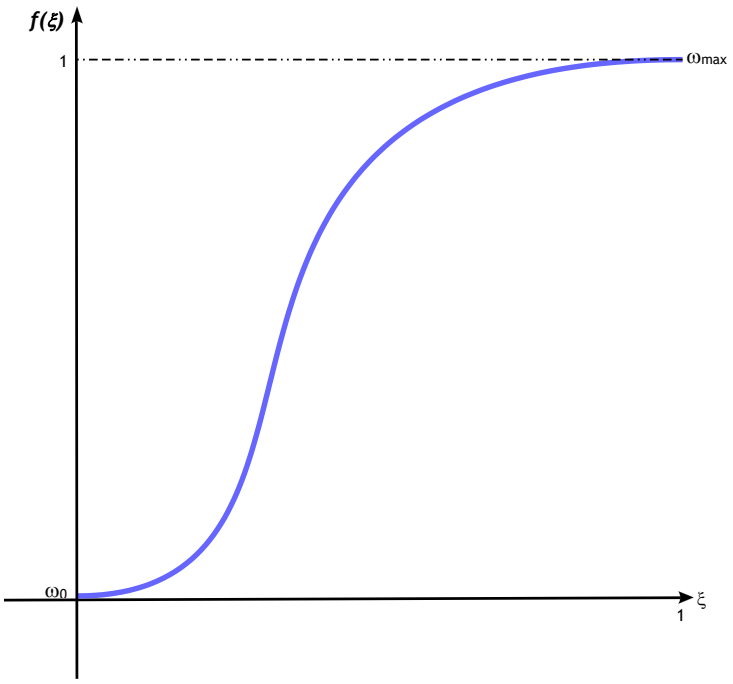


Figure 3.1: Dropout rate as a function of side effects level for people on antiretroviral drugs.

The drop out rates is model by function (3.4). We allow the dropouts to re-enter treatment programs at rates θ_1 and θ_2 for the private and public health care systems respectively although at different rates. Individuals under treatment in the private and public health care systems eventually develop AIDS at rates α_2 and α_3 respectively. Those who drop out will also develop AIDS at rates α_4 and α_5 for the private and public health care systems respectively. We assume a disease-related mortality rate, δ for those in the AIDS class. The model description presented is reinforced by the model diagram in Figure 3.2.

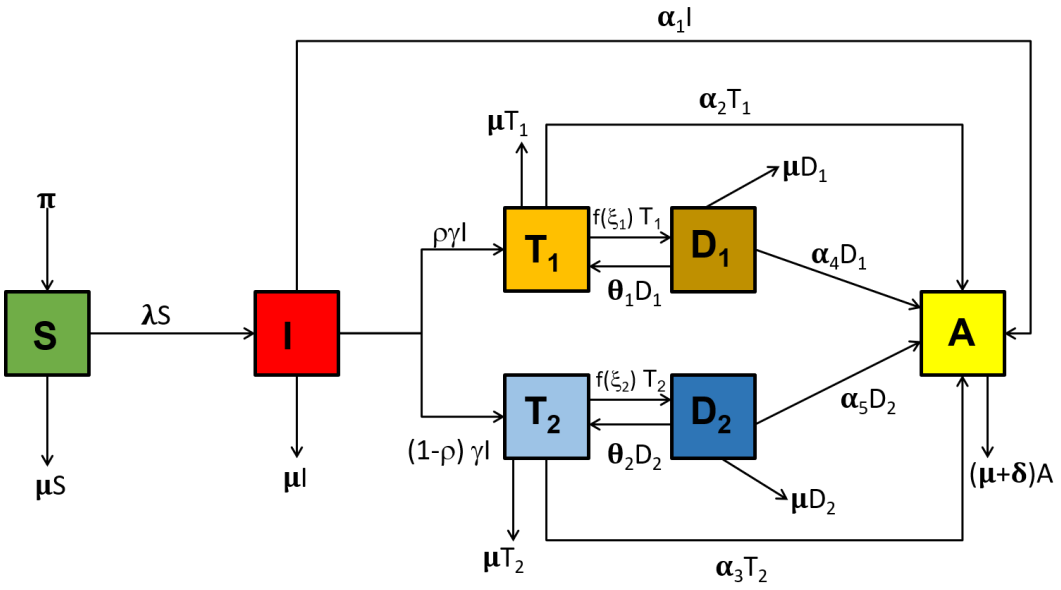


Figure 3.2: The flow diagram showing the HIV/AIDS dynamics

The assumptions, model description and Figure 3.2 give rise to the following set of nonlinear ordinary differential equations

$$\left.\begin{aligned}
\frac{dS}{dt} &= \pi - (\lambda + \mu)S, \\
\frac{dI}{dt} &= \lambda S - (\mu + \alpha_1 + \gamma)I, \\
\frac{dT_1}{dt} &= \gamma\rho I - (\mu + \alpha_2 + f(\xi_1))T_1 + \theta_1 D_1, \\
\frac{dT_2}{dt} &= \gamma(1-\rho)I - (\mu + \alpha_3 + f(\xi_2))T_2 + \theta_2 D_2, \\
\frac{dD_1}{dt} &= f(\xi_1)T_1 - (\mu + \theta_1 + \alpha_4)D_1, \\
\frac{dD_2}{dt} &= f(\xi_2)T_2 - (\mu + \theta_2 + \alpha_5)D_2, \\
\frac{dA}{dt} &= \alpha_1 I + \alpha_2 T_1 + \alpha_3 T_2 + \alpha_4 D_1 + \alpha_5 D_2 - (\mu + \delta)A.
\end{aligned}\right\} \tag{3.5}$$

with initial conditions $S(0) = S_0 > 0$, $I(0) = I_0 \geq 0$, $T_1(0) = T_{1(0)} \geq 0$,

$T_2(0) = T_{2(0)} \geq 0$, $D_1(0) = D_{1(0)} \geq 0$, $D_2(0) = D_{2(0)} \geq 0$, $A(0) = A_0 > 0$, where we assume that all the model parameters are positive.

3.3 Model properties and analysis

3.3.1 Positivity of solutions

We want to consider the positivity of the model system (3.5). We want to prove that all the state variables remain non-negative and the solutions of the model (3.5) with positive initial conditions will remain positive for all $t \in [0, \infty)$. This is definitely a condition to check since the model monitors the human population. And the system of equations in (3.5) monitors the flow between seven sub-population. Hence all parameters are assumed to be non-negative.

Theorem 3.3.1. *Given the initial conditions of the model system* (3.5) *are* $S(0) > 0, I(0) > 0, T_1(0) > 0, T_2(0) > 0, D_1(0) > 0, D_2(0) > 0, A(0) > 0$. *The resulting solutions are all non-negative for all* $t \in [0, \infty)$.

Proof. It follows from the first equation of the model system (3.5) that

$$\frac{dS}{dt} = \pi - (\lambda + \mu)S \geq -(\lambda + \mu)S.$$

Therefore

$$\frac{dS}{dt} \geq -(\lambda + \mu)S. \tag{3.6}$$

Integrating both sides of equation (3.6) gives

$$S(t) \geq S(0) \exp\left[\int_0^t -(\lambda + \mu)dt\right] > 0.$$

Hence $S(t)$ is always positive for $S(0) > 0$.

Similarly, from the second equation of the model system (3.5), we obtain

$$\frac{dI}{dt} = \lambda S - (\alpha_1 + \mu + \gamma)I \geq -(\alpha_1 + \mu + \gamma)I,$$

whose solution is given by

$$I(t) \geq I(0)e^{-(\alpha_1+\mu+\gamma)} > 0.$$

Similarly, it can be shown that the state variables $T_1(0) > 0, T_2(0) > 0$, $D_1(0) > 0, D_2(0) > 0, A(0) > 0$, for all $t > 0$ respectively. Hence the proof. □

3.3.2 Invariant region

Theorem 3.3.2. *The set* $\Omega = \left\{(S, I, T_1, T_2, D_1, D_2, A) \in \mathbb{R}^7_+ | 0 \leq N \leq \frac{\pi}{\mu}\right\}$ *is positively invariant as a globally attractive set of model system* (3.5).

Proof. The rate of change of the total population given by

$$\frac{dN}{dt} = \pi - \mu N - \delta A \leq \pi - \mu N. \tag{3.7}$$

Solving equation (3.7) gives

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

Therefore

$$N(t) \leq \frac{\pi}{\mu} + \left(N(0) - \frac{\pi}{\mu}\right) e^{-\mu t}. \tag{3.8}$$

□

It is important to note that if $N(0) < \frac{\pi}{\mu}$ then $N(t) \leq \frac{\pi}{\mu}$. Therefore, every solution with initial condition in $\mathbb{R}^7_+$ remains in that region. This implies that the set Ω is a positively invariant set for model system (3.5). On the other hand, if $N(0) > \frac{\pi}{\mu}$ then $\lim_{t\to\infty} N(t) = \frac{\pi}{\mu}$. So the set Ω is a globally attractive set for the model system (3.5). Thus the model is well posed and it can be said that it is epidemiologically meaningful.

3.3.3 Steady states analysis

In this section, we consider two steady states for the model system (3.5), the disease-free equilibrium is the point in which there is no more disease that is present in the population and the endemic equilibrium is the state in which disease persist in the population.

We obtain the steady (equilibrium) points by setting the right-hand sides of the system of equations (3.5) to zero so that

$$\pi - (\lambda + \mu)S^* = 0 \tag{3.9}$$
$$\lambda S^* - (\alpha_1 + \mu + \gamma)I^* = 0 \tag{3.10}$$
$$\gamma\rho I^* - (\mu + \alpha_2 + f(\xi_1))T_1^* + \theta_1 D_1^* = 0 \tag{3.11}$$
$$\gamma(1-\rho)I^* - (\mu + \alpha_3 + f(\xi_2))T_2^* + \theta_2 D_2^* = 0 \tag{3.12}$$
$$f(\xi_1)T_1^* - (\theta_1 + \mu + \alpha_4)D_1^* = 0 \tag{3.13}$$
$$f(\xi_2)T_2^* - (\theta_2 + \mu + \alpha_5)D_2^* = 0 \tag{3.14}$$
$$\alpha_1 I^* + \alpha_2 T_1^* + \alpha_3 T_2^* + \alpha_4 D_1^* + \alpha_5 D_2^* - (\mu + \delta)A^* = 0. \tag{3.15}$$

From equation (3.13) we have

$$D_1^* = \frac{f(\xi_1)T_1^*}{(\mu + \theta_1 + \alpha_4)} = \psi_1 T_1^*, \tag{3.16}$$

where

$$\psi_1 = \frac{f(\xi_1)}{(\mu + \theta_1 + \alpha_4)}.$$

$\frac{1}{(\mu + \theta_1 + \alpha_4)}$ is the average time an infected individual stays in drop out class D_1, from the private health care system.
Equation (3.14) gives

$$D_2^* = \frac{f(\xi_2)T_2^*}{(\mu + \theta_2 + \alpha_5)} = \psi_2 T_2^*, \tag{3.17}$$

where

$$\psi_2 = \frac{f(\xi_2)}{(\mu + \theta_2 + \alpha_5)}.$$

$\frac{1}{(\mu + \theta_2 + \alpha_5)}$ is the average time an infected individual stays in the drop out class, D_2, from the public health care system.
Substituting equation (3.16) into (3.11) we have

$$T_1^* = \frac{\gamma\rho I^*}{(\mu + \alpha_2 + f(\xi_1) - \theta_1\psi_1)} = \psi_3 I^*, \tag{3.18}$$

$\frac{1}{(\mu + \alpha_2 + f(\xi_1))}$ is the average time an infected individual stays in compartment T_1,

where

$$\begin{aligned}\psi_3 &= \frac{\gamma\rho}{(\mu+\alpha_2+f(\xi_1)-\theta_1\psi_1)} = \frac{\gamma\rho}{(\mu+\alpha_2+f(\xi_1))-\dfrac{\theta_1 f(\xi_1)}{\mu+\theta_1+\alpha_4}} \\ &= \frac{\gamma\rho}{(\mu+\alpha_2+f(\xi_1))\left[1-\left(\dfrac{\theta_1}{\mu+\theta_1+\alpha_4}\right)\left(\dfrac{f(\xi_1)}{\mu+\alpha_2+f(\xi_1)}\right)\right]} \\ &= \frac{\gamma\rho}{(\mu+\alpha_2+f(\xi_1))(1-x_1x_2)} = \frac{\gamma\rho}{(\mu+\alpha_2+f(\xi_1))(1-\phi_1)},\end{aligned}$$

where

$$x_1 = \frac{\theta_1}{(\mu+\theta_1+\alpha_4)}, \qquad x_2 = \frac{f(\xi_1)}{(\mu+\alpha_2+f(\xi_1))}$$
$$\phi_1 = x_1x_2.$$

We note that x_1 is the proportion of individuals that drop out from the private health care system class D_1 that move back to treatment in the private health care system T_1 and x_2 is the proportion of individuals in the private health care system T_1 that drop out from treatment.
Therefore,
ϕ_1 is the proportion of individuals that drop out of D_1 and are reintegrated into treatment in the private health care system, T_1.

Substituting equation (3.17) into (3.12) we have

$$T_2^* = \frac{\gamma(1-\rho)I^*}{(\mu+\alpha_3+f(\xi_2)-\theta_2\psi_2)} = \psi_4 I^*, \tag{3.19}$$

$\dfrac{1}{(\mu+\alpha_3+f(\xi_2))}$ is the average time an infected individual stays in private health care system class T_1

and

$$\psi_4 = \frac{\gamma(1-\rho)}{(\mu+\alpha_3+f(\xi_2)-\theta_2\psi_2)} = \frac{\gamma(1-\rho)}{(\mu+\alpha_3+f(\xi_2))-\dfrac{\theta_2 f(\xi_2)}{\mu+\theta_2+\alpha_5}}$$

$$= \frac{\gamma(1-\rho)}{(\mu+\alpha_3+f(\xi_2))\left[1-\left(\dfrac{\theta_2}{\mu+\theta_2+\alpha_5}\right)\left(\dfrac{f(\xi_2)}{\mu+\alpha_3+f(\xi_2)}\right)\right]}$$

$$= \frac{\gamma(1-\rho)}{(\mu+\alpha_3+f(\xi_2))(1-x_3x_4)} = \frac{\gamma(1-\rho)}{(\mu+\alpha_3+f(\xi_2))(1-\phi_2)},$$

where

$$x_3 = \frac{\theta_2}{\mu+\theta_2+\alpha_5}, \qquad x_4 = \frac{f(\xi_2)}{\mu+\alpha_3+f(\xi_2)}$$
$$\phi_2 = x_3x_4.$$

The epidemiological interpretation of the expression is such that;
x_3 is the proportion of individual that drop out from public health care system compartment D_2, and move back to the treatment class T_2,
x_4 is the proportion of individuals in the public health care system class T_2, that drop out of treatment.
Therefore
ϕ_2 is the proportion of individuals that drop out from compartment D_2 and are reintegrated into the treatment class T_2.
Substituting equation (3.18) into (3.16) we have

$$D_1^* = \psi_1\psi_3 I^* = \psi_5 I^*, \tag{3.20}$$

where

$$\psi_5 = \psi_1\psi_3 = \frac{f(\xi_1)}{(\mu+\theta_1+\alpha_4)} \times \frac{\gamma\rho}{(\mu+\alpha_2+f(\xi_1))(1-\phi_1)}$$

$$= \frac{f(\xi_1)}{(\mu+\alpha_2+f(\xi_1))} \times \frac{\gamma\rho}{(\mu+\theta_1+\alpha_4)(1-\phi_1)} = \frac{x_2\gamma\rho}{(\mu+\theta_1+\alpha_4)(1-\phi_1)}.$$

Substituting equation (3.19) into (3.17) we have

$$D_2^* = \psi_2\psi_4 I^* = \psi_6 I^*, \tag{3.21}$$

where

$$\psi_6 = \psi_2\psi_4 = \frac{f(\xi_2)}{(\mu+\theta_2+\alpha_5)} \times \frac{\gamma(1-\rho)}{(\mu+\alpha_3+f(\xi_2))(1-\phi_2)}$$

$$= \frac{f(\xi_2)}{(\mu+\alpha_3+f(\xi_2))} \times \frac{\gamma(1-\rho)}{(\mu+\theta_2+\alpha_5)(1-\phi_2)} = \frac{x_4\gamma(1-\rho)}{(\mu+\theta_2+\alpha_5)(1-\phi_2)}.$$

Substituting equations (3.18), (3.19), (3.20) and (3.21) into (3.15) we have

$$A^* = \frac{(\alpha_1+\alpha_2\psi_3+\alpha_3\psi_4+\alpha_4\psi_5+\alpha_5\psi_6)I^*}{(\mu+\delta)} = \psi_7 I^*, \tag{3.22}$$

where

$$\psi_7 = \frac{(\alpha_1+\alpha_2\psi_3+\alpha_3\psi_4+\alpha_4\psi_5+\alpha_5\psi_6)}{(\mu+\delta)}$$

$$= \frac{1}{(\mu+\delta)}\left[\alpha_1 + \frac{\alpha_2}{(\mu+\alpha_2+f(\xi_1))} \times \frac{\gamma\rho}{(1-\phi_1)} + \frac{\alpha_3}{(\mu+\alpha_3+f(\xi_2))} \times \frac{\gamma(1-\rho)}{(1-\phi_2)} + \frac{\alpha_4}{(\mu+\theta_1+\alpha_4)} \times \frac{x_2\gamma\rho}{(1-\phi_1)} + \frac{\alpha_5}{(\mu+\theta_2+\alpha_5)} \times \frac{x_4\gamma(1-\rho)}{(1-\phi_2)}\right]$$

$$= \frac{1}{(\mu+\delta)}\left[\alpha_1 + \frac{x_5\gamma\rho}{(1-\phi_1)} + \frac{x_6\gamma(1-\rho)}{(1-\phi_2)} + \frac{x_2x_7\gamma\rho}{(1-\phi_1)} + \frac{x_4x_8\gamma(1-\rho)}{(1-\phi_2)}\right],$$

where

$$x_5 = \frac{\alpha_2}{(\mu+\alpha_2+f(\xi_1))}, x_6 = \frac{\alpha_3}{(\mu+\alpha_3+f(\xi_2))}, x_7 = \frac{\alpha_4}{(\mu+\theta_1+\alpha_4)},$$
$$x_8 = \frac{\alpha_5}{(\mu+\theta_2+\alpha_5)}.$$

The epidemiological interpretations of some of the terms are as follows; x_5 is the proportion of individual in compartment T_1 that move to the AIDS compartment A.
x_6 is the proportion of individual in compartment T_2 that move to AIDS compartment A.
x_7 is the proportion of individual in compartment D_1 that move to AIDS compartment A and x_8 is the proportion of individual in compartment D_2 that move to AIDS compartment A.

Substituting equations (3.18), (3.19), (3.20), (3.21) and (3.22) into (3.2) we have

$$\lambda = \frac{\beta I^*(1+\eta_1\psi_3+\eta_2\psi_4+\eta_3\psi_5+\eta_4\psi_6+\eta_5\psi_7)}{N} = \frac{\psi_8 I^*}{N}, \tag{3.23}$$

where

$$\psi_8 = \beta(1+\eta_1\psi_3+\eta_2\psi_4+\eta_3\psi_5+\eta_4\psi_6+\eta_5\psi_7).$$

Substituting equation (3.23) into (3.10) we have

$$\frac{\psi_8 I^* S^*}{N} - (\mu+\gamma+\alpha_1)I^* = 0$$
$$\left[\frac{\psi_8 S^*}{N} - (\mu+\gamma+\alpha_1)\right] I^* = 0$$

Therefore

$$I^* = 0$$
$$\frac{S^*}{N} = \frac{(\mu+\gamma+\alpha_1)}{\psi_8} = \frac{1}{\mathfrak{R}_o}, \tag{3.24}$$

where

$$\mathfrak{R}_o = \frac{\psi_8}{(\mu+\gamma+\alpha_1)} = \left\{\frac{\beta}{(\mu+\gamma+\alpha_1)} + \frac{\beta\eta_1\gamma\rho}{(\mu+\alpha_2+f(\xi_1))(1-\phi_1)(\mu+\gamma+\alpha_1)}\right.$$

$$+\frac{\beta\eta_2\gamma(1-\rho)}{(\mu+\alpha_3+f(\xi_2))(1-\phi_2)(\mu+\gamma+\alpha_1)} + \frac{\beta\eta_3 x_2\gamma\rho}{(\mu+\theta_1+\alpha_4)(1-\phi_1)(\mu+\gamma+\alpha_1)}$$

$$+\frac{\beta\eta_4 x_4\gamma(1-\rho)}{(\mu+\theta_2+\alpha_5)(1-\phi_2)(\mu+\gamma+\alpha_1)} + \frac{\eta_5}{(\mu+\delta)}\left[\frac{\beta\alpha_1}{(\mu+\gamma+\alpha_1)}+\right.$$
$$\frac{\beta x_5\gamma\rho}{(1-\phi_1)(\mu+\gamma+\alpha_1)} + \frac{\beta x_6\gamma(1-\rho)}{(1-\phi_2)(\mu+\gamma+\alpha_1)} + \frac{\beta x_2 x_7\gamma\rho}{(1-\phi_1)(\mu+\gamma+\alpha_1)}$$
$$\left.\left.+\frac{\beta x_4 x_8\gamma(1-\rho)}{(1-\phi_2)(\mu+\gamma+\alpha_1)}\right]\right\}$$

$$= R_I + R_{T_1} + R_{T_2} + R_{D_1} + R_{D_2} + R_A. \tag{3.25}$$

and

$$R_I = \frac{\beta}{(\mu+\gamma+\alpha_1)}, \qquad R_{T_1} = \frac{\beta\eta_1\gamma\rho}{(\mu+\alpha_2+f(\xi_1))(1-\phi_1)(\mu+\gamma+\alpha_1)}$$

$$R_{T_2} = \frac{\beta\eta_2\gamma(1-\rho)}{(\mu+\alpha_3+f(\xi_2))(1-\phi_2)(\mu+\gamma+\alpha_1)},$$

$$R_{D_1} = \frac{\beta\eta_3 x_2\gamma\rho}{(\mu+\theta_1+\alpha_4)(1-\phi_1)(\mu+\gamma+\alpha_1)},$$

$$R_{D_2} = \frac{\beta\eta_4 x_4\gamma(1-\rho)}{(\mu+\theta_2+\alpha_5)(1-\phi_2)(\mu+\gamma+\alpha_1)}, \qquad R_A = \frac{1}{(\mu+\delta)}\left[\frac{\beta\alpha_1\eta_5}{(\mu+\gamma+\alpha_1)}+\right.$$
$$\frac{\beta x_5\gamma\rho\eta_5}{(1-\phi_1)(\mu+\gamma+\alpha_1)} + \frac{\beta x_6\gamma(1-\rho)\eta_5}{(1-\phi_2)(\mu+\gamma+\alpha_1)} + \frac{\beta x_2 x_7\gamma\rho\eta_5}{(1-\phi_1)(\mu+\gamma+\alpha_1)}+$$
$$\left.\frac{\beta x_4 x_8\gamma(1-\rho)\eta_5}{(1-\phi_2)(\mu+\gamma+\alpha_1)}\right]$$

$\frac{1}{(\mu+\gamma+\alpha_1)}$ is the average time an infected individual stays in the infected class I, while
$\frac{1}{(\mu+\delta)}$ is the average time an infected individual stays in the full blown AIDS class A.
If $I^* = 0$ then from equation (3.10) we have

$$S^* = \frac{\pi}{\mu}$$

A back substitution of $I^* = 0$ into equations (3.18), (3.19), (3.20), (3.21) and (3.22) results in the disease free equilibrium

$$E_0^* = (S^*, I^*, T_1^*, T_2^*, D_1^*, D_2^*, A^*) = \left(\frac{\pi}{\mu}, 0, 0, 0, 0, 0, 0\right).$$

Substituting equations (3.18), (3.19), (3.20) and (3.21) into (3.1) we have

$$N = S^* + (1+\psi_3+\psi_4+\psi_5+\psi_6)I^* = S^* + \psi_9 I^*, \tag{3.26}$$

where

$$\psi_9 = (1+\psi_3+\psi_4+\psi_5+\psi_6).$$

Substituting equation (3.26) into (3.24) we have

$$\frac{S^*}{S^* + \psi_9 I^*} = \frac{1}{\Re_o}$$
$$I^* = \frac{S^*(\Re_o - 1)}{\psi_9}. \tag{3.27}$$

Substituting equations (3.23), (3.26) and (3.27) into (3.9) we obtain

$$S^* = \frac{\pi \Re_o \psi_9}{(\Re_o - 1)\psi_8 + \mu \Re_o \psi_9} \tag{3.28}$$

$$I^* = \frac{\pi(\Re_o - 1)\Re_o}{(\Re_o - 1)\psi_8 + \mu \Re_o \psi_9} \tag{3.29}$$

Substituting equation (3.29) into (3.18), (3.19), (3.20), (3.21) and (3.22) we have the following

$$T_1^* = \frac{\psi_3 \pi(\Re_o - 1)\Re_o}{(\Re_o - 1)\psi_8 + \mu \Re_o \psi_9} \tag{3.30}$$

$$T_2^* = \frac{\psi_4 \pi(\Re_o - 1)\Re_o}{(\Re_o - 1)\psi_8 + \mu \Re_o \psi_9} \tag{3.31}$$

$$D_1^* = \frac{\psi_5 \pi(\Re_o - 1)\Re_o}{(\Re_o - 1)\psi_8 + \mu \Re_o \psi_9} \tag{3.32}$$

$$D_2^* = \frac{\psi_6 \pi(\Re_o - 1)\Re_o}{(R_0 - 1)\psi_8 + \mu \Re_o \psi_9} \tag{3.33}$$

$$A^* = \frac{\psi_7 \pi(\Re_o - 1)\Re_o}{(\Re_o - 1)\psi_8 + \mu \Re_o \psi_9} \tag{3.34}$$

The expressions $(S^*, I^*, T_1^*, T_2^*, D_1^*, D_2^*, A^*)$ give the endemic equilibrium E_1. Note that if $\Re_o = 1$, the endemic equilibrium collapses to the disease-free equilibrium. We thus have the following theorem on the existence of the endemic equilibrium.

Theorem 3.3.3. *If $\Re_o \leq 1$, model (3.5) always has a disease free equilibrium E_0. However, if $\Re_o > 1$ the model has a unique endemic equilibrium E_1.*

3.3.4 The reproductive number

The reproductive number $\mathfrak{R}_o$ generated in equation (3.25) can be defined as the average number of secondary infections caused by an infectious individual during the period of infection [21]. In epidemiology modelling, the reproductive number, $\mathfrak{R}_o$, is used to find the conditions necessary to eradicate a disease [55]. It can be derived by using the next-generation matrix method proposed by [21] and [86]. This involves finding the largest spectral radius of the next generation matrix. A conclusion is then made based on the value of $\mathfrak{R}_o$. This means that when $\mathfrak{R}_o < 1$, each infected individual produces on average, less than one new infected individual during his or infectious period and hence the disease dies out. If $\mathfrak{R}_o > 1$, each infected individual produces more than one new infected individual and hence the disease invades population.

$$\mathfrak{R}_o = \rho\left(FV^{-1}\right),$$

where, F is the new infection term and V other transfer terms.

$$F = \begin{pmatrix} \beta & \beta\eta_1 & \beta\eta_2 & \beta\eta_3 & \beta\eta_4 & \beta\eta_5 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \end{pmatrix}$$

and

$$V = \begin{pmatrix} Q_1 & 0 & 0 & 0 & 0 & 0 \\ -\gamma\rho & Q_2 & 0 & -\theta_1 & 0 & 0 \\ -\gamma(1-\rho) & 0 & Q_3 & 0 & -\theta_2 & 0 \\ 0 & -f(\xi_1) & 0 & Q_4 & 0 & 0 \\ 0 & 0 & -f(\xi_2) & 0 & Q_5 & 0 \\ -\alpha_1 & -\alpha_2 & -\alpha_3 & -\alpha_4 & -\alpha_5 & Q_6 \end{pmatrix}$$

where

$$\begin{aligned} &Q_1 = \mu + \alpha_1 + \gamma \qquad Q_2 = \mu + \alpha_2 + f(\xi_1) \quad Q_3 = \mu + \alpha_3 + f(\xi_2) \\ &Q_4 = \mu + \theta_1 + \alpha_4 Q_5 = \mu + \theta_2 + \alpha_5 \qquad Q_6 = \mu + \delta. \end{aligned} \tag{3.35}$$

The spectral radius of the next generation matrix FV^{-1} i.e the largest eigenvalue of FV^{-1}. is the model basic reproductive number, which is denoted by $\mathfrak{R}_o$ is given by

$$\rho(FV^{-1}) = \mathfrak{R}_o = R_I + R_{T_1} + R_{T_2} + R_{D_1} + R_{D_2} + R_A.$$

The reproductive number, and precisely the effective reproductive number, in equation (3.25) has the following epidemiological interpretations:

- R_I is the contribution of the infected individuals in I to the reproduction number.
- R_{T_1} is the contribution of the infected individuals in T_1 to the reproduction number.
- R_{T_2} is the contribution of the infected individuals in T_2 to the reproduction number.
- R_{D_1} is the contribution of the infected individuals in R_{D_1} to the reproduction number.
- R_{D_2} is the contribution of the infected individuals in R_{D_2} to the reproduction number.
- R_A is the reproduction number as a result of the individuals with full-blown AIDS in compartment A.

Theorem 3.3.4. *The disease free equilibrium is locally asymptotically stable if* $\mathfrak{R}_o < 1$ *and unstable if* $\mathfrak{R}_o > 1$.

Proof. The proof follows the result in [86]. □

3.3.5 Global stability of the equilibria

In this section, we prove the global stability of the model equilibria E_0 and E_1. To prove the global stability, Lyapunov functions, such as the ones used in [64], will be used to prove the global stabilities of the disease-free and endemic equilibrium.

3.3.5.1 Global stability of disease-free equilibrium

Theorem 3.3.5. *The disease-free equilibrium of the model system (3.5) is globally asymptotically stable in Ω if $\mathfrak{R}_o < 1$ and unstable otherwise.*

The proof of the theorem is given in Appendix A.1

3.3.5.2 Global stability of endemic equilibrium

To prove the global stability of the endemic equilibrium, we make an assumption that the population does not change over the modelling time. That is, $\pi = \mu N + \delta A$ holds. This assumption is made for mathematical tractability and may not be reflective of what would happen in reality especially in developing countries.

Theorem 3.3.6. *The endemic equilibrium of the model system (3.5) is globally asymptotically stable in Ω if $\pi = \mu N + \delta A$ and $\mathfrak{R}_o > 1$.*

The proof of the theorem is given in Appendix A.2

3.4 Numerical simulations

In this section, to illustrate the dynamic behaviour of model system (3.5), simulations are carried out in Matlab by using the range of parameters in Table 3.3 which are also used for the data fitting. We determine the population of dropouts from treatment when the reproduction number $\mathfrak{R}_o$ is greater than one and when it is less than one. A few of the parameters are known. The unknown parameters are therefore estimated. Therefore, it is important to carefully study the disease dynamics, putting into consideration individual differences, location, social-economic status while selecting parameter values. Our focus is on Zimbabwe given that the model will be validated using data from Warren Park in Zimbabwe. The death rate $\mu = 0.016$ was calculated from the life expectancy in Zimbabwe which was taken to be 61.16years [85]. However, according to statistics, the life expectancy of Zimbabwe has been varying, in 1992 it was 55.34years and later dropped to 44.11 in 2002 [85]. We used the following initial conditions for the classes in model system (3.5): $S(0) = 87768$, $I(0) = 10$, $T_1(0) = 6$, $T_2(0) = 5$, $D_1(0) = 4$, $D_2(0) = 6$, $A(0) = 0$. The values of the initial conditions were hypothetically chosen based on the HIV prevalence rates

in Harare, Zimbabwe [72], considering the population of Warren Park in Harare, Zimbabwe [24] and the data collected from Warren park polyclinic in Zimbabwe.

3.4.1 Application to data from Warren Park in Zimbabwe

Southern Africa is the hardest hit by the epidemic. Zimbabwe has been grossly affected by HIV, with the first reported HIV infection case in 1985 [28]. As of 2012, the Zimbabwe Demographic and Health Survey (ZDHS) had a national estimate of HIV prevalence at 15% [5]. Even though HIV/AIDS is a severe epidemic, prevalence has begun to show signs of decline in Zimbabwe but the country is still ranked among the top 10 countries in the world [4]. Warren Park polyclinic located in Harare, Zimbabwe, is one of the clinics that treat HIV/AIDS patients in Harare. Information from the Ministry of Health classifies Warren Park Poly Clinic as a Level 5 clinic-(with the highest ranking when it comes to data quality). This implies that they have entered into the Electronic Patient Monitoring System (EPMS) all patients who were in the hospital booklets that had HIV/AIDS since 2000.

In this section, we fit the model system (3.5) to the data of individuals that dropout from treatments which is obtained from Warren Park from $(2000 - 2017)$. We only make use of the available data from one clinic. For data fitting, parameters that give the best fit are estimated with the use of the Least Square method in Matlab, where the unknown parameters are estimated by assigning upper and lower bounds. The coefficient of determination R^2 (which is used to determine how well the model fits the data) is 0.773, this implies that the model fit the data with 77.3%.

Figure 3.3: The total number of enrollment into ART treatment from 2000 – 2017, retention and attrition at Warren Park Poly Clinic. A total of 3235 people had been initiated for ART, 2519 of these (77.867%) were still retained in care and were regularly attending clinic visits and 716 of these (22.132%) were found to have dropped out of the care system.

Table 3.1: Retention and attrition by disaggregation using age

Age group	Retention			Attrition		
	Male	Female	Total	Male	Female	Total
< 1						
$1 - 9$	9	11	20	4	2	6
$10 - 14$	14	12	26	3	6	9
$15 - 19$	7	22	29	6	6	12
$20 - 24$	16	93	109	10	28	38
$25 - 49$	550	1268	1818	165	371	536
≥ 50	225	292	517	51	64	115

From Table (3.1), it can be seen that there are no children that are under the age of 1 enrolled in treatment in the clinic. This shows that there has been a great effort in the prevention of mother to child transmission. Likewise, attrition was found to be higher among the age group $25 - 49$.

Table 3.2: Data set that shows the cumulative number of infected individuals that drop out of treatment in Warren Park, Zimbabwe from 2000-2017.

Year	Attrition from treatment
2000	0
2001	0
2002	0
2003	2
2004	2
2005	7
2006	22
2007	35
2008	53
2009	83
2010	136
2011	177
2012	219
2013	254
2014	412
2015	591
2016	712
2017	716

From Figure 3.4, the results show that the total number of people who drop out of treatments each year in Warren Park has been increasing. This also shows that each year there is always a record of individuals that are on ARV drugs but drop out of treatment in each year, a clear indication of the consistent data recording. Therefore, strategies must be put in place to make individuals that drop out of treatment return back to treatment.

Please note that the data use does not differentiate between private and public health care systems. Therefore, in the model fitting, we added together both the private and public health care systems.

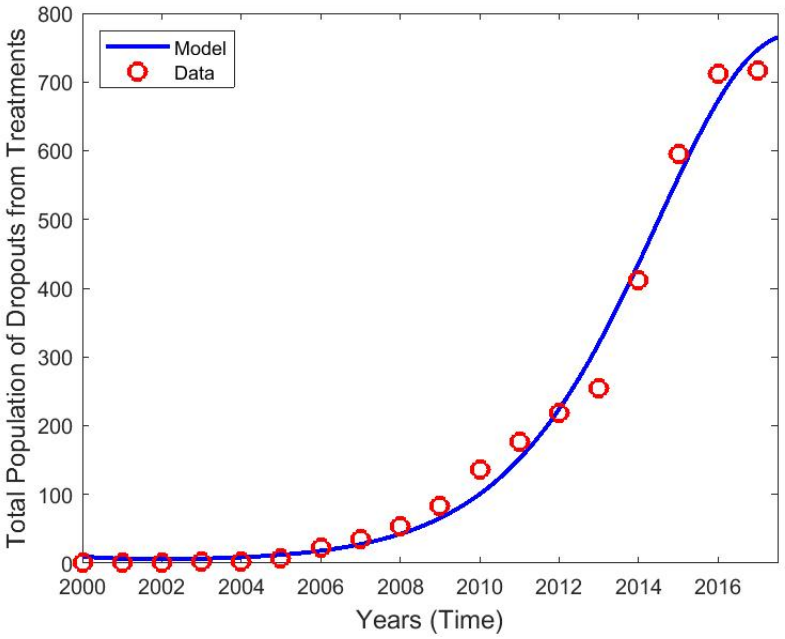
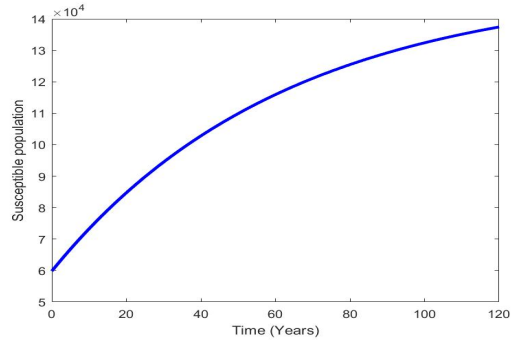


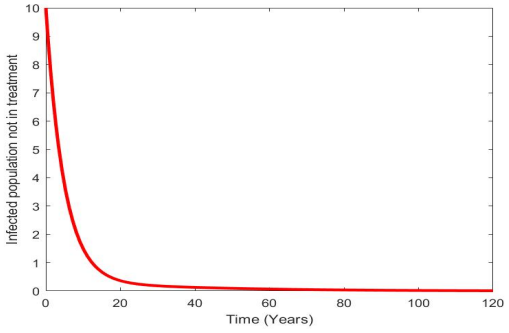
Figure 3.4: Model system (3.5) fitted to data for individuals that dropout from treatment from $(2000 - 2017)$. The solid line indicates the model fit to the data and the circles indicate the actual data.

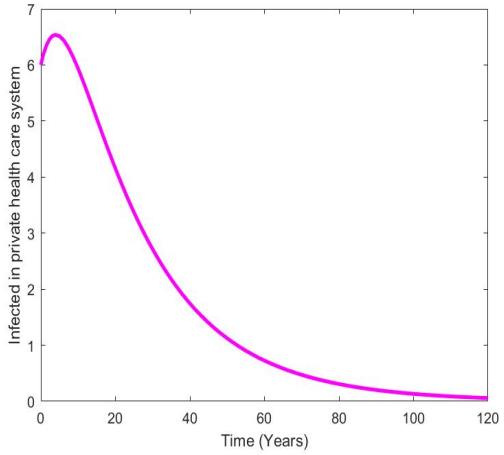
3.4.2 Time series plots

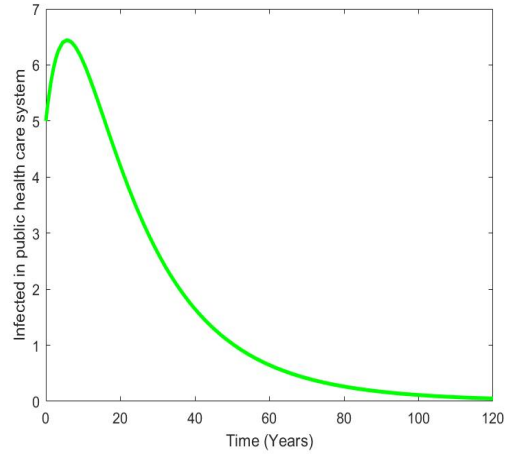
Table 3.3: Range of values used for the parameters and the estimated values that give the best fit. Units are in year^{-1}

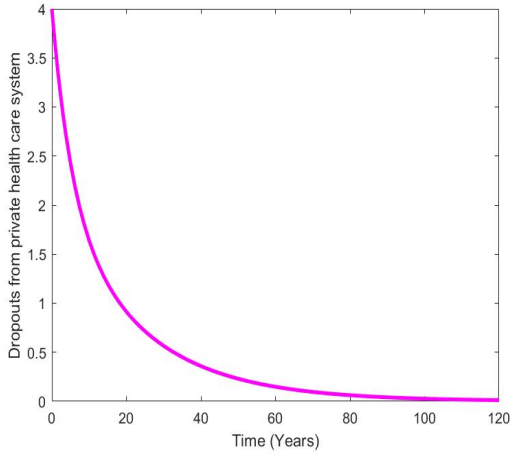
Parameter	Description	Range	Source
π	Recruitment	(2000 - 3000)	Estimated
μ	Natural mortality rate	0.016	[85]
γ	Rate at which I proceed to T_1 and T_2	(0 - 0.6)	Estimated
ρ	Proportion of γ to T_1 and T_2	(0.1 - 0.73)	Estimated
α_1	Progression rate to AIDS from infected individuals I	(0.05 - 0.2)	Estimated
α_2	Progression rate to AIDS from T_1	(0 - 0.5)	Estimated
α_3	Progression rate to AIDS from T_2	(0.0998 - 0.4)	Estimated
α_4	Progression rate to AIDS from D_1	(0.001 - 0.7)	Estimated
α_5	Progression rate to AIDS from T_2	(0.001 - 0.090)	Estimated
θ_1	Rate at which D_1 move back to T_1	0.02 - 0.099	Estimated
θ_2	Rate at which D_2 move back to T_2	(0.05 - 0.099)	Estimated
$f(\xi_1)$	Rate at which T_1 move to D_1 due to side effect of ART	(0 - 0.06)	Estimated
$f(\xi_2)$	Rate at which T_2 move to D_2 due to side effect of ART	(0 - 0.069)	Estimated
β	Effective transmission rate	(0.1 - 0.8)	Estimated
η_1	Relative infectivity due to T_1 class	(0.1 - 0.5)	Estimated
η_2	Relative infectivity due to T_2 class	(0.15 - 0.7)	Estimated
η_3	Relative infectivity due to D_1 class	(1 - 1.05)	Estimated
η_4	Relative infectivity due to D_2 class	(1 - 1.08)	Estimated
η_5	Relative infectivity due to AIDS class	(1 - 1.10)	Estimated
δ	Disease induced death rate	(0.001 - 0. 07)	Estimated

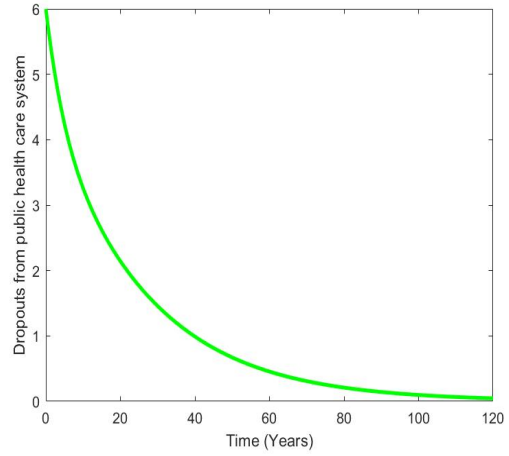












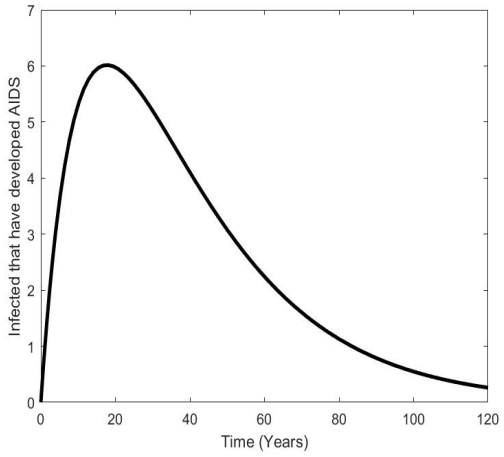
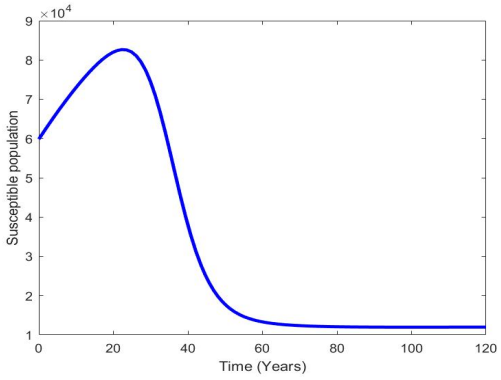
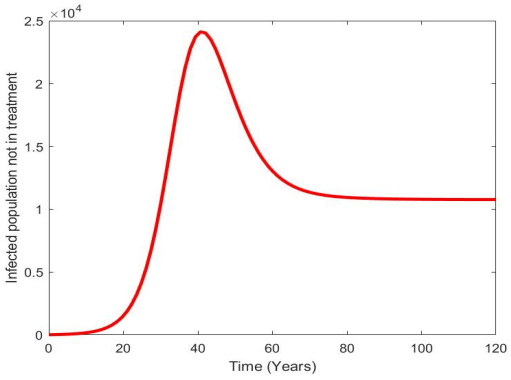


Figure 3.5: The result of simulations of the dynamics of Model system (3.5) for the estimated parameter values $\pi = 2412, \mu = 0.016, \gamma = 0.098, \rho = 0.45, \alpha_1 = 0.0412, \alpha_2 = 0.0214, \alpha_3 = 0.0312, \alpha_4 = 0.0521, \alpha_5 = 0.052, \theta_1 = 0.076, \theta_2 = 0.071, \rho = 0.45, \delta = 0.043, f(\xi_1) = 0.021, f(\xi_2) = 0.034, \eta_1 = 0.257, \eta_2 = 0.345, \eta_3 = 1.016, \eta_4 = 1.03, \eta_5 = 1.04, \beta = 0.004$, where $\Re_o = 0.0469$. The value of $\Re_o < 1$ describes a stable disease-free state.





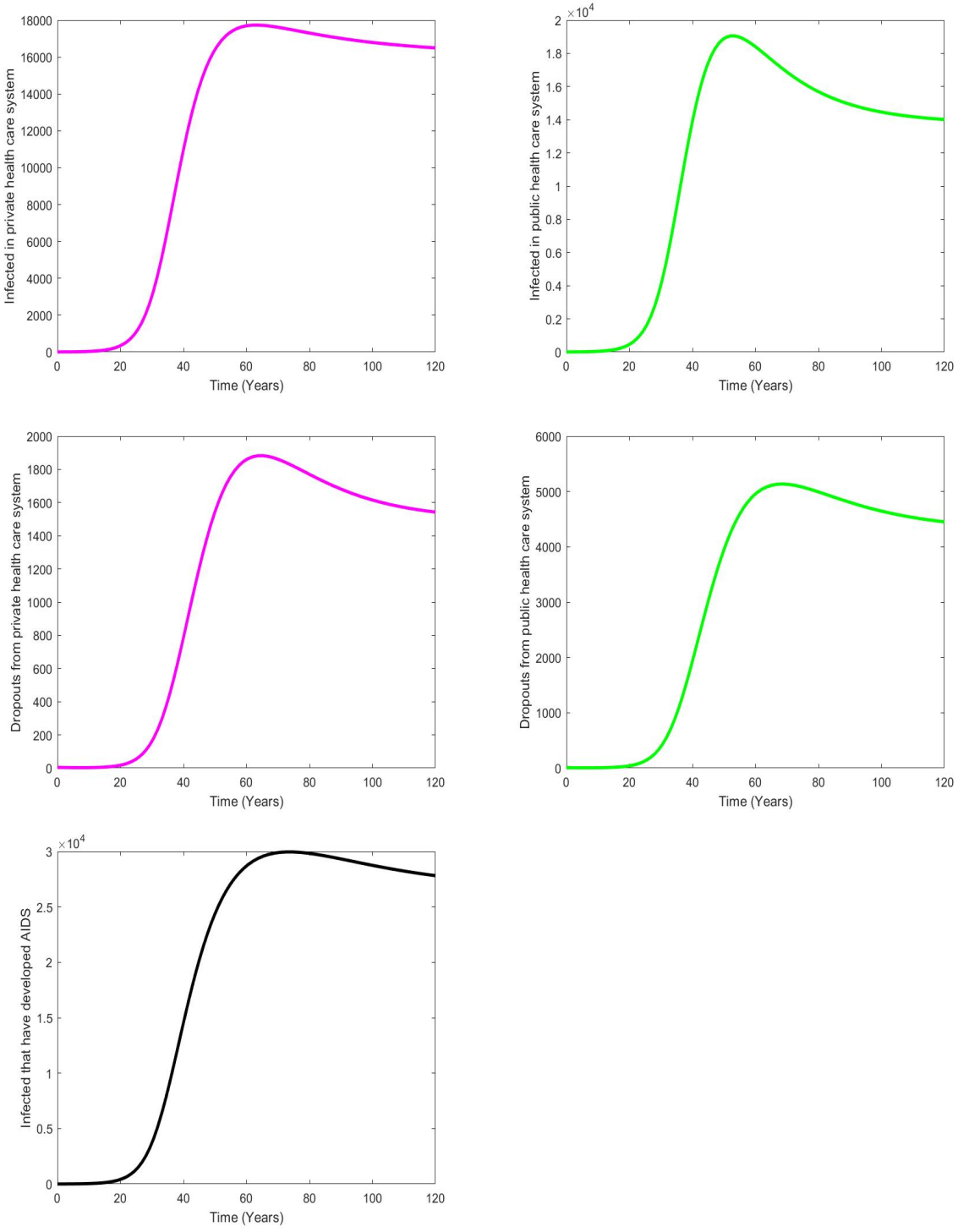


Figure 3.6: The result of simulations of the dynamics of Model system (3.5) for the estimated parameter values$\pi = 2412, \mu = 0.016, \gamma = 0.098, \rho = 0.45, \alpha_1 = 0.0412, \alpha_2 = 0.0214, \alpha_3 = 0.0312, \alpha_4 = 0.0521, \alpha_5 = 0.052, \theta_1 = 0.076, \theta_2 = 0.071, \rho = 0.45, \delta = 0.043, f(\xi_1) = 0.021, f(\xi_2) = 0.034, \eta_1 = 0.257, \eta_2 = 0.345, \eta_3 = 1.016, \eta_4 = 1.03, \eta_5 = 1.04, \beta = 0.313$, where $\mathfrak{R}_o = 5.1599$. The value of $\mathfrak{R}_o > 1$ describes a an endemic state.

In Figure 3.5, it can be observed that model system (3.5) approaches a stable disease-free state when reproduction number $\mathfrak{R}_o = 0.0469$. The time series plots for the infected and dropouts reduce to zero asymptotically. The same trends are depicted for the treatments and AIDS compartments. This implies that the disease-free equilibrium is globally stable when $\mathfrak{R}_o < 1$ and unstable otherwise.

In Figure 3.6, it can also be observed that the model system (3.5) is at a stable endemic state since the reproduction number $\mathfrak{R}_o = 5.1599$. The infected and dropouts compartments increases due to the fact that the disease persists in the population. It can also be seen that the private health care system class of infectives not under treatment peaks at close to 18000 when compared to close to 20000 of that of the public health care system.

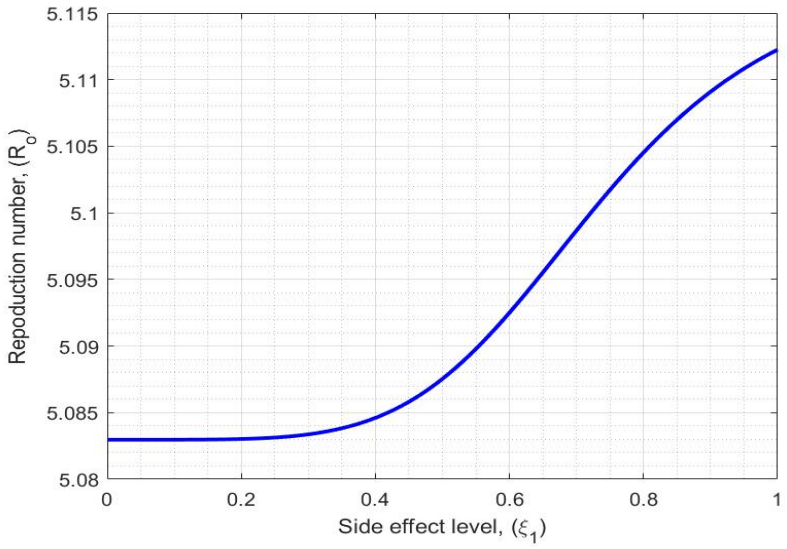


Figure 3.7: $\mathfrak{R}_o$ as a function of side effect level of people on ARV drugs in the private health care system. The rest of the parameter values are: $\omega_{max} = 0.7$, $\omega_0 = 0.1$, $k = 0.1, q = 0.6$, $\pi = 2412, \mu = 0.016, \gamma = 0.098, \rho = 0.45, \alpha_1 = 0.0412, \alpha_2 = 0.0214, \alpha_3 = 0.0312, \alpha_4 = 0.0521, \alpha_5 = 0.052, \theta_1 = 0.076, \theta_2 = 0.071, \rho = 0.45, \delta = 0.043, f(\xi_1) = 0.021, \eta_1 = 0.257, \eta_2 = 0.345, \eta_3 = 1.016, \eta_4 = 1.03, \eta_5 = 1.04, \beta = 0.313$.

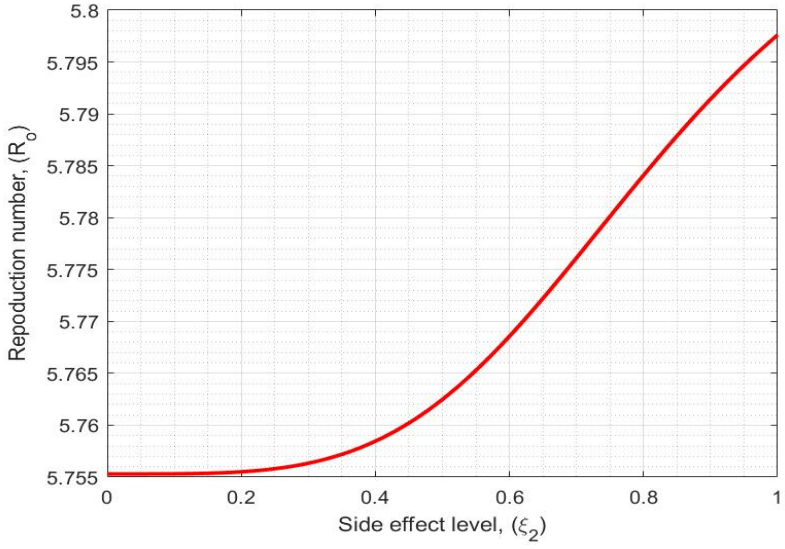


Figure 3.8: $\mathfrak{R}_o$ as a function of side effect level of people on ARV drugs in the public health care system. The rest of the parameter values are: $\omega_{max} = 0.9$, $\omega_0 = 0.2$, $k = 0.1, q = 0.6$, $\pi = 2412, \mu = 0.016, \gamma = 0.098, \rho = 0.45, \alpha_1 = 0.0412, \alpha_2 = 0.0214, \alpha_3 = 0.0312, \alpha_4 = 0.0521, \alpha_5 = 0.052, \theta_1 = 0.076, \theta_2 = 0.071, \rho = 0.45, \delta = 0.043, f(\xi_1) = 0.021, \eta_1 = 0.257, \eta_2 = 0.345, \eta_3 = 1.016, \eta_4 = 1.03, \eta_5 = 1.04, \beta = 0.313$.

Figures 3.7 and 3.8 are obtained by replacing the estimated values of $f(\xi_1)$ and $f(\xi_2)$ respectively with the functional response $f(\xi_i)$ in the expression in (3.4) for variables ξ_1 and ξ_2 in (3.25). In Figure 3.7 it is observed that there is an inverse relationship between $\mathfrak{R}_o$ and ξ_1, this shows that as the side effect level of people on antiretroviral drugs increases, the reproductive number increases. Also, Figure 3.8 shows an inverse relationship between $\mathfrak{R}_o$ and ξ_2. Therefore, it is important to reduce the toxicity of ARV drugs so as to reduce it's side effects on infected individuals on antiretroviral treatment. This will in turn help in fighting the AIDS epidemic.

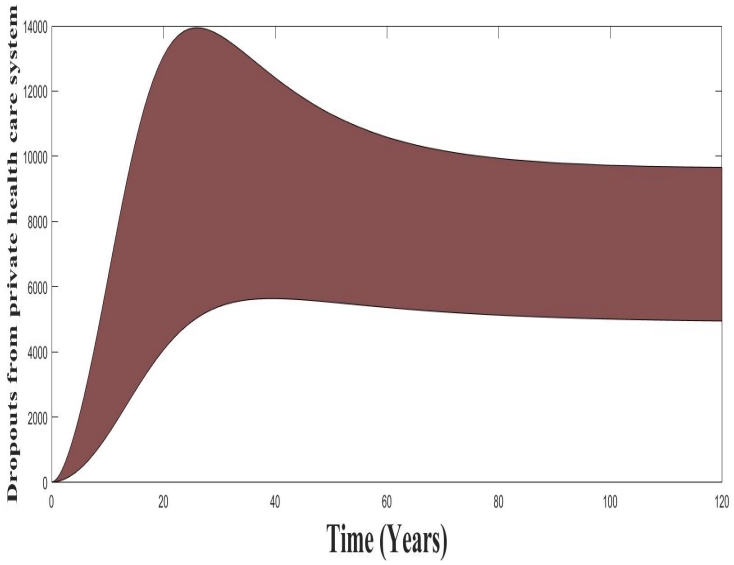


Figure 3.9: Potential number of dropouts over time, which is the population that dropout from private health care systems with $\omega_{max} = 0.5$ and $\omega_0 = 0.01$.

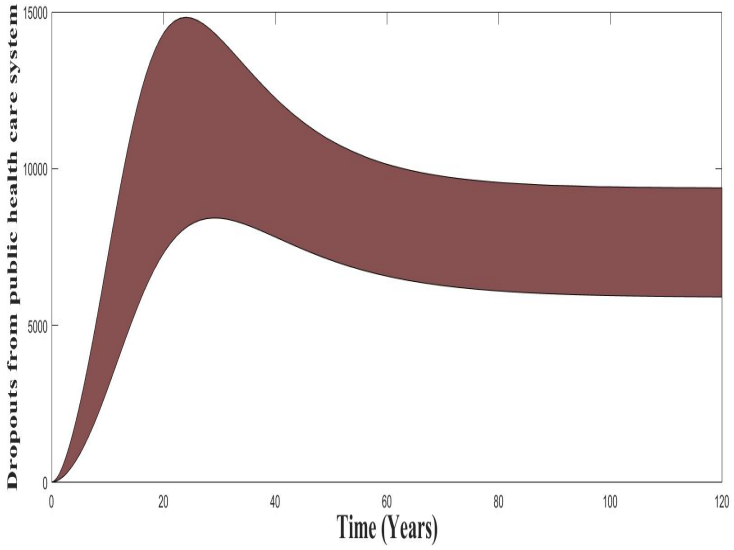


Figure 3.10: Potential number of dropouts over time, which is the population that dropout from public health care systems with $\omega_{max} = 0.5$ and $\omega_0 = 0.01$.

In Figure 3.9, the impact of the dropout rate parameter $f(\xi_1)$ due to side effects of the antiretroviral drugs on the infected population under treatment

in the private health care system was investigated. It was paramount to know how side effects affect the dropouts in order to design interventions on how to reduce them. The shaded area in 3.9 represents the potential number of dropouts over time. We observed that as side effect increases, the number of dropouts from treatment increases significantly. In such a scenario, we are able to quantify the impact of side effects on the number of dropouts. Also, the same holds for the public health care system in Figure 3.10 considering $f(\xi_2)$. The difference is that the potential number of dropouts overtime is higher in the public health care system when compared to the private health care system.

3.5 Sensitivity analysis

Sensitivity analysis is the study of how the changes in parameters or variation in parameter inputs in a model can lead to a response in the output [93]. We use sensitivity analysis to show which parameter has a great effect on the reproduction number $\mathfrak{R}_o$ either with a positive or negative correlation [62]. Sensitivity analysis also enables us to know important parameters that are capable of altering the value of the output or that can cause a change in the structure of the model [68]. We use the Latin Hypercube Sampling (LHS) method. The main reason for LHS/PRCC sensitivity analysis is because it is a type of sensitivity analysis that enables the use of all parameters space of the model with just a minimum number of computer simulations [14].

In this work, we estimated the effect of variation of parameters to the sensitivity of the reproduction number $\mathfrak{R}_o$ using Matlab. This enabled us to determine the impact of each parameter in system (3.5) for a chosen outcome variable.

The estimated range of parameters used for the simulations are found in Table 3.3. Parameters with positive sensitivity indices imply that there will be increase in the reproduction number $\mathfrak{R}_o$ whenever they are increased (positive correlation) while parameters with negative sensitivity indices imply the opposite.

From Figure 3.11, it shows that positive correlation exists between $\Re_o$ and $f(\xi_1)$, also positive correlation exists between $\Re_o$ and $f(\xi_2)$. It indicates that side effects of antiretroviral drugs play an important role in increasing the epidemic and hence adequate measures must be put in place to reduce the side effects of the ARV drugs in order to reduce the rate of dropout from treatment.

Also from Figure 3.11, it can be seen that negative correlation exist between $\Re_o$ and γ, θ_1, θ_2. This implies that treatment intervention that has been put in place should be sustained and dropouts should be traced and encouraged to move back to treatment programs for the control of the epidemics.

Table 3.4: Sensitivity indices of the parameters that is used to carryout the simulation

Parameter	Sensitivity index sign
π	+
μ	-
γ	-
ρ	-
α_1	+
α_2	+
α_3	+
α_4	+
α_5	+
θ_1	-
θ_2	-
$f(\xi_1)$	+
$f(\xi_2)$	+
β	+
η_1	+
η_2	+
η_3	+
η_4	+
η_5	+
δ	-

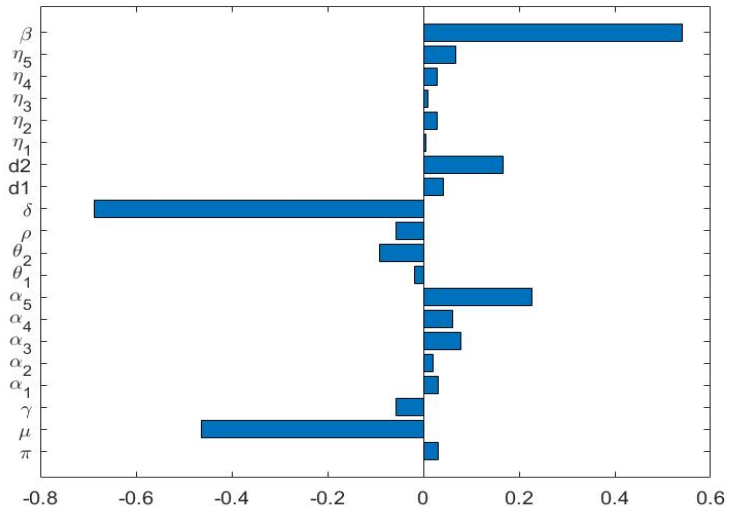
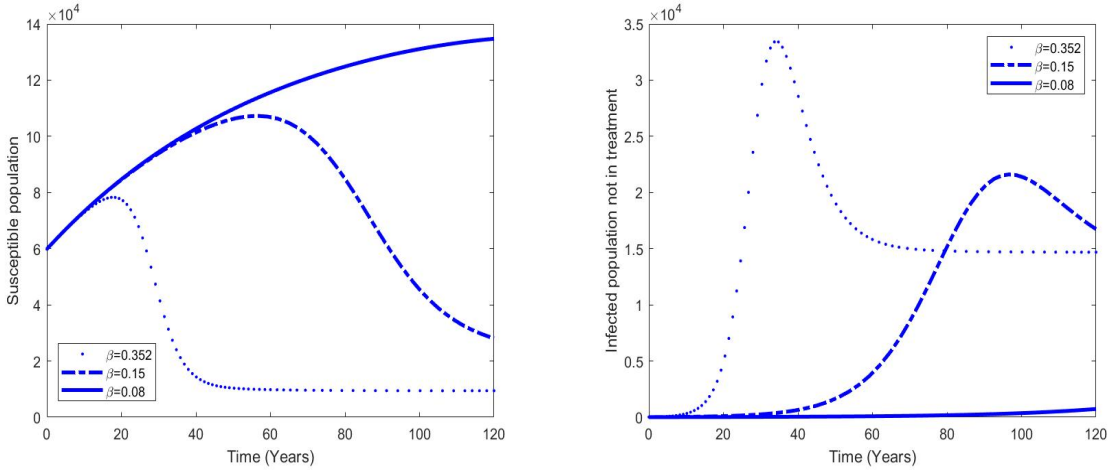


Figure 3.11: The Latin Hypercube Sampling-Partial Rank Correlation Coefficients (LHS/PRCCs) for the range of parameters from. Note d1 and d2 represent $f(\xi_1)$ and $f(\xi_2)$ respectively. It can be seen from the plot that the parameters that are positive have the high chance of making the epidemic worse and the parameters that are negative have a high potential of reducing the epidemic.

3.5.1 Effects of varying β on the dynamics of HIV/AIDS

In order to investigate the effect of effective transmission rate β on the dynamics of HIV/AIDS, we run a simulation on Model system (3.5) by using different values of β. The result is shown in Figure 3.12.



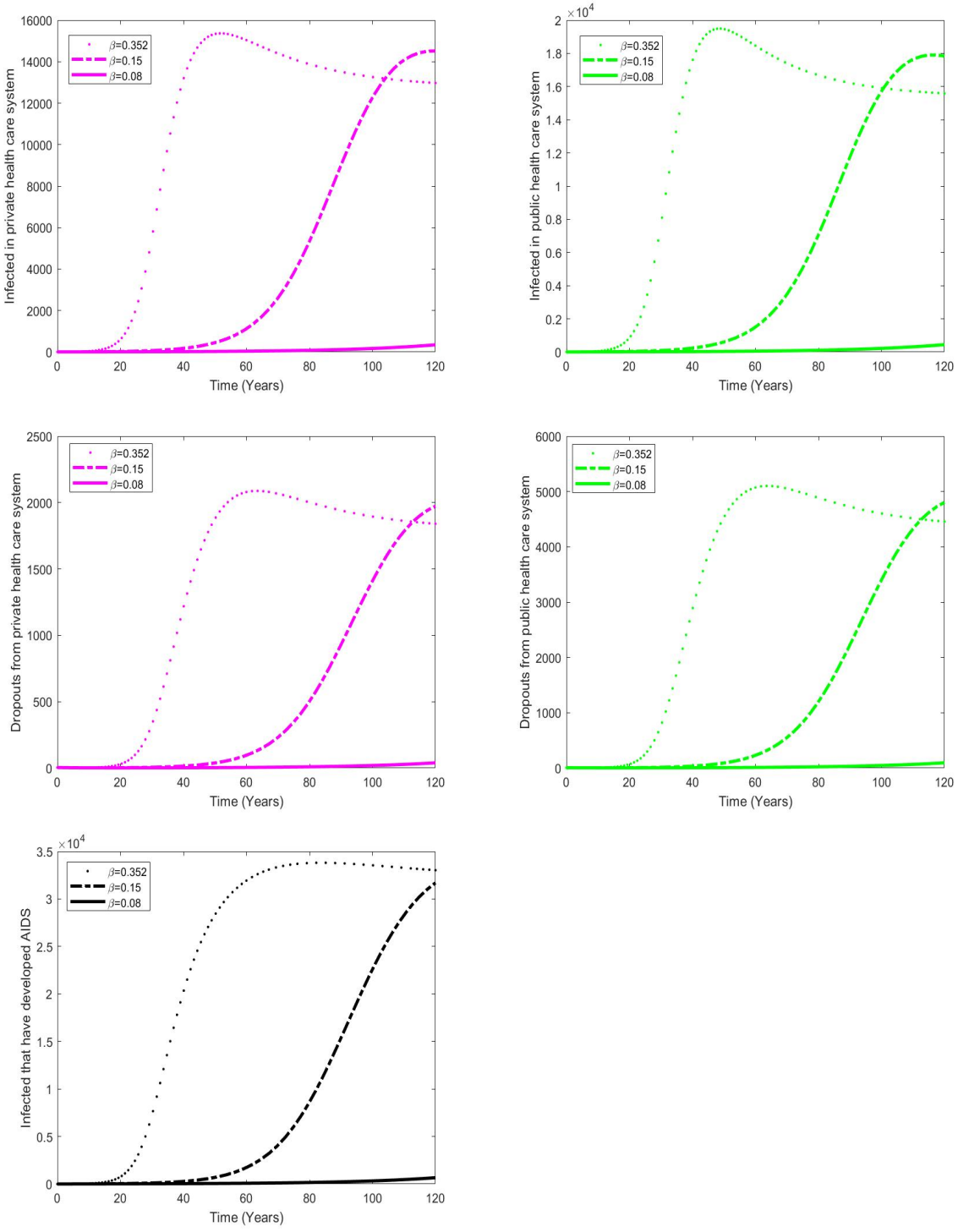


Figure 3.12: The result of simulations of the dynamics of Model system (3.5) for the estimated parameter values $\pi = 2412, \mu = 0.016, \gamma = 0.098, \rho = 0.45, \alpha_1 = 0.0412, \alpha_2 = 0.0214, \alpha_3 = 0.0312, \alpha_4 = 0.0521, \alpha_5 = 0.052, \theta_1 = 0.076, \theta_2 = 0.071, \rho = 0.45, \delta = 0.043, f(\xi_1) = 0.021, f(\xi_2) = 0.034, \eta_1 = 0.257, \eta_2 = 0.345, \eta_3 = 1.016, \eta_4 = 1.03, \eta_5 = 1.043$. The result shows the way the steady states transit from the disease-free state to endemic state as β increases.

From Figure 3.12, it can be seen that the dynamics of model system (3.5) changes as the transmission rate (β) increases. This implies that β is an important parameter in the dynamics of HIV/AIDS. The populations of each class change from the stable disease-free state to an endemic state. This is definitely correct because from the interpretation of Figure 3.12 $\mathfrak{R}_o$ increases as β increases. Therefore, biologically it can be confirmed because when the rate at which people get infected increases, then this, in turn, will increase the reproduction number. Thus, if there is no intervention regarding the epidemics, then the disease will continue to increase in the population. There are quite a number of reasons that could cause this, either as a result of unavailability or low use of condoms, high sexual risk (multiple partners), high rate of attrition from ARV and probable resistance to ARV drugs.

3.5.2 Effects of varying γ on the infected and treatment classes

We investigated the population of the infected and treatment classes of Model system (3.5) as treatment rate (γ) increases.

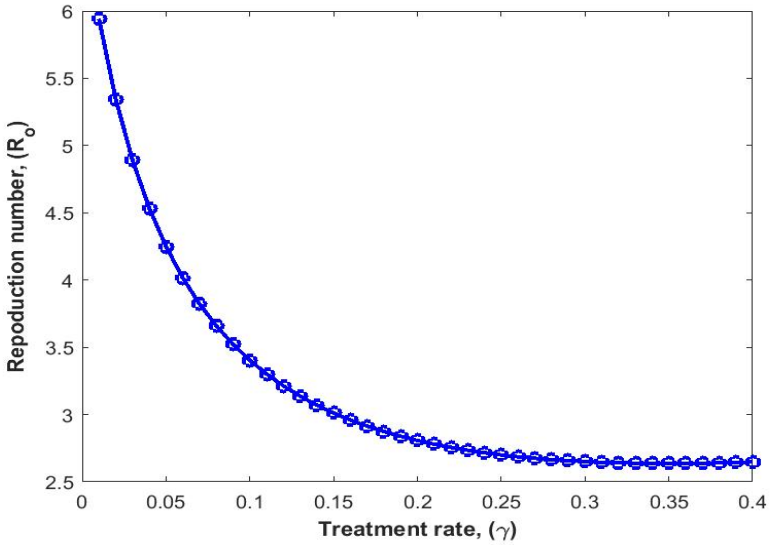


Figure 3.13: Effect of varying γ on $\mathfrak{R}_o$.

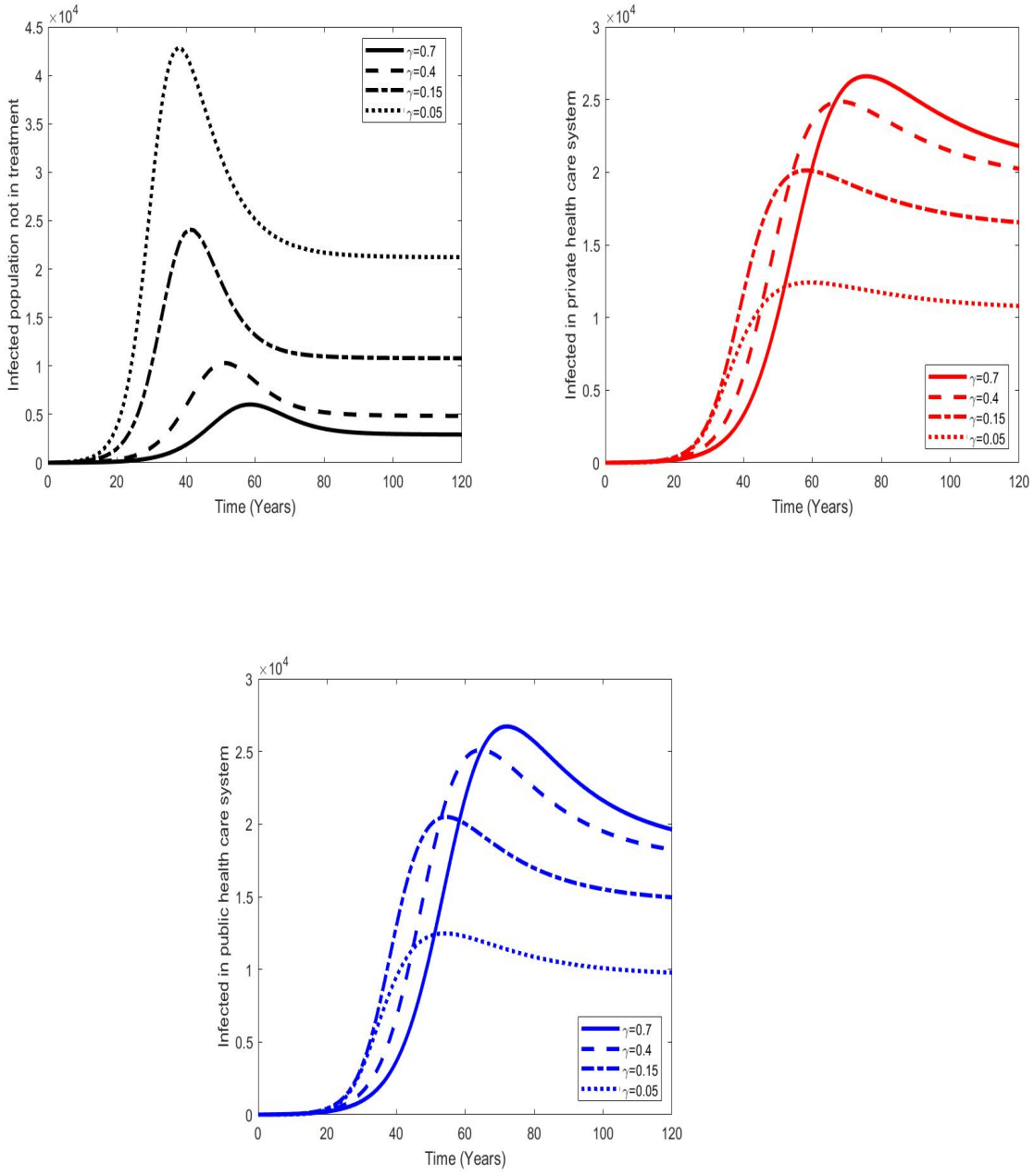


Figure 3.14: The result of simulations of the dynamics of Model system (3.5) for the estimated parameter values $\pi = 2412, \mu = 0.016, \rho = 0.45, \alpha_1 = 0.0412, \alpha_2 = 0.0214, \alpha_3 = 0.0312, \alpha_4 = 0.0521, \alpha_5 = 0.052, f(\xi_1) = 0.021, f(\xi_2) = 0.034, \theta_1 = 0.076, \theta_2 = 0.071, \rho = 0.45, \delta = 0.043, \eta_1 = 0.257, \eta_2 = 0.345, \eta_3 = 1.016, \eta_4 = 1.03, \eta_5 = 1.04, \beta = 0.313$. The result shows the dynamics of the infected and treatment populations as γ increases.

We note from Figure 3.13 that as γ increases the reproduction number decreases. This is an indication that a lot of efforts must be made so as to increase compliance to treatment which is already in place and to enrol more people living with HIV/AIDS into treatment and also to encourage individuals not to drop out from treatment in order to reduce the burden of the disease.

Figure (3.14) shows the result of varying γ on the infected and treatment population. It can be seen that as γ increases the infected population decreases and the treatment population increases. The biological implication is that as more people that are infected are enrolled in treatment, the viral load in the individuals reduces and the density of the infected population reduces. This, in turn, will make the reproduction number to reduce as people start receiving ART and there is adherence to the treatment. Therefore, individuals must be encouraged to enrol in treatment for the burden of the disease to reduce.

3.5.3 Effects of varying θ_1, θ_2, $f(\xi_1)$, $f(\xi_2)$ on the dynamics of the dropout compartments

In order to determine the effects of θ_1, θ_2, $f(\xi_1)$, $f(\xi_2)$ on the dynamics of the dropouts of the model system (3.5) we vary the parameters and observe how the time series plot change as the parameters change. The results of the simulations are shown in Figures 3.15, 3.16, 3.17 and 3.18.

Figure 3.15 shows that increasing $f(\xi_1)$ and $f(\xi_2)$ increases the number of D_1 and D_2 with $D_2 > D_1$. This implies that when side effects to ARV drugs increases, individuals that drop out of treatment increases which also, in turn, makes the reproduction number $\mathfrak{R}_o$ to increase. As a result, reduction of side effects has the potential to impact retention of individuals under treatment. Figure 3.15 quantifies the effects of side effects on the number of dropouts.

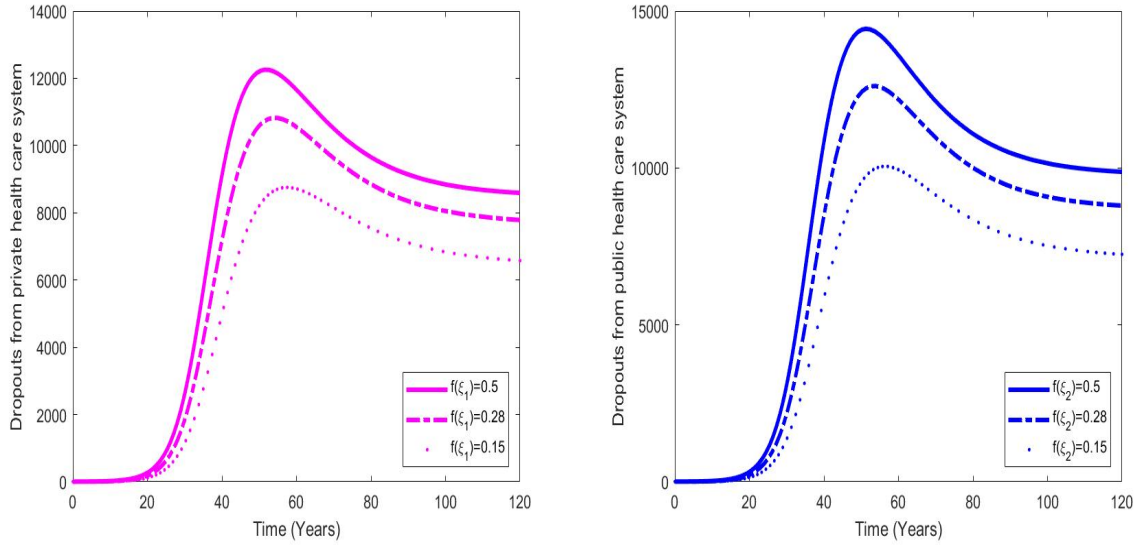


Figure 3.15: Variation of the model system (3.5) time series plots when $f(\xi_1)$ and $f(\xi_2)$ are varied using the parameter values $\pi = 2412, \mu = 0.016, \gamma = 0.098, \rho = 0.45, \alpha_1 = 0.0412, \alpha_2 = 0.0214, \alpha_3 = 0.0312, \alpha_4 = 0.0521, \alpha_5 = 0.052, \theta_1 = 0.076, \theta_2 = 0.071, \rho = 0.45, \delta = 0.043, \eta_1 = 0.257, \eta_2 = 0.345, \eta_3 = 1.016, \eta_4 = 1.03, \eta_5 = 1.04, \beta = 0.313$.

Figure 3.16 shows that increasing $f(\xi_1)$ and $f(\xi_2)$ decreases the number of people in private health care system T_1 and public health care system T_2. It is thus important for infected individuals to remain in treatment to maintain viral suppression which in turn reduces the spread of the epidemic.
Figure 3.17 shows that as θ_1 and θ_2 increases, the population of D_1 and D_2 decreases respectively. This implies that when the rate at which people move back into treatment after dropout increases, then the reproduction number $\mathfrak{R}_o$ decreases. So it is important that individuals that dropout from treatment be encouraged to move back to treatment so as to control the disease escalation due to the potential of viral suppression controlling the spread of the epidemic.

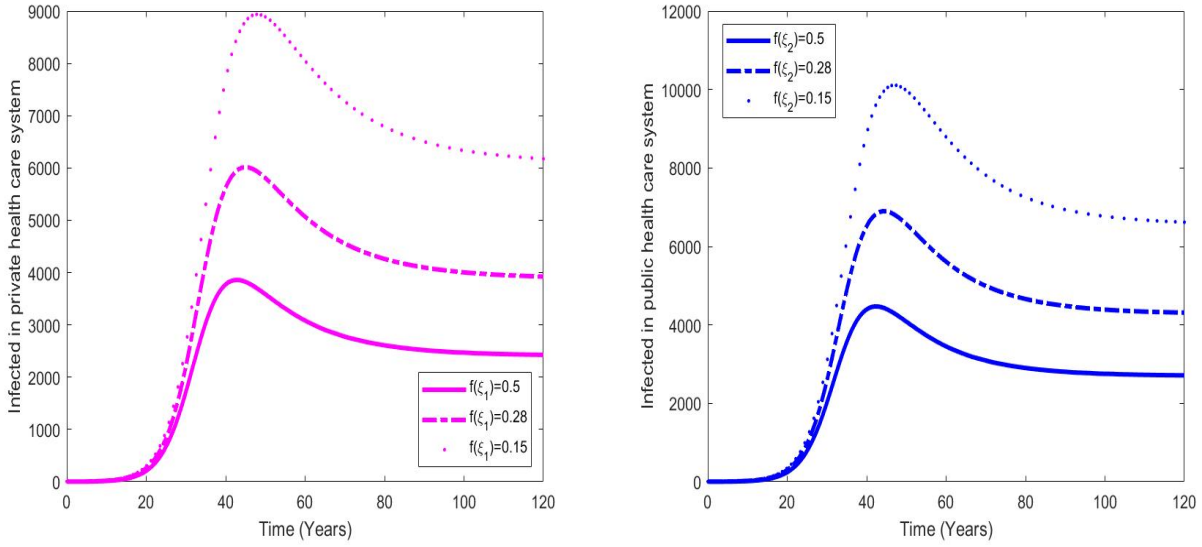


Figure 3.16: Variation of the model system (3.5) time series plots when $f(\xi_1)$ and $f(\xi_2)$ are varied using the parameter values $\pi = 2412, \mu = 0.016, \gamma = 0.098, \rho = 0.45, \alpha_1 = 0.0412, \alpha_2 = 0.0214, \alpha_3 = 0.0312, \alpha_4 = 0.0521, \alpha_5 = 0.052, \theta_1 = 0.076, \theta_2 = 0.071, \rho = 0.45, \delta = 0.043, \eta_1 = 0.257, \eta_2 = 0.345, \eta_3 = 1.016, \eta_4 = 1.03, \eta_5 = 1.04, \beta = 0.313$.

Furthermore, Figure 3.18 shows that as θ_1 and θ_2 increases, the population of T_1 and T_2 increases respectively. Biologically, this means that since individuals that move back will start taking ARV drugs back, then the reproduction number $\mathfrak{R}_o$ decreases which will make the viral load reduce and also affecting others will also be minimized.

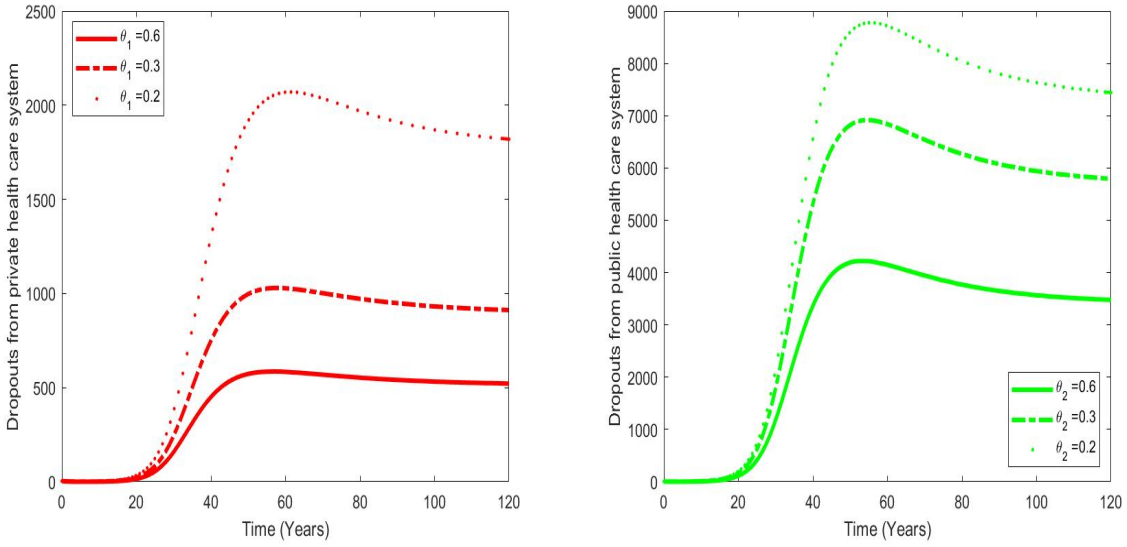


Figure 3.17: Variation of the model system (3.5) time series plots when θ_1 and θ_2 are varied using the parameter values $\pi = 2412, \mu = 0.016, \gamma = 0.098, \rho = 0.45, \alpha_1 = 0.0412, \alpha_2 = 0.0214, \alpha_3 = 0.0312, \alpha_4 = 0.0521, \alpha_5 = 0.052, f(\xi_1) = 0.021, f(\xi_2) = 0.034, \rho = 0.45, \delta = 0.043, \eta_1 = 0.257, \eta_2 = 0.345, \eta_3 = 1.016, \eta_4 = 1.03, \eta_5 = 1.04, \beta = 0.313$.

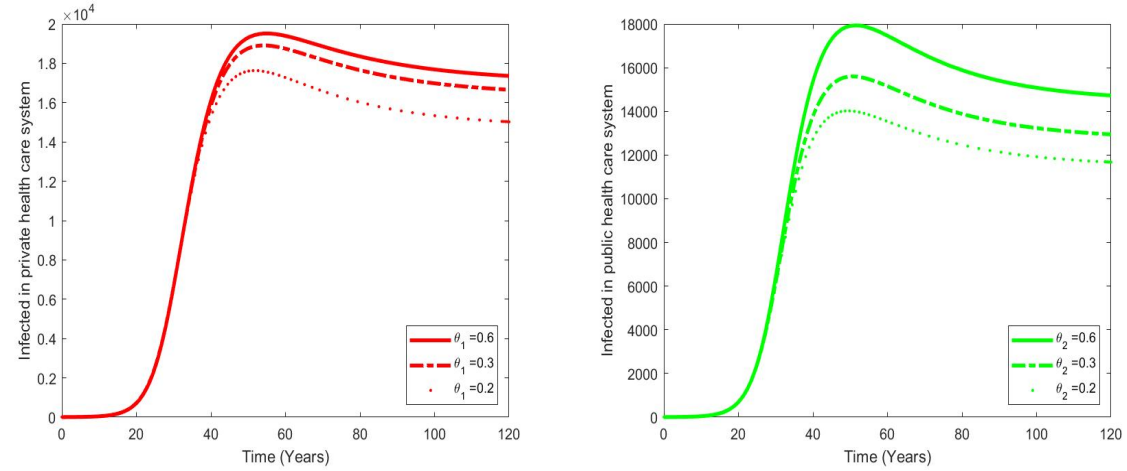


Figure 3.18: Variation of the model system (3.5) time series plots when θ_1 and θ_2 are varied using the parameter values $\pi = 2412, \mu = 0.016, \gamma = 0.098, \rho = 0.45, \alpha_1 = 0.0412, \alpha_2 = 0.0214, \alpha_3 = 0.0312, \alpha_4 = 0.0521, \alpha_5 = 0.052, f(\xi_1) = 0.021, f(\xi_2) = 0.034, \rho = 0.45, \delta = 0.043, \eta_1 = 0.257, \eta_2 = 0.345, \eta_3 = 1.016, \eta_4 = 1.03, \eta_5 = 1.04, \beta = 0.313$.

Contour plot in Figures 3.19 and 3.20 are used to ascertain the relationship between some selected pairs of parameters and $\mathfrak{R}_o$. Figure 3.19 shows that when both θ_1 and θ_2 (the rate at which individuals that drop out of treatment return back to treatment) are increased, they decrease the reproduction number $\mathfrak{R}_o$. Biologically, moving back to treatment after dropout has a positive impact on the reproduction number $\mathfrak{R}_o$. However, from Figure 3.20 when both $f(\xi_1)$ and $f(\xi_2)$ (side effects to ARV drug) are increased, the reproduction number increases. Also, we can notice that the reproduction number $\mathfrak{R}_o$ increases significantly as side effects increases. Therefore, we can conclude that the rate at which individuals dropout from treatment is a major concern for health policymakers. Thus, adequate public health measures such as sensitizing individuals on ART and managing side effects should be escalated in order to control people from dropping out of treatment, so as to control HIV/AIDS.

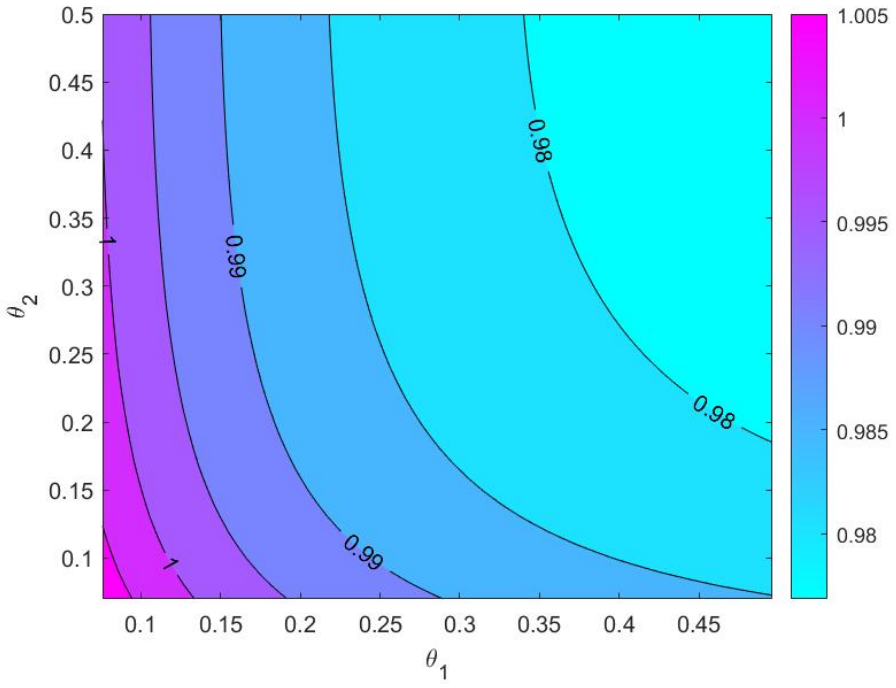


Figure 3.19: Contour plot of $\mathfrak{R}_o$ as a function of θ_1 and θ_2.

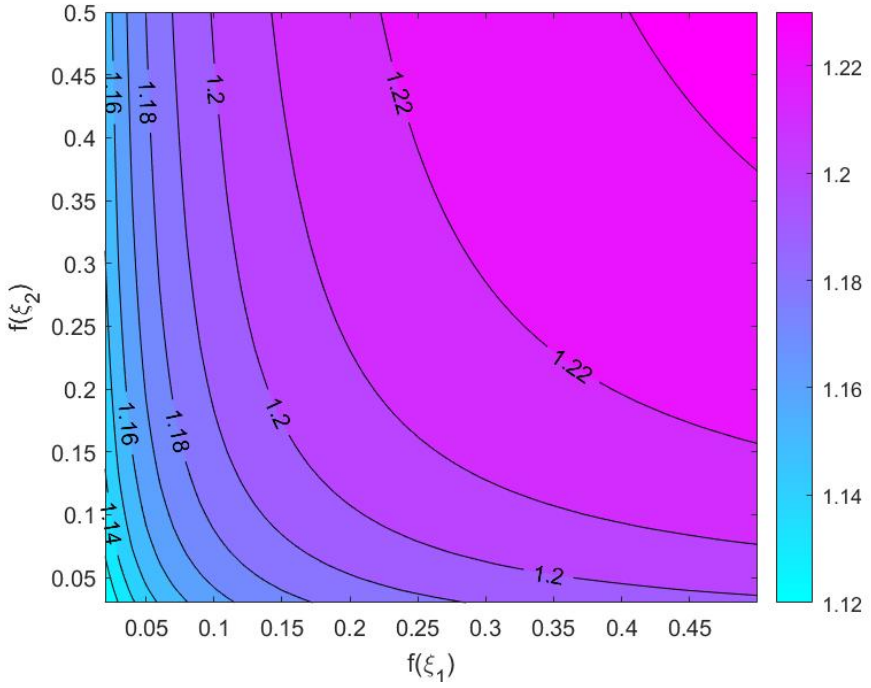


Figure 3.20: Contour plot of $\mathfrak{R}_o$ as a function of $f(\xi_1)$ and $F(\xi_2)$.

This study of the potential impact of health care systems and dropouts on the dynamics of HIV/AIDS together with recommendations are summarised in 4.

Chapter 4

Discussions and conclusions

In this thesis, we proposed a deterministic model for HIV/AIDS. We included the treatment of individuals with respect to the type of health care system (private or public) in which they are enrolled. Dropouts from treatment are as a result of side effects to ARV drugs. We explicitly computed the steady states: the disease-free and endemic equilibrium points of the model system (3.5). The basic reproduction number $\mathfrak{R}_o$ was obtained and used for the analysis of the steady states. Apart from proving the existence of the endemic state of model system (3.5), we also established theorems that provide the global stabilities of the disease and endemic states. Lyapunov functions are presented to prove the global stabilities of the disease-free and endemic equilibrium points of the model system (3.5). The results show that disease-free equilibrium point is globally asymptotically stable for $\mathfrak{R}_o < 1$ and endemic equilibrium is globally stable for $\mathfrak{R}_o > 1$. The global stability result suggests that the model has a forward transcritical bifurcation as shown in Figure 4.1.

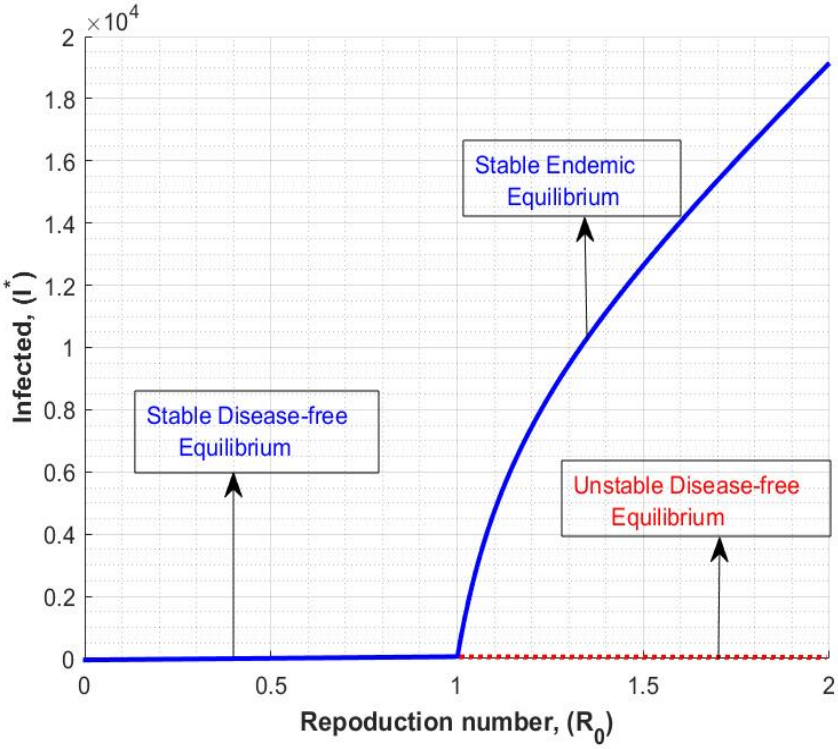


Figure 4.1: Forward transcritical bifurcation for R_0.

The implications of global stability, is that, irrespective of the initial conditions, every trajectory in the invariant region tends to the disease free equilibrium point if $\mathfrak{R}_o < 1$. On the other hand, if $\mathfrak{R}_o > 1$, then all the trajectories in the invariant region tend to the endemic equilibrium point. These results have implications on the epidemic, and the elimination of the epidemic depends on the value of $\mathfrak{R}_o$.

Simulations were carried out to track the dynamics of the model system (3.5) at both the disease and endemic equilibrium points. Time series plots are given to show the dynamics of each compartment over time for the cases $\mathfrak{R}_o < 1$ and $\mathfrak{R}_o > 1$.

The results obtained from the sensitivity analysis enabled us to determine the parameters which have a significant impact on the dynamics of the disease. Sensitivity indices were obtained for various parameters. We note that reducing parameters with positive signs of their sensitivity indices reduces the reproduction number $\mathfrak{R}_o$, hence a reduction in the growth of the epidemic. Therefore, interventions should target on reducing such parameters. The sensitivity analysis and numerical results also show that the side effects

of ARV drugs have a positive correlation with the reproduction number $\mathfrak{R}_o$. This implies that decreasing side effects of ARV drugs decreases $\mathfrak{R}_o$. Therefore when side effects to ARV drugs decrease, individuals that drop out from treatment also decreases thus reducing the transmission of the disease. This, in turn, also will reduce the rate at which individuals develop AIDS and as a result help in the control of the disease. Thus, when the number of individuals that return to treatment after dropout increases, this will in turn help in reducing the reproduction number $\mathfrak{R}_o$. This result is supported by the known relationship between disease transmission by virally suppressed individuals who are assumed to have a reduced chance of transmitting the virus to the uninfected.

The model system (3.5) was fitted to data of individuals that drop out of treatment in order to see the trends of individuals that drop out of treatment as shown in Fig. 3.4. We emphasize here that while the model is divided into two healthcare systems, the data that was used for the fitting of the model was not divided according to the healthcare system. Since Warren Park, is a middle income suburb, we assumed that the drop outs from the two healthcare systems can be combined for the fitting process. The model is fitted using the least squares method and is found to fit relatively well to the available data. Since the data is not separated according to the healthcare system, the modelling framework presented in this thesis suggests that data from the private and public health care system should be presented separately for the sole purpose of monitoring HIV/AIDS in both systems. It is, however, important to note that most of the data collected are donor-funded and as such, donors deal directly with the public health care systems.

In conclusion, an increase in side effects of ARV drugs could bring about an increase of individuals that dropout from treatment, which will have a great impact on the dynamics of HIV/AIDS. The quantification of the side effects is an important research exercise that warrants investigation.

Like any modelling adventure, this work has some limitations. First, the majority of the parameters are estimated. We had to make use of the iterative method using Matlab in order to get an estimated value for the pa-

rameters as a result of the fact that there is no availability of published data on the parameters. Second, we used data from just one clinic but data from both private and public health care systems could give a better estimates for our parameters. Third, the model we use does not put into consideration vertical transmission and other forms of transmission, which have greatly impacted the HIV/AIDS epidemic globally. Fourth, the model does not consider other forms of interventions, such as PrEP, media campaigns, voluntary male circumcision. In addition, the drop out rate may not necessarily be constant throughout the epidemic period. Last, Stochasticity that can be attributed to the side effect level of people on ARV drugs could also have an influence on the pattern of the infection. Therefore, considering a stochastic approach could give a better picture of the dynamics of the dropout classes. Despite these shortcomings, the model presents a foundation for further investigations of different healthcare systems, especially in countries with function private and public health care systems. This forms our future research, as we extend the current work.

Appendix A

Global stability of the equilibria

A.1 Proof of theorem 3.3.5

Proof. Let us consider the following Lyapunov function

$$V = I + \nu_1 T_1 + \nu_2 T_2 + \nu_3 D_1 + \nu_4 D_2 + \nu_5 A, \tag{A.1}$$

where $\nu_i, i = 1, \cdots, 5$ are positive constants that will be determined.

- $V = 0$ at the steady state, since $I(t) = T_1(t) = T_2(t) = D_1(t) = D_2(t) = A(t) = 0$ at (Disease Free Equilibrium).
- $V > 0$ at any other point not equal to the steady state (DFE), since $I(t) > 0, T_1(t) > 0, T_2(t) > 0, D_1(t) > 0, D_2(t) > 0, A(t) > 0$.
- $\dot{V} < 0$, then the steady state is globally stable.

Differentiating equation (A.1) with respect to t, we have

$$\dot{V} = \dot{I} + \nu_1 \dot{T_1} + \nu_2 \dot{T_2} + \nu_3 \dot{D_1} + \nu_4 \dot{D_2} + \nu_5 \dot{A}. \tag{A.2}$$

Substituting (3.5) into (A.2), we have

$$\begin{aligned}\dot{V} = {} & \lambda S - Q_1 I + \nu_1[\gamma\rho I - Q_2 T - 1 + \theta_1 D - 1] + \nu_2[\gamma(1-\rho)I - Q_3 T_2 + \\ & \theta_2 D_2] + \nu_3[f(\xi_1)T_1 - Q_4 D - 1] + \nu_4[f(\xi_2)T_2 - Q_5 D_2] + \nu_5[\alpha_1 I + \alpha_2 T_1 + \\ & \alpha_3 T_2 + \alpha_4 D_1 + \alpha_5 D_2 - Q_6 A],\end{aligned} \tag{A.3}$$

where the values of $Q_i, i = 1, \cdots, 6$ are expressed in equation (3.35).

Substituting equation (3.2) into (A.3), we have

$$\dot{V} = \left[\frac{\beta S}{N} - Q_1 + \nu_1\gamma\rho + \nu_2(\gamma(1-\rho)) + \nu_5\alpha_1\right] I + \left[\frac{\eta_1\beta S}{N} - \nu_1 Q_2 + \nu_3 f(\xi_1) + \nu_5\alpha_2\right] T_1 + \left[\frac{\eta_2\beta S}{N} - \nu_2 Q_3 + \nu_4 f(\xi_2) + \nu_5\alpha_3\right] T_2 + \left[\frac{\eta_3\beta S}{N} + \nu_1\theta_1 - \nu_3 Q_4 + \nu_5\alpha_4\right] D_1 + \left[\frac{\eta_4\beta S}{N} + \nu_2\theta_2 - \nu_4 Q_5 + \nu_5\alpha_5\right] D_2 + \left[\frac{\eta_5\beta S}{N} - \nu_5 Q_6\right] A. \tag{A.4}$$

From equation (3.8), we know that $\frac{N}{S} \leq 1$. Substituting it into equation (A.4) gives

$$\begin{aligned}\dot{V} &\leq [\beta - Q_1 + \nu_1\gamma\rho + \nu_2(\gamma(1-\rho)) + \nu_5\alpha_1]\, I + [\eta_1\beta - \nu_1 Q_2 + \nu_3 f(\xi_1) + \nu_5\alpha_2] T_1 + [\eta_2\beta - \nu_2 Q_3 + \nu_4 f(\xi_2) + \nu_5\alpha_3]\, T_2 + [\eta_3\beta + \nu_1\theta_1 - \nu_3 Q_4 + \nu_5\alpha_4]\, D_1 \\ &\quad + [\eta_4\beta + \nu_2\theta_2 - \nu_4 Q_5 + \nu_5\alpha_5]\, D_2 + [\eta_5\beta - \nu_5 Q_6]\, A \\ &\leq Q_1\left[\frac{\beta}{Q_1} + \frac{\nu_1\gamma\rho}{Q_1} + \frac{\nu_2(\gamma(1-\rho))}{Q_1} + \frac{\nu_5\alpha_1}{Q_1} - 1\right] I + [\eta_1\beta - \nu_1 Q_2 + \nu_3 f(\xi_1) \\ &\quad + \nu_5\alpha_2] T_1 + [\eta_2\beta - \nu_2 Q_3 + \nu_4 f(\xi_2) + \nu_5\alpha_3]\, T_2 + [\eta_3\beta + \nu_1\theta_1 - \nu_3 Q_4 + \nu_5\alpha_4] \\ &\quad D_1 + [\eta_4\beta + \nu_2\theta_2 - \nu_4 Q_5 + \nu_5\alpha_5]\, D_2 + [\eta_5\beta - \nu_5 Q_6]\, A\end{aligned} \tag{A.5}$$

Solving for $\nu_i, i = 1, \cdots, 5$ so that the coefficient of T_1, T_2, D_1, D_2, A are zero, we have

$$\nu_1 = \frac{\beta[Q_4(Q_6\eta_1 + \alpha_2\eta_5) + f(\xi_1)(Q_6\eta_3 + \alpha_4\eta_5)]}{Q_6[Q_2Q_4 - f(\xi_1)\theta_1]} \tag{A.6}$$

$$\nu_2 = \frac{\beta[Q_5(Q_6\eta_2 + \alpha_3\eta_5) + f(\xi_2)(Q_6\eta_4 + \alpha_5\eta_5)]}{Q_6[Q_3Q_5 - f(\xi_2)\theta_2]} \tag{A.7}$$

$$\nu_3 = \frac{\beta[Q_2(Q_6\eta_3 + \alpha_4\eta_5) + \theta_1(Q_6\eta_1 + \alpha_2\eta_5)]}{Q_6[Q_2Q_4 - f(\xi_1)\theta_1]} \tag{A.8}$$

$$\nu_4 = \frac{\beta[Q_3(Q_6\eta_4 + \alpha_5\eta_5) + \theta_2(Q_6\eta_2 + \alpha_3\eta_5)]}{Q_6[Q_3Q_5 - f(\xi_2)\theta_2]} \tag{A.9}$$

$$\nu_5 = \frac{\beta\eta_5}{Q_6}. \tag{A.10}$$

Substituting equations (A.6) - (A.10) into (A.5) gives

$$\dot{V} \leq Q_1 \left[\frac{\beta}{Q_1} + \frac{\beta\alpha_1\eta_5}{Q_1Q_6} + \frac{\beta\gamma\rho[Q_4(Q_6\eta_1 + \alpha_2\eta_5) + f(\xi_1)(Q_6\eta_3 + \alpha_4\eta_5)]}{Q_1Q_6[Q_2Q_4 - f(\xi_1)\theta_1]} + \frac{\beta\gamma(1-\rho)[Q_5(Q_6\eta_2 + \alpha_3\eta_5) + f(x_2(Q_6\eta_4 + \alpha_5\eta_5))]}{Q_1Q_6[Q_3Q_5 - f(\xi_2)\theta_2]} - 1 \right] I$$

$$\leq Q_1 \left[\frac{\beta}{Q_1} + \frac{\beta\alpha_1\eta_5}{Q_1Q_6} + \frac{\beta\gamma\rho\eta_1Q_4}{Q_1(Q_2Q_4 - f(\xi_1)\theta_1)} + \frac{\beta\gamma\rho\alpha_2\eta_5Q_4}{Q_1Q_6(Q_2Q_4 - f(\xi_1)\theta_1)} + \frac{\beta\gamma\rho\eta_3 f(\xi_1)}{Q_1(Q_2Q_4 - f(\xi_1)\theta_1)} + \frac{\beta\gamma\rho\alpha_4\eta_5 f(\xi_1)}{Q_1Q_6(Q_2Q_4 - f(\xi_1)\theta_1)} + \frac{\beta\gamma(1-\rho)\eta_2Q_5}{Q_1(Q_3Q_5 - f(\xi_2)\theta_2)} + \frac{\beta\gamma(1-\rho)\alpha_3\eta_5Q_5}{Q_1Q_6(Q_3Q_5 - f(\xi_2)\theta_2)} + \frac{\beta\gamma(1-\rho)\eta_4 f(\xi_2)}{Q_1(Q_3Q_5 - f(\xi_2)\theta_2)} + \frac{\beta\gamma(1-\rho)\alpha_5\eta_5 f(\xi_2)}{Q_1Q_6(Q_3Q_5 - f(\xi_2)\theta_2)} - 1 \right] I$$

$$\leq Q_1 \left[\frac{\beta}{Q_1} + \frac{\beta\gamma\rho\eta_1}{Q_1Q_2\left(1 - \frac{f(\xi_1)\theta_1}{Q_2Q_4}\right)} + \frac{\beta\gamma(1-\rho)\eta_2}{Q_1Q_3\left(1 - \frac{f(\xi_2)\theta_2}{Q_3Q_5}\right)} + \frac{\beta\gamma\rho\eta_3 f(\xi_1)}{Q_1Q_2Q_4\left(1 - \frac{f(\xi_1)\theta_1}{Q_2Q_4}\right)} + \frac{\beta\gamma(1-\rho)\eta_4 f(\xi_2)}{Q_1Q_3Q_5\left(1 - \frac{f(\xi_2)\theta_2}{Q_3Q_5}\right)} + \frac{\beta\alpha_1\eta_5}{Q_1Q_6} + \frac{\beta\gamma\rho\alpha_2\eta_5}{Q_1Q_2Q_6\left(1 - \frac{f(\xi_1)\theta_1}{Q_2Q_4}\right)} + \frac{\beta\gamma(1-\rho)\alpha_3\eta_5}{Q_1Q_3Q_6\left(1 - \frac{f(\xi_2)\theta_2}{Q_3Q_5}\right)} + \frac{\beta\gamma\rho\alpha_4\eta_5 f(\xi_1)}{Q_1Q_2Q_4Q_6\left(1 - \frac{f(\xi_1)\theta_1}{Q_2Q_4}\right)} + \frac{\beta\gamma(1-\rho)\alpha_5\eta_5 f(\xi_2)}{Q_1Q_3Q_5Q_6\left(1 - \frac{f(\xi_2)\theta_2}{Q_3Q_5}\right)} - 1 \right] I$$

$$\leq Q_1 \left[\frac{\beta}{Q_1} + \frac{\beta\gamma\rho\eta_1}{Q_1Q_2\,(1-\phi_1)} + \frac{\beta\gamma(1-\rho)\eta_2}{Q_1Q_3\,(1-\phi_2)} + \frac{\beta\gamma\rho\eta_3\xi_2}{Q_1Q_4\,(1-\phi_1)} + \frac{\beta\gamma(1-\rho)\eta_4\xi_4}{Q_1Q_5\,(1-\phi_2)} + \frac{\beta\alpha_1\eta_5}{Q_1Q_6} + \frac{\beta\gamma\rho\eta_5\xi_5}{Q_1Q_6\,(1-\phi_1)} + \frac{\beta\gamma(1-\rho)\eta_5\xi_6}{Q_1Q_6\,(1-\phi_2)} + \frac{\beta\gamma\rho\eta_5\xi_2\xi_7}{Q_1Q_6\,(1-\phi_1)} + \frac{\beta\gamma(1-\rho)\eta_5\xi_4\xi_8}{Q_1Q_6\,(1-\phi_2)} - 1 \right] I$$

$$\leq Q_1[(R_I + R_{T_1} + R_{T_2} + R_{D_1} + R_{D_2} + R_A) - 1]I$$

$$\leq Q_1(\mathfrak{R}_o - 1)I. \tag{A.11}$$

Note that $\dot{V} \leq 0$ for $\mathfrak{R}_o$ with a strict inequality when $\mathfrak{R}_o < 1$. So the largest invariant set of $\frac{dv}{dt} = 0$ is $(0,0,0,0,0,0)$. By Lasalle's invariant principle from [45] we conclude that model (3.5) is globally asymptotically stable at E_0. Epidemiologically this means that the disease dies out eventually regardless of the initial states of the system. □

A.2 Proof of theorem 3.3.6

Proof. Lets consider equation (3.9) - (3.15) at steady states, so that

$$\pi = \lambda S^* + \mu S^*, \tag{A.12}$$

$$(\alpha_1 + \mu + \gamma) = \frac{\lambda S^*}{I^*}, \tag{A.13}$$

$$(\mu + \alpha_2 + f(\xi_1)) = \frac{\gamma\rho I^*}{T_1^*} + \frac{\theta_1 D_1^*}{T_1^*}, \tag{A.14}$$

$$(\mu + \alpha_3 + f(\xi_2)) = \frac{\gamma(1-\rho) I^*}{T_2^*} + \frac{\theta_2 D_2^*}{T_2^*}, \tag{A.15}$$

$$(\theta_1 + \mu + \alpha_4) = \frac{f(\xi_1) T_1^*}{D_1^*}, \tag{A.16}$$

$$(\theta_2 + \mu + \alpha_5) = \frac{f(\xi_2) T_2^*}{D_2^*}, \tag{A.17}$$

$$(\mu + \delta) = \frac{\alpha_1 I^*}{A^*} + \frac{\alpha_2 T_1^*}{A^*} + \frac{\alpha_3 T_2^*}{A^*} + \frac{\alpha_4 D_1^*}{A^*} + \frac{\alpha_5 D_2^*}{A^*}. \tag{A.18}$$

Lets consider the following Lyapunov function

$$\begin{aligned} V = {} & (S - S^* \ln S) + \tau_1 (I - I^* \ln I) + \tau_2 (T_1 - T_1^* \ln T_1) + \tau_3 (T_2 - T_2^* \ln T_2) \\ & + \tau_4 (D_1 - D_1^* \ln D_1) \tau_5 (D_2 - D_2^* \ln D_2) + \tau_6 (A - A^* \ln A), \end{aligned} \tag{A.19}$$

where, τ_i, $i = 1, \cdots, 6$ are constants that will be determined.

Differentiating V with respect to time (t) yields

$$\begin{aligned} \dot{V} = {} & \left(1 - \frac{S^*}{S}\right) \dot{S} + \tau_1 \left(1 - \frac{I^*}{I}\right) \dot{I} + \tau_2 \left(1 - \frac{T_1^*}{T_1}\right) \dot{T}_1 + \tau_3 \left(1 - \frac{T_2^*}{T_2}\right) \dot{T}_2 + \\ & \tau_4 \left(1 - \frac{D_1^*}{D_1}\right) \dot{D}_1 + \tau_5 \left(1 - \frac{D_2^*}{D_2}\right) \dot{D}_2 + \tau_6 \left(1 - \frac{A^*}{A}\right) \dot{A}. \end{aligned} \tag{A.20}$$

Substituting the expressions for $\dot{S}, \dot{I}, \dot{T}_1, \dot{T}_2, \dot{D}_1, \dot{D}_2, \dot{A}$ from the model system (3.5) into (A.20), we have

$$\begin{aligned}\dot{V} = &\left(1-\frac{S^*}{S}\right)(\pi-(\lambda+\mu)S)+\tau_1\left(1-\frac{I^*}{I}\right)(\lambda S-(\alpha_1+\mu+\gamma)I)+\\ &\tau_2\left(1-\frac{T_1^*}{T_1}\right)(\gamma\rho I-(\mu+\alpha_2+f(\xi_1))T_1+\theta_1 D_1)+\tau_3\left(1-\frac{T_2^*}{T_2}\right)\\ &(\gamma(1-\rho)I-(\mu+\alpha_3+f(\xi_2))T_2+\theta_2 D_2)+\tau_4\left(1-\frac{D_1^*}{D_1}\right)(f(\xi_1)T_1-\\ &(\theta_1+\mu+\alpha_4)D_1)+\tau_5\left(1-\frac{D_2^*}{D_2}\right)(F(\xi_2)T_2-(\theta_2+\mu+\alpha_5)D_2)\\ &+\tau_6\left(1-\frac{A^*}{A}\right)(\alpha_1 I+\alpha_2 T_1+\alpha_3 T_2+\alpha_4 D_1+\alpha_5 D_2-(\mu+\delta)A). \quad \text{(A.21)}\end{aligned}$$

Substituting the expressions from equation (A.12) - (A.18), we have

$$\begin{aligned}\dot{V} = &\left(1-\frac{S^*}{S}\right)(\mu S^*+\lambda S^*-\mu S-\lambda S)+\tau_1\left(1-\frac{I^*}{I}\right)\left(\lambda S-\frac{\lambda S^* I}{I^*}\right)+\\ &\tau_2\left(1-\frac{T_1^*}{T_1}\right)\left(\gamma\rho I-\frac{\gamma\rho I^* T_1}{T_1^*}-\frac{\theta_1 D_1^* T_1}{T_1^*}+\theta_1 D_1\right)+\tau_3\left(1-\frac{T_2^*}{T_2}\right)\\ &\left(\gamma(1-\rho)I-\frac{\gamma(1-\rho)I^* T_2}{T_2^*}-\frac{\theta_2 D_2^* T_2}{T_2^*}+\theta_2 D_2\right)+\tau_4\left(1-\frac{D_1^*}{D_1}\right)\\ &\left(f(\xi_1)T_1-\frac{f(\xi_1)T_1^* D_1}{D_1^*}\right)+\tau_5\left(1-\frac{D_2^*}{D_2}\right)\left(f(\xi_2)T_2-\frac{f(\xi_2)T_2^* D_2}{D_2^*}\right)\\ &+\tau_6\left(1-\frac{A^*}{A}\right)\left(\alpha_1 I+\alpha_2 T_1+\alpha_3 T_2+\alpha_4 D_1+\alpha_5 D_2-\frac{\alpha_1 I^* A}{A^*}-\frac{\alpha_2 T_1^* A}{A^*}-\right.\\ &\left.\frac{\alpha_3 T_2^* A}{A^*}-\frac{\alpha_4 D_1^* A}{A^*}-\frac{\alpha_5 D_2^* A}{A^*}\right). \quad \text{(A.22)}\end{aligned}$$

Calculating terms relating to state variable S from equation (A.22) and substituting equation (3.2), we have

$$\begin{aligned}&\left(1-\frac{S^*}{S}\right)(\mu S^*+\lambda S^*-\mu S-\lambda S),\\ &=\left(1-\frac{S^*}{S}\right)\left(\mu S^*+\frac{\beta I^* S^*}{N}+\frac{\beta\eta_1 T_1^* S^*}{N}+\frac{\beta\eta_2 T_2^* S^*}{N}+\frac{\beta\eta_3 D_1^* S^*}{N}+\right.\\ &\frac{\beta\eta_4 D_2^* S^*}{N}+\frac{\beta\eta_5 A^* S^*}{N}-\mu S-\frac{\beta I S}{N}-\frac{\beta\eta_1 T_1 S}{N}-\frac{\beta\eta_2 T_2 S}{N}-\\ &\left.\frac{\beta\eta_3 D_1 S}{N}-\frac{\beta\eta_4 D_2 S}{N}-\frac{\beta\eta_5 A S}{N}\right). \quad \text{(A.23)}\end{aligned}$$

Substitute $\frac{\beta}{N} = \beta_0$ into equation (A.23) and simplify, we have

$$= -\mu\left(\frac{(S-S^*)^2}{S}\right) + \beta_0 I^* S^*\left(1-\frac{S^*}{S}\right)\left(1-\frac{IS}{I^*S^*}\right) + \beta_0\eta_1 T_1^* S^*\left(1-\frac{S^*}{S}\right)\left(1-\frac{T_1 S}{T_1^* S^*}\right) + \beta_0\eta_2 T_2^* S^*\left(1-\frac{S^*}{S}\right)\left(1-\frac{T_2 S}{T_1^* S^*}\right) + \beta_0\eta_3 D_1^* S^*\left(1-\frac{S^*}{S}\right)\left(1-\frac{D_1 S}{D_1^* S^*}\right) + \beta_0\eta_4 D_2^* S^*\left(1-\frac{S^*}{S}\right)\left(1-\frac{D_2 S}{D_2^* S^*}\right) + \beta_0\eta_5 A^* S^*\left(1-\frac{S^*}{S}\right)\left(1-\frac{AS}{A^* S^*}\right). \tag{A.24}$$

Let

$$\frac{S}{S^*} = r, \frac{I}{I^*} = u, \frac{T_1}{T_1^*} = v, \frac{T_2}{T_2^*} = w, \frac{D_1}{D_1^*} = x, \frac{D_2}{D_2^*} = y, \frac{A}{A^*} = z. \tag{A.25}$$

Substitute equation (A.25) into (A.24) and simplify, we have

$$= -\mu\left(\frac{(S-S^*)^2}{S}\right) + \beta_0 I^* S^*\left(1-ru-\frac{1}{r}+u\right) + \beta_0\eta_1 T_1^* S^*\left(1-rv-\frac{1}{r}+v\right) + \beta_0\eta_2 T_2^* S^*\left(1-rw-\frac{1}{r}+w\right) + \beta_0\eta_3 D_1^* S^*\left(1-rx-\frac{1}{r}+x\right) + \beta_0\eta_4 D_2^* S^*\left(1-ry-\frac{1}{r}+y\right) + \beta_0\eta_5 A^* S^*\left(1-rz-\frac{1}{r}+z\right). \tag{A.26}$$

Calculating terms relating to state variable I from equation (A.22) and substituting equation (3.2), we have

$$\tau_1\left(1-\frac{I^*}{I}\right)\left(\lambda S-\frac{\lambda S^* I}{I^*}\right),$$
$$= \tau_1\left(1-\frac{I^*}{I}\right)\left(\frac{\beta IS}{N}+\frac{\beta\eta_1 T_1 S}{N}+\frac{\beta\eta_2 T_2 S}{N}+\frac{\beta\eta_3 D_1 S}{N}+\frac{\beta\eta_4 D_2 S}{N}+\frac{\beta\eta_5 AS}{N}-\frac{\beta I^* S^* I}{NI^*}-\frac{\beta\eta_1 T_1^* S^* I}{NI^*}-\frac{\beta\eta_2 T_2^* S^* I}{NI^*}-\frac{\beta\eta_3 D_1^* S^* I}{NI^*}-\frac{\beta\eta_4 D_2^* S^* I}{NI^*}-\frac{\beta\eta_5 A^* S^* I}{NI^*}\right). \tag{A.27}$$

Substitute $\frac{\beta}{N} = \beta_0$ into equation (A.27) and simplify, gives

$$= \tau_1\beta_0 I^* S^* \left(1 - \frac{I^*}{I}\right)\left(\frac{IS}{I^*S^*} - \frac{I}{I^*}\right) + \tau_1\beta_0\eta_1 T_1^* S^* \left(1 - \frac{I^*}{I}\right)\left(\frac{T_1 S}{T_1^* S^*} - \frac{I}{I^*}\right) + \tau_1\beta_0\eta_2 T_2^* S^* \left(1 - \frac{I^*}{I}\right)\left(\frac{T_2 S}{T_2^* S^*} - \frac{I}{I^*}\right) + \tau_1\beta_0\eta_3 D_1^* S^* \left(1 - \frac{I^*}{I}\right)\left(\frac{D_1 S}{D_1^* S^*} - \frac{I}{I^*}\right) + \tau_1\beta_0\eta_4 D_2^* S^* \left(1 - \frac{I^*}{I}\right)\left(\frac{D_2 S}{D_2^* S^*} - \frac{I}{I^*}\right) + \tau_1\beta_0\eta_5 A^* S^* \left(1 - \frac{I^*}{I}\right)\left(\frac{AS}{A^* S^*} - \frac{I}{I^*}\right). \tag{A.28}$$

Substitute equation (A.25) into (A.28) and simplify, yields

$$= \tau_1\beta_0 I^* S^* (ru - u - r + 1) + \tau_1\beta_0\eta_1 T_1^* S^* \left(rv - u - \frac{rv}{u} + 1\right) + \tau_1\beta_0\eta_2 T_2^* S^* \left(rw - u - \frac{rw}{u} + 1\right) + \tau_1\beta_0\eta_3 D_1^* S^* \left(rx - u - \frac{rx}{u} + 1\right) + \tau_1\beta_0\eta_4 D_2^* S^* (ry - u - \frac{ry}{u} + 1) + \tau_1\beta_0\eta_5 A^* S^* \left(rz - u - \frac{rz}{u} + 1\right). \tag{A.29}$$

Calculating terms relating to state variable T_1 from equation (A.22), we have

$$\tau_2\left(1 - \frac{T_1^*}{T_1}\right)\left(\gamma\rho I - \frac{\gamma\rho I^* T_1}{T_1^*} - \frac{\theta_1 D_1^* T_1}{T_1^*} + \theta_1 D_1\right),$$
$$= \tau_2\gamma\rho I^*\left(1 - \frac{T_1^*}{T_1}\right)\left(\frac{I}{I^*} - \frac{T_1}{T_1^*}\right) + \tau_2\theta_1 D_1^*\left(1 - \frac{T_1^*}{T_1}\right)\left(\frac{D_1}{D_1^*} - \frac{T_1}{T_1^*}\right). \tag{A.30}$$

Substitute equation (A.25) into (A.30) and simplify, we have

$$= \tau_2\gamma\rho I^*\left(u - v - \frac{u}{v} + 1\right) + \tau_2\theta_1 D_1^*\left(x - v - \frac{x}{v} + 1\right). \tag{A.31}$$

Calculating terms relating to state variable T_2 from equation (A.22), we have

$$\tau_3\left(1 - \frac{T_2^*}{T_2}\right)\left(\gamma(1-\rho)I - \frac{\gamma(1-\rho)I^* T_2}{T_2^*} - \frac{\theta_2 D_2^* T_2}{T_2^*} + \theta_2 D_2\right),$$
$$= \tau_3\gamma(1-\rho)I^*\left(1 - \frac{T_2^*}{T_2}\right)\left(\frac{I}{I^*} - \frac{T_2}{T_2^*}\right) + \tau_3\theta_2 D_2^*\left(1 - \frac{T_2^*}{T_2}\right)\left(\frac{D_2}{D_2^*} - \frac{T_2}{T_2^*}\right). \tag{A.32}$$

Substitute equation (A.25) into (A.32) and simplify, we have

$$= \tau_3\gamma(1-\rho)I^*\left(u - w - \frac{u}{w} + 1\right) + \tau_3\theta_2 D_2^*\left(y - w - \frac{y}{w} + 1\right). \tag{A.33}$$

Calculating terms relating to state variable D_1 from equation (A.22), we have

$$\tau_4\left(1-\frac{D_1^*}{D_1}\right)\left(f(\xi_1)T_1-\frac{f(\xi_1)T_1^*D_1}{D_1^*}\right),$$
$$=\tau_4 f(\xi_1)T_1^*\left(1-\frac{D_1^*}{D_1}\right)\left(\frac{T_1}{T_1^*}-\frac{D_1}{D_1^*}\right). \tag{A.34}$$

Substitute equation (A.25) into (A.34) and simplify, we have

$$=\tau_4 f(\xi_1)T_1^*\left(v-x-\frac{v}{x}+1\right). \tag{A.35}$$

Calculating terms relating to state variable D_2 from equation (A.22), we have;

$$\tau_5\left(1-\frac{D_2^*}{D_2}\right)\left(f(\xi_2)T_2-\frac{f(\xi_2)T_2^*D_2}{D_2^*}\right),$$
$$=\tau_5 f(\xi_2)T_2^*\left(1-\frac{D_2^*}{D_2}\right)\left(\frac{T_2}{T_2^*}-\frac{D_2}{D_2^*}\right). \tag{A.36}$$

Substitute equation (A.25) into (A.36) and simplify, we have

$$=\tau_5 f(\xi_2)T_2^*\left(w-y-\frac{w}{y}+1\right). \tag{A.37}$$

Calculating terms relating to state variable A from equation (A.22), we have

$$\tau_6\left(1-\frac{A^*}{A}\right)\left(\alpha_1 I+\alpha_2 T_1+\alpha_3 T_2+\alpha_4 D_1+\alpha_5 D_2-\frac{\alpha_1 I^* A}{A^*}-\frac{\alpha_2 T_1^* A}{A^*}-\right.$$
$$\left.\frac{\alpha_3 T_2^* A}{A^*}-\frac{\alpha_4 D_1^* A}{A^*}-\frac{\alpha_5 D_2^* A}{A^*}\right),$$
$$=\tau_6\alpha_1 I^*\left(1-\frac{A^*}{A}\right)\left(\frac{I}{I^*}-\frac{A}{A^*}\right)+\tau_6\alpha_2 T_1^*\left(1-\frac{A^*}{A}\right)\left(\frac{T_1}{T_1^*}-\frac{A}{A^*}\right)+$$
$$=\tau_6\alpha_3 T_2^*\left(1-\frac{A^*}{A}\right)\left(\frac{T_2}{T_2^*}-\frac{A}{A^*}\right)+\tau_6\alpha_4 D_1^*\left(1-\frac{A^*}{A}\right)\left(\frac{D_1}{D_1^*}-\frac{A}{A^*}\right)$$
$$+\tau_6\alpha_5 D_2^*\left(1-\frac{A^*}{A}\right)\left(\frac{D_2}{D_2^*}-\frac{A}{A^*}\right). \tag{A.38}$$

Substitute equation (A.25) into (A.38) and simplify, we have

$$=\tau_6\alpha_1 I^*\left(u-z-\frac{u}{z}+1\right)+\tau_6\alpha_2 T_1^*\left(v-z-\frac{v}{z}+1\right)+\tau_6\alpha_3 T_2^*$$
$$\left(w-z-\frac{w}{z}+1\right)+\tau_6\alpha_4 D_1^*\left(x-z-\frac{x}{z}+1\right)+\tau_6\alpha_5 D_2^*\left(y-z-\frac{y}{z}+1\right). \tag{A.39}$$

Combining the expressions in equations (A.26), (A.29), (A.31), (A.33), (A.35), (A.37), and (A.39), equation (A.22) becomes

$$\dot{V} = -\mu\left(\frac{(S-S^*)^2}{S}\right) + f(r,u,v,w,x,y,z),$$

where

$$\begin{aligned} f(r,u,v,w,x,y,z) = {} & \beta_0 I^* S^* + \beta_0\eta_1 T_1^* S^* + \beta_0\eta_2 T_2^* S^* + \beta_0\eta_3 D_1^* S^* + \beta_0\eta_4 D_2^* \\ & S^* + \beta_0\eta_5 A^* S^* + \tau_1\beta_0 I^* S^* + \tau_1\beta_0\eta_1 T_1^* S^* + \tau_1\beta_0\eta_2 T_2^* S^* + \\ & \tau_1\beta_0\eta_3 D_1^* S^* + \tau_1\beta_0\eta_4 D_2^* S^* + \tau_1\beta_0\eta_5 A^* S^* + \tau_2\gamma\rho I^* + \\ & \tau_2\theta_1 D_1^* + \tau_3\gamma(1-\rho)I^* + \tau_3\theta_2 D_2^* + \tau_4 f(\xi_1)T_1^* + \tau_5 f(\xi_2)T_2^* \\ & + \tau_6\alpha_1 I^* + \tau_6\alpha_2 T_1^* + \tau_6\alpha_3 T_2^* + \tau_6\alpha_4 D_1^* + \tau_6\alpha_5 D_2^* + ru(\tau_1\beta_0 \\ & I^* S^* - \beta_0 I^* S^*) + rv(\tau_1\beta_0\eta_1 T_1^* S^* - \beta_0\eta_1 T_1^* S^*) + rw(\tau_1\beta_0\eta_2 \\ & T_2^* S^* - \beta_0\eta_2 T_2^* S^*) + rx(\tau_1\beta_0\eta_3 D_1^* S^* - \beta_0\eta_3 D_1^* S^*) + ry(\tau_1 \\ & \beta_0\eta_4 D_2^* S^* - \beta_0\eta_4 D_2^* S^*) + rz(\tau_1\beta_0\eta_5 A^* S^* - \beta_0\eta_5 A^* S^*) + \\ & \frac{1}{r}\Big(- \beta_0 I^* S^* - \beta_0\eta_1 T_1^* S^* - \beta_0\eta_2 T_2^* S^* - \beta_0\eta_3 D_1^* S^* - \\ & \beta_0\eta_4 D_2^* S^* - \beta_0\eta_5\Big) + u(\beta_0 I^* S^* - \tau_1\beta_0 I^* S^* - \tau_1\beta_0\eta_1 T_1^* S^* - \\ & \tau_1\beta_0\eta_2 T_2^* S^* - \tau_1\beta_0\eta_3 D_1^* S^* - \tau_1\beta_0\eta_4 D_2^* S^* - \tau_1\beta_0\eta_5 A^* S^* \\ & + \tau_2\gamma\rho I^* + \tau_3\gamma(1-\rho)I^* + \tau_6\alpha_1 I^*) + v(\beta_0\eta_1 T_1^* S^* - \tau_2 \\ & \gamma\rho I^* - \tau_2\theta_1 D_1^* + \tau_4 f(\xi_1)T_1^* + \tau_6\alpha_2 T_1^*) + w(\beta_0\eta_2 T_2^* S^* - \\ & \tau_3\gamma(1-\rho)I^* - \tau_3\theta_2 D_2^* + \tau_5 f(\xi_2)T_2^* + \tau_6\alpha_3 T_2^*) + x(\beta_0\eta_3 \\ & D_1^* S^* + \tau_2\theta_1 D_1^* - \tau_4 f(\xi_1)T_1^* + \tau_6\alpha_4 D_1^*) + y(\beta_0\eta_4 D_2^* S^* + \\ & \tau_3\theta_2 D_2^* + \tau_5 f(\xi_2)T_2^* + \tau_6\alpha_5 D_2^*) + z(\beta_0\eta_5 A^* S^* - \tau_6\alpha_1 I^* - \\ & \tau_6\alpha_2 T_1^* - \tau_6\alpha_3 T_2^* - \tau_6\alpha_4 D_1^* - \tau_6\alpha_5 D_2^*) + r(-\tau_1\beta_0 I^* S^*) + \\ & \frac{rv}{u}\Big(- \tau_1\beta_0\eta_1 T_1^* S^*\Big) + \frac{rw}{u}\Big(- \tau_1\beta_0\eta_2 T_2^* S^*\Big) + \frac{rx}{u}\Big(- \tau_1 \\ & \beta_0\eta_3 D_1^* S^*\Big) + \frac{ry}{u}\Big(- \tau_1\beta_0\eta_4 D_2^* S^*\Big) + \frac{rz}{u}\Big(- \tau_1\beta_0\eta_5 A^* S^*\Big) \end{aligned}$$

$$+\frac{u}{v}(-\tau_2\gamma\rho I^*)+\frac{x}{v}(-\tau_2\theta_1 D_1^*)+\frac{u}{w}\Big(-\tau_3\gamma(1-\rho)I^*\Big)$$
$$+\frac{y}{w}\Big(-\tau_3\theta_2 D_2^*\Big)+\frac{v}{x}(-\tau_4 f(\xi_1)T_1^*)+\frac{w}{y}(-\tau_5 f(\xi_2)T_2^*)+$$
$$\frac{u}{z}\Big(-\tau_6\alpha_1 I^*\Big)+\frac{v}{z}\Big(-\tau_6\alpha_2 T_1^*\Big)+\frac{w}{z}\Big(-\tau_6\alpha_3 T_2^*\Big)+$$
$$\frac{x}{z}\Big(-\tau_6\alpha_4 D_1^*\Big)+\frac{y}{z}\Big(-\tau_6\alpha_5 D_2^*\Big). \tag{A.40}$$

Solving for $\tau_i, i = 1,\cdots,6$ by using equation (A.40), all the coefficients of $ru, rw, rx, ry, rz, z, u, v, w, x, y, z$ becomes zero. Thus, we have

$$\tau_1 = 1,$$
$$\tau_2 = \frac{S^*(\beta_0\eta_1 T_1^* + \beta_0\eta_3 D_1^*)}{\gamma\rho I^*} + \frac{A^*S^*(\alpha_2 T_1^* + \alpha_4 D_1^*)\beta_0\eta_5}{\gamma\rho I^* P},$$
$$\tau_3 = -\frac{S^*(\beta_0\eta_2 T_2^* + \beta_0\eta_4 D_2^*)}{\gamma(\rho-1)I^*} + \frac{A^*S^*(\alpha_3 T_2^* + \alpha_5 D_2^*)\beta_0\eta_5}{\gamma(\rho-1)I^* P},$$
$$\tau_4 = \frac{\beta_0\eta_3\gamma\rho I^* S^* D_1^* P}{\gamma\rho I^* f(\xi_1)T_1^* P} + \frac{\beta_0\eta_5\gamma\rho D_1^* I^* A^* S^*}{\gamma\rho I^* f(\xi_1)T_1^* P} + \frac{\beta_0\eta_1\theta_1 D_1^* S^* T_1^* P}{\gamma\rho I^* f(\xi_1)T_1^* P} +$$
$$\frac{\beta_0\eta_3\theta_1 D_1^* S^* D_1^* P}{\gamma\rho I^* f(\xi_1)T_1^* P} + \frac{\beta_0\eta_5\alpha_2\theta_1 D_1^* T_1^* A^* S^*}{\gamma\rho I^* f(\xi_1)T_1^* P} + \frac{\beta_0\eta_5\alpha_4\theta_1 D_1^* A^* S^* D_1^*}{\gamma\rho I^* f(\xi_1)T_1^* P},$$
$$\tau_5 = \frac{\beta_0\eta_4\gamma(1-\rho)I^* S^* D_2^* P}{\gamma(1-\rho)I^* f(\xi_2)T_2^* P} + \frac{\beta_0\eta_5\gamma(1-\rho)D_2^* I^* A^* S^*}{\gamma(1-\rho)I^* f(\xi_2)T_2^* P} + \frac{\beta_0\eta_2\theta_2 D_2^* S^* T_2^* P}{\gamma(1-\rho)I^* f(\xi_2)T_2^* P}$$
$$+\frac{\beta_0\eta_4\theta_2 D_2^* S^* D_2^* P}{\gamma(1-\rho)I^* f(\xi_2)T_2^* P} + \frac{\beta_0\eta_5\alpha_3\theta_2 D_2^* T_2^* A^* S^*}{\gamma(1-\rho)I^* f(\xi_2)T_2^* P} + \frac{\beta_0\eta_5\alpha_5\theta_2 D_2^* A^* S^* D_2^*}{\gamma(1-\rho)I^* f(\xi_2)T_2^* P},$$
$$\tau_6 = \frac{\beta_0\eta_5 A^* S^*}{P},$$

where

$$P = I^*\alpha_1 + T_1^*\alpha_2 + T_2^*\alpha_3 + D_1^*\alpha_4 + D_2^*\alpha_5.$$

Substituting $\tau_i, i = 1, \cdots, 6$ into equation (A.40), simplifying and collecting like terms, we have

$$
\begin{aligned}
f(r,u,v,w,x,y,z) = {} & \beta_0 I^* S^* \left(2 - r - \frac{1}{r}\right) + \beta_0 \eta_1 T_1^* S^* \left(3 - \frac{1}{r} - \frac{rv}{u} - \frac{u}{v}\right) + \\
& \beta_0 \eta_2 T_2^* S^* \left(3 - \frac{1}{r} - \frac{rw}{u} - \frac{u}{w}\right) + \beta_0 \eta_3 D_1^* S^* \left(4 - \frac{1}{r} - \frac{rx}{u}\right. \\
& \left. - \frac{u}{v} - \frac{v}{x}\right) + \beta_0 \eta_4 D_2^* S^* \left(4 - \frac{1}{r} - \frac{ry}{u} - \frac{u}{w} - \frac{w}{y}\right) + \beta_0 \eta_5 \\
& A^* S^* \left(2 - \frac{1}{r} - \frac{rz}{u}\right) + \frac{\beta_0 \eta_5 \alpha_2 \theta_1 D_1^* T_1^* A^* S^*}{\gamma \rho I^* P} \left(2 - \frac{x}{v} - \frac{v}{x}\right) \\
& + \frac{\beta_0 \eta_5 \alpha_4 \theta_1 D_1^* A^* S^* D_1^*}{\gamma \rho I^* f(\xi_1) T_1^* P} \left(2 - \frac{x}{v} - \frac{v}{x}\right) + \frac{\beta_0 \eta_5 \alpha_2 A^* S^* T_1^*}{P} \\
& \left(2 - \frac{v}{z} - \frac{u}{v}\right) + \frac{\beta_0 \eta_5 \alpha_3 \theta_2 D_2^* T_2^* A^* S^*}{\gamma (1-\rho) I^* P} \left(2 - \frac{y}{w} - \frac{w}{y}\right) \\
& + \frac{\beta_0 \eta_5 \alpha_5 \theta_2 D_2^* A^* S^* D_2^*}{\gamma (1-\rho) I^* P} \left(2 - \frac{y}{w} - \frac{w}{y}\right) + \\
& \frac{\beta_0 \eta_5 \alpha_3 A^* S^* T_2^*}{P} \left(2 - \frac{w}{z} - \frac{u}{w}\right) + \frac{\beta_0 \eta_1 \theta_1 D_1^* S^* T_1^*}{\gamma \rho I^*} \\
& \left(2 - \frac{x}{v} - \frac{v}{x}\right) + \frac{\beta_0 \eta_5 \alpha_4 A^* S^* D_1^*}{P} \left(3 - \frac{x}{z} - \frac{u}{v} - \frac{v}{x}\right) + \\
& \frac{\beta_0 \eta_5 \alpha_5 A^* S^* D_2^*}{P} \left(3 - \frac{y}{z} - \frac{u}{w} - \frac{w}{y}\right) + \frac{\beta_0 \eta_3 \theta_1 D_1^* S^* D_1^*}{\gamma \rho I^*} \\
& \left(2 - \frac{x}{v} - \frac{v}{x}\right) + \frac{\beta_0 \eta_2 \theta_2 D_2^* S^* T_2^*}{\gamma (1-\rho) I^*} \left(2 - \frac{y}{w} - \frac{w}{y}\right) \\
& + \frac{\beta_0 \eta_5 \alpha_1 A^* S^* I^*}{P} \left(1 - \frac{u}{z}\right) + \frac{\beta_0 \eta_2 \theta_2 D_2^* S^* T_2^* D_2^*}{\gamma (1-\rho) I^*} \\
& \left(2 - \frac{y}{w} - \frac{w}{y}\right). \qquad \text{(A.41)}
\end{aligned}
$$

By the arithmetic-mean-geometric mean inequality, we note that

$$\left(2-r-\frac{1}{r}\right)\leq 0,\left(3-\frac{1}{r}-\frac{rv}{u}-\frac{u}{v}\right)\leq 0,\left(3-\frac{1}{r}-\frac{rw}{u}-\frac{u}{w}\right)\leq 0,$$
$$\left(4-\frac{1}{r}-\frac{rx}{u}-\frac{u}{v}-\frac{v}{x}\right)\leq 0,\left(4-\frac{1}{r}-\frac{ry}{u}-\frac{u}{w}-\frac{w}{y}\right)\leq 0,$$
$$\left(2-\frac{x}{v}-\frac{v}{x}\right)\leq 0,\left(2-\frac{v}{z}-\frac{u}{v}\right)\leq 0,\left(2-\frac{y}{w}-\frac{w}{y}\right)\leq 0,\left(2-\frac{w}{z}-\frac{u}{w}\right)\leq 0,$$
$$\left(3-\frac{x}{z}-\frac{u}{v}-\frac{v}{x}\right)\leq 0,\left(3-\frac{y}{z}-\frac{u}{w}-\frac{w}{y}\right)\leq 0,\left(1-\frac{u}{z}\right)\leq 0,$$
$$\left(2-\frac{1}{r}-\frac{rz}{u}\right)\leq 0.$$

Thus, it implies that

$$\dot{V}=-\mu\left(\frac{(S-S^*)^2}{S}\right)+f(r,u,v,w,x,y,z)\leq 0.$$

Also $\dot{V}=0$ only if $r=1, u=v=w=x=y=z$. Thus, the function V satisfies the Lyapunov stability theorem. This implies that the set $\left\{(S,I,T_1,T_2,D_1,D_2,A)\in\Omega|\dot{V}(S,I,T_1,T_2,D_1,D_2,A)=0\right\}$ consist only the point E_1 (Endemic equilibrium). Therefore, by Lyapunov's direct method, E_1 is globally asymptotically stable in the region Ω. By Lasalle's invariant principle from [45] we conclude that model (3.5) is globally asymptotically stable at E_1. Epidemiologically this means that the disease persist regardless of the initial states of the system.

□

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