A MATHEMATICAL MODEL OF HIV/AIDS POPULATION DYNAMICS WITH TREATMENT FAILURE AND TREATMENT DROPOUTS IN THE ERA OF UNIVERSAL TEST AND TREAT APPROACH.

BY

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Abstract

Antiretroviral therapy is currently the major intervention against HIV infection.However, with increased access to treatment through the universal test and treat approach, potential barriers to the overall success of this strategy such as treatment dropouts and treatment failure arise.We constructed a deterministic mathematical model of HIV/AIDS to study the possible effects of treatment failure and treatment dropouts on the population dynamics of the infection.The model incorporated a universal test and treat scenario and a separate sub population of treatment dropouts.The disease free and endemic equilibria is computed and the basic reproduction number $\mathcal{R}_0$ of the model, is determined using the next generation matrix method.Numerical simulations are presented to investigate the effect of treatment failure and treatment dropouts on the dynamics of the model and on the $\mathcal{R}_0$.From the expression of $\mathcal{R}_0$ it is shown that the treatment dropout class contributes to the overall model reproduction number.Results of the numerical simulations show that an increase in treatment dropouts leads to an increased transimission of the HIV infection in a population.Also, the results indicate that even in the absence of treatment dropouts and treatment failure the basic reproduction number remains above unit, highlighting the need for several control measures to end the epidemic.Treatment failure is shown to increase the maximum size of the AIDS class.The results from this study demonstrate the need to focus on increasing efforts of reducing treatment dropouts in combination with other intervention strategies, through monitoring adherence and identifying and enrolling back to antiretroviral therapy(ART) of treatment dropouts.Also there is need to improve on early diagnosis of treatment failure such that those on treatment do not progress to AIDS before they are put on second or third line ART.

Declaration

I, Calvin Nhendo, declare that this work is original and is not submitted to any University for the award of any degree.

Student Signature..... Date.....

Supervisor Signature..... Date.....

Dedication

To my beloved Tendy and Waka

Acknowledgements

I would like to thank God for giving me the strength to start and finish this research.My profound gratitude goes to Dr E. Chigidi for her assistance and guidance throughout the course of this dissertation.To my family and friends, thank you for all your support and encouragement throughout my studies.Much thanks to Precious Chiwira for her assistance with data fitting using R software and the National AIDS Council for providing the data.

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List of Abbreviations

Abbreviation	Meaning
HIV	Human immunodeficiency virus
AIDS	Acquired immune deficiency syndrome
UTT	Universal test and treat
DFE	Disease free equilibrium
EE	Endemic equilibrium
ART	Antiretroviral therapy
WHO	World health organisation
UNAIDS	Joint United Nations Programme on HIV/AIDS
ODE	Ordinary differential equation

Chapter 1

Introduction

1.1 General Introduction

1.1.1 Epidemiology of HIV/AIDS

HIV continues to be a major global public health issue, having claimed more than 35 million lives so far (WHO, 2018).At a global level, it is estimated that in 2016 alone, there were about 1.8 million new HIV infections, a decline from 2.1 million new infections recorded in 2015(UNAIDS, 2017).Although HIV incidence appears to be declining in general, in Sub-Saharan Africa the number of new infections remains high (Murray et al., 2014).Evidence shows that most people living with HIV are in low and middle-income countries (UNAIDS, 2017).Zimbabwe has one of the highest HIV prevalence in sub-Saharan Africa at 13.3%, with 1.3 million people living with HIV in 2017 and around 41000 new infections are recorded every year (WHO, 2018).The adult HIV prevalence in Zimbabwe has been on a decrease over the last ten years, from 16.5% in 2007 to 13.3% in 2017 as shown by the epidemic curve in Figure 1.1.

1.1.2 Universal test and treat (UTT) approach in HIV

Globally, 59% of adults and 52% of children living with HIV were receiving lifelong antiretroviral therapy (ART) in 2017(WHO, 2018). ART is currently the major intervention against HIV infection. In 2016 the WHO further expanded their HIV treatment guidelines from the eligibility criteria of $\leq$ 350 cells/μL CD4 count to targeted testing and immediate enrolment into ART (WHO, 2016).This move was necessitated by findings that not only does ART provide individual benefits such as increased life expectancy and reduced morbidity it also provides public benefits of reduced infectivity of those on treatment hence reducing incidence(Granich et al., 2009; UNAIDS, 2014). These expanded

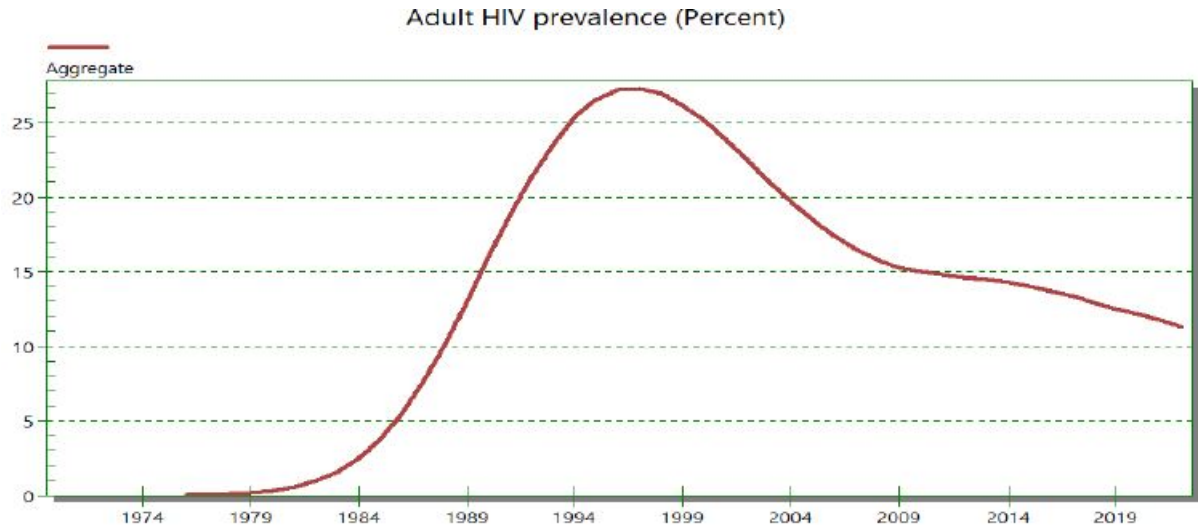

Figure 1.1: *SOURCE:GAM ZIMBABWE COUNTRY REPORT 2017*

guidelines that recommend treatment regardless of CD4 cell count, are referred to here as universal test and treat(UTT).UTT approach is defined as an intervention strategy in which the population at risk is screened for HIV infection and diagnosed HIV infected individuals receive early treatment(Nah et al., 2017).In support of the Joint United Nations Programme on HIV/AIDS (UNAIDS, 2014) 90-90-90 targets, Zimbabwe began to adopt the expanded guidelines in 2016 and currently 84% of HIV+ adults are on ART and 73% of all people receiving antiretroviral therapy have durable viral suppression, thereby reducing morbidity, mortality and onward HIV transmission (UNAIDS, 2018).

Since the introduction of UTT, empirical evidence indicate that UTT has led to reductions in nearly all epidemiological aspects of HIV/AIDS.For example a recent randomised controlled trial (RCT) assessed the impact of UTT among people enrolling in HIV care in the Kingdom of eSwatini, from 2014 to 2017(Khan et al., 2018).After six months in HIV care, patients enrolling under UTT had higher levels of viral suppression than those enrolling under the standard of care condition.In addition, two large-scale randomised studies conducted to examine the impact of UTT in Botswana from 2013 to 2018 showed that HIV incidence in the UTT communities was 30% lower than that of the control communities and the viral suppression rate was higher in communities under UTT than in the control communities(Makhema et al., 2019).However, though immediate ART reduces virological failure as shown by the studies quoted above, there is evidence of it increasing treatment dropout.Treatment dropout and poor adherence are risk factors of drug resistance which leads to treatment failure, especially when those who would have dropped out of treatment are re initiated (Matare et al., 2015; Kan et al., 2017).For example, an observational cohort study found significantly higher ART attrition rate among HIV patients with CD4 count $>$ 500 cells/μL (Tang et al., 2017).Moreover, in a nationwide cohort study of ART timing in China between 2011-2015 by Zhao and colleagues , sig-

nificantly greater risk of treatment dropout was found among those who had a baseline CD4 count $>$ 350 cells/μL (Zhao et al., 2018).Such findings pose a potential barrier to achieving the new WHO treatment guidelines and success of the UTT approach because, allowing treatment of all HIV positive patients regardless of their cd4 counts means that we have more people with higher cd4 counts being treated and as a result more treatment dropouts are expected.

1.1.3 HIV treatment failure

ART treatment failure is defined as progression of disease and high risk of mortality after beginning of ART(Aldous and Haubrich, 2009).It can be assessed by clinical failure, immunologic failure or virological failure(Deeks et al., 2009).Factors that can contribute to HIV treatment failure include drug resistance, drug toxicity, or poor adherence to ART.Studies conducted in East Africa have revealed a higher prevalence of immunologic failure ranging from 11 to 57% among patients on ART(Reynolds et al., 2009; Jaka et al., 2009; Ahoua et al., 2009).In a study by Mutasa-Apollo and colleagues in Zimbabwe, treatment failure rate which was based on a clinical/immunologic definition was 0.2% lower than the average treatment failure rate of 2.64% reported for Africa(Mutasa-Apollo et al., 2014).ART plays a critical role in the medical management of HIV infected individuals by restoring the immune function and minimizes HIV related outcomes. However treatment failure minimizes these advantages and leads to an increment of morbidity and mortality with poor quality of life in HIV patients.Hence the current study seeks to determine the effect of treatment failure and treatment dropouts on achieving HIV elimination in a population, given an increased access to ART.

1.1.4 Treatment dropout

Although major gains have been made in combating HIV infection and its deplorable effects, significant challenges remain in the implementation of HIV treatment services.These challenges include, among others, the issue of treatment dropouts.Those individuals who either stop treatment or are lost from treatment programs are referred to as treatment dropouts.The majority of these dropouts are due to loss to follow-up.Globally, attrition rates from ART is around 20%(Renaud-Théry et al., 2010).However,studies from sub-Saharan Africa have shown that the cumulative incidence of dropout after 3 years of follow-up can be up to 35% with even higher rates seen among young people(Fox and Rosen, 2010).In particular, among patients initiating ART, dropout from treatment is as high as 30 to 50 % at 1 year in some programs(Koole et al., 2014).Similar studies in Zimbabwe found rates of patient attrition at 6, 12, 24 and 36 months to be 9.3%, 21.9%, 31.2% and 35.6%, respectively (Mutasa-Apollo et al., 2014).Due to increased ac-

cess to treatment as a result of the adoption of UTT approach, higher rates of loss to follow-up are expected and this is an important threat to the success of HIV treatment programs.Those patients that are lost to follow-up can interrupt their treatment, resulting in continued HIV transmission , disease progression and death.In addition those who dropout may end up being re- initiated into treatment programs and may contribute to drug resistance and subsequent treatment failure(Klein et al., 2014).

1.2 Background

HIV testing and subsequent treatment of infected individuals as soon as possible is currently the main intervention against HIV infection.In 2013 the UNAIDS set ambitious target known as the 90-90-90 targets, premised on the need, by 2020, to have 90 percent of all PLHIV know their HIV status, 90 percent of all PLHIV diagnosed with HIV receive sustained ART, and 90 percent of all PLHIV receiving ART have viral suppression(UNAIDS, 2014).By the year 2030, UNAIDS is even aiming to achieve 95–95-95 at a global level.Several studies have shown that early initiation and expanded ART of HIV patients results in decreased morbidity,mortality and HIV transmission and substantial herd immunity could be attained assuming that a high adherence level is maintained for decades (Granich et al., 2009; Garnett and Baggaley, 2009; Montaner et al., 2014).In light of these findings the WHO (2016) consolidated ART guidelines was birthed,which changed the strategy of HIV treatment to include all HIV positive individuals regardless of their cd4+ count, usually reffered to as the UTT approach.

In line with this strategy, Zimbabwe began to adopt the WHO recommendations in 2016 in order to increase ART access.As of 2018 90% of people living with HIV in Zimbabwe knew their status and an estimated 88% of all people living with HIV where receiving antiretroviral therapy(UNAIDS, 2018). However, evidence shows that if patients cannot be retained in HIV care through long-term adherence to ART, such strategies may fall short of expected gains(Stricker et al., 2014).Treating all means that we have a higher proportion of ART patients who are less motivated to adhere or continue with treatment especially those who start at higher cd4 counts because these patients consider themselves or feel 'healthy' and are usually asymptomatic(Charurat et al., 2010).Poor adherence to ART is one of the stongest predictors of treatment failure.In addition those who dropout of treatment may get re-initiated with advanced disease thereby increase likelihood of treatment failure and death.

The initial modelling analysis of expanded ART which was done in South Africa in 2009 suggested that the transmission-prevention effects of ART, when implemented in the context of UTT, could nearly eliminate HIV transmission in a generalised epidemic(Granich

et al., 2009).However, findings from this ground breaking study where based on unrealistic and optimistic scenarios such as ART scale-up that reaches full coverage by 2016 and 100% annual uptake of voluntary HIV testing and high adherence levels .Afterwards , several studies that examined UTT focused on the HIV transmission related outcomes (e.g. prevalence and incidence), health and economic outcomes of the approach while few studies in Southern Africa quantified the unintended consequences and real-world challenges of UTT, such as development of resistance (Granich et al., 2012; Kimmel et al., 2018).Though various aspects of the UTT have been investigated such as frequency of testing, test coverage and initiation of ART(Granich et al., 2009; Kretzschmar et al., 2013),none have explicitly focused on the role of treatment failure and treatment dropout in attempts to drive the infection towards elimination .In a study by Nah and coworkers, they noted that retention in care to prevent treatment dropout and ensuring adherence to achieve a successful viral load suppression, are some of the tasks to be ensured to attain and maintain the population effects of UTT (Nah et al., 2017).Therefore, a mathematical model analysis which incorporates the role of treatment dropouts and treatment failure can give insights into the future outcomes of UTT, given these real- world challenges.

1.3 Statement of the problem

Increase in ART access through UTT approach is associated with an increase in treatment failure and treatment dropout which in turn delay the achievement of a decline of new HIV infections and achievement HIV elimination.While most studies on UTT have focused on the health and economic outcomes of the approach, the possible negating effects of treatment failure and treatment dropouts on the impact of UTT have not been extensively studied.

1.4 Research question

How do the issues of treatment failure and treatment dropouts affect the overall effectiveness of ART scale up programs?

1.5 Aim and Objectives

1.5.1 Aim of the study

The main aim of the study is to assess the impact of universal test and treat approach on HIV/AIDS dynamics in a population, taking into consideration treatment dropout and treatment failure.

1.5.2 Specific objectives

The specific objectives of the study are to:

- Design a model for the transmission dynamics of HIV/AIDS that incorporates test and treat approach, treatment failure and treatment drop-outs.
- Determine the basic reproduction number for this model analysis.
- Find the model equilibria and analyse their stability.
- Analyse the impact of treatment failure and dropouts on the basic reproduction number and apply this in providing recommendations on HIV care.

1.6 Significance of the study

This study will provide a mathematical model that can be used to explain and predict the effects of treatment failure and treatment dropouts on the dynamics of HIV infection with expanded access to ART.Results of the contribution of these factors in the population dynamics of HIV/AIDS can assist policy makers to apply and focus on new strategies to improve management of treatment failure and treatment dropouts, leading to optimal outcomes in HIV/AIDS management.

1.7 Dissertation structure

This dissertation consists of five chapters. Chapter 1 comprises the introduction of the study.Chapter 2 highlights some mathematical tools that are used throughout the rest of this dissertation.Chapter 3 provides a literature review in mathematical modelling of HIV/AIDS and models of the UTT approach to HIV/AIDS management are examined.In Chapter 4 we construct an HIV/AIDS model with UTT, treatment failure and treatment dropouts.Model analysis is done in Chapter 5 and this involves determination of the disease free and endemic equilibrium points and their local stability. Also, the next generation matrix will be used to compute the basic reproduction number for the model.Numerical simulations are carried out to assess the effects of treatment failure and treatment dropouts on the dynamics of the epidemic .The discussion and conclusion are given in Chapter 6.

Chapter 2

Mathematical Tools

This chapter presents some basic mathematical theories and methodologies that will be used in this dissertation.Fundamental theorems of ordinary differential equations and concepts such as Lyapunov function theorem,Hartman-Grobman theorem,Linearization and the Next generation method are presented.In the final section of this chapter we present some epidemiological concepts relevant to this study.

2.1 Mathematical Preliminaries

2.1.1 Ordinary differential equations

Material for this section is obtained from (Wiggins, 2003) and (Strogatz, 2018).

Differential equations are relations between a function and its derivatives. When the function depends upon a single variable, the resulting differential equation is ordinary as opposed to *partial* .Only the ordinary differential equations(ODE) will be considered in this dissertation.In compartmental disease models, the independent variable is time t, the rate of transfer between compartments are expressed mathematically by the derivatives of the compartments with respect to time.
We consider the *first order ordinary differential equation* initial value problem of the form,

$$\frac{dx}{dt} = f(x,t), \quad x(0) = x_0 \tag{2.1}$$

where $f(x)$ is bounded in a neighbourhood of the initial condition,$t \in \mathbb{R}$ is an independent variable, $x(t)$ is a dependent variable (unknown function) and $f : \mathbb{R}^n \to \mathbb{R}^n$ is a vector field.Equation (3.1) is known as a nonautonomous ordinary differential equation.If f does not depend explicitly on time, then (3.1) is called autonomous and takes the following form,for $x \in \mathbb{U} \subset \mathbb{R}^n$

$$\dot{x} = f(x), \quad x(0) = X \in \mathbb{R}^n \tag{2.2}$$

The over dot in (3.2) represents the derivative with respect to time ($\frac{dx}{dt}$).For $f_i : \mathbb{R}^n \to \mathbb{R}^n$ and $x_i \in \mathbb{R}^n$ a system of ODEs is defined when $n > 1$ otherwise, for $n = 1$ the equation is scalar and (3.2) is is referred to as a vector field on $\mathbb{R}^n$.The system of ODEs to be analysed in this thesis is autonomous and takes the form $\dot{x} = f(x)$, with $x \in \mathbb{R}^5_+$ and $f : \mathbb{R}^5_+ \to \mathbb{R}^5_+$.

Definition 1. *(The initial value problem).A first order ODE, $\dot{x} = f(x,t)$, together with an initial condition $x(t_0) = x_0$ is called an* ***initial value problem*** *.The initial condition $x(t_0) = x_0$ represents the position of the objects at some initial time t_0. A solution of an initial value problem is a differentiable function $x(t)$ such that $\dot{x} = f(t, x(t))$ for all t in an interval containing t_0 where $x(t)$ is defined and $x(t_0) = x_0$.*

Definition 2. *By a solution of* (3.2)*, we mean a continuously differentiable function $x : I(X) \to \mathbb{R}^n$ such that $x(t)$ satisfies* (3.2)*. Where $x(0) = X \in \mathbb{R}^n$*

Definition 3. *(Well-posedness). System* (3.1) *is well-posed if solutions exist, are unique, and for systems describing populations, remain bounded and nonnegative for all nonnegative initial conditions.*

Theorem 1. *(Cauchy-Lipschitz). Consider the differential equation* (3.2)*. with $x \in \mathbb{R}^n$ and suppose that $f \in \mathbf{C}^1$.Then there exists a unique solution of* (3.2) *such that $x(t_0) = x_0$, where $t_0 \in \mathbb{R}^n$,defined on the largest interval $t_0 \in I$ on which $f \in \mathbf{C^1}$.*

Theorem 2. *Let f and its partial derivatives $\partial F_i/\partial x_j$ in* (3.2) *be continuous in $\mathbb{R}^n$ and let $x_0 \in \mathbb{R}^n$ and $t_0 \in \mathbb{R}^n$.Then there is an interval $|t - t_0| < h$ in which there exists a unique solution $x(t) = \phi(t)$ of the system that also satisfies the initial conditions.*

2.1.2 Equilibria and Stability of solutions for autonomous systems

Material from this section can be found in (Wiggins, 2003) and (Wairimu, 2012).

Definition 4. *(Equilibrium point). A point $\bar{x} \in \mathbb{R}^n$ is an equilibrium point of the system* (3.2) *if $f(\bar{x}, t) = 0$ i.e., a solution which does not change with time.The term "equilibrium point" can be used interchangeably with the following: "fixed point", "stationary point" or "steady state".*

Let $\bar{x}(t)$ be any solution of (3.2). Then, $\bar{x}(t)$ is stable given solutions starting near $\bar{x}(t)$ remain close to $\bar{x}(t)$ for all future times.Also, if nearby solutions converge to $\bar{x}(t)$ as $t \to \infty$ then the fixed point is said to be asymptotically stable.

Definition 5. *(Stable and unstable equilibrium point).* $\bar{x}(t)$ *is said to be stable (or Lyapunov stable) if, given* $\epsilon > 0$*, there exists a* $\sigma = \sigma(\epsilon) > 0$ *such that, for any other solution,* $y(t)$*, of* (3.2) *satisfying* $|\bar{x}(t_0) - y(t_0)| < \sigma$*, then* $|\bar{x}(t) - y(t)| < \epsilon$ *for* $t > t_0$*,* $t_0 \in \mathbb{R}^n$

Therefore, a solution which is not stable according to this definition is referred to as unstable.

Definition 6. *(Attractivity). The steady state* $\bar{x}$ *is said to be attractive if there exists a neighbourhood* $U \in \Omega$ *of* $\bar{x}$ *such that for any initial condition* x *belonging to* U*, the corresponding solution of* (3.2) *is defined for all* $t \geq 0$ *and tends to* $\bar{x}$ *as* $t \to \infty$*.*

Definition 7. *(Asymptotically stable equilibrium point).* $\bar{x}(t)$ *is asymptotically stable if it is Lyapunov stable and for any other solution,* $y(t)$*, of* (3.2)*, there exists a constant* $b > 0$ *such that, if* $|\bar{x}(t_0) - y(t_0)| < b$*, then* $\lim_{t\to\infty} |\bar{x}(t) - y(t)| = 0$*.In simpler terms* $\bar{x}$ *is said to be stable if solutions starting near it at a given time, remain near it for all later times.If nearby solutions actually converge to* $\bar{x}$ *at* $t \to \infty$ *it is said to be asymptotically stable meaning it is both Lyapunov stable and attractive.*

Definition 8. *(Global stability). We say an equilibrium point* $\bar{x}$ *is globally stable if it is stable for all initial conditions* $x_0 \in \mathbb{R}^n$*.*

2.1.3 Linearization

We will be using information from (Wiggins, 2003).

The stability of $\bar{x}(t)$ is determined by first understanding the nature of solution near $\bar{x}(t)$.Let

$$x = \bar{x}(t) + y, \quad y \in \mathbb{R}^n. \tag{2.3}$$

Substituting (3.3) into (3.2) and Taylor expanding about $\bar{x}$ gives

$$\dot{x} = \dot{\bar{x}} + \dot{y} = f(\bar{x}(t)) + Df(\bar{x}(t))y + \mathcal{O}(|y|^2), \tag{2.4}$$

where Df is the derivative of f and $|.|$ denotes a norm on $\mathbb{R}^n$.To obtain (3.4) f must be at least twice differentiable.Using the fact that $\dot{\bar{x}}(t) = f(\bar{x}(t))$, (3.4) becomes

$$\dot{y} = Df(\bar{x}(t))y + \mathcal{O}(|y|^2) \tag{2.5}$$

Equation (3.5) describes the evolution of orbits near $\bar{x}$.For stability we are concerned with the behaviour of solutions arbitrarily close to $\bar{x}(t)$,so it seems reasonable to study the associated linear system

$$\dot{y} = Df(\bar{x}(t))y. \tag{2.6}$$

Therefore, the question of stability of $\bar{x}(t)$ involves two steps.Firstly, determine if the $y = 0$ solution of (3.6) is stable and then show that the stability(or instability) of the $y = 0$ solution of (3.6) implies stability (or instability) of $\bar{x}(t)$.However, if $\bar{x}(t)$ is an equilibrium solution, i.e $f(\bar{x}) = 0$, then $Df(\bar{x})$ is a matrix with constant entries, and the solution of (3.6) through the point $y_0 \in \mathbb{R}^n$ at $t = 0$ can be written as

$$y(t) = e^{Df(\bar{x}(t))}y_0 \tag{2.7}$$

If all eigenvalues of $Df(\bar{x})$ have negative real parts it means that $y(t)$ is asymptotically stable.

Theorem 3. *Suppose all of the eigenvalues of $Df(\bar{x})$ have negative real parts. Then the equilibrium solution $x = \bar{x}$ of the nonlinear vector field (3.2) is asymptotically stable.*

Definition 9. ***(Hyperbolic Fixed Point)**. Let $x = \bar{x}$ be a fixed point of $\dot{x} = f(x)$, $x \in \mathbb{R}^n$. Then $\bar{x}$ is called a hyperbolic fixed point if none of the eigenvalues of $Df(\bar{x})$ have zero real part.A hyperbolic fixed point is called a saddle if some, but not all, of the eigenvalues have positive real parts. If all the eigenvalues have negative real part, then the hyperbolic fixed point is stable and if all of the eigenvalues have positive real part, then it is unstable.*

Definition 10. *A **nonhyperbolic fixed point** is a fixed point having the real part of some of the eigenvalues associated to the linearized system equal to zero,that is, these eigenvalues are purely imaginary.Such fixed point is said to be a center if the system is linear.*

Theorem 4. *(Hartman and Grobman). Assume that $\bar{x} \in \mathbb{R}^n$ is a hyperbolic equilibrium (all eigenvalues of the Jacobian matrix evaluated at $\bar{x}$ have nonzero real part). Then, in a small neighbourhood of $\bar{x}$, the nonlinear system behaves in a similar manner as the linearized system.*

2.1.4 Routh-Hurwitz criteria

The Routh-Hurwitz criterion is necessary for establishing the local stability of solutions of a dynamical system.This criterion provides a systematic way to show that the linearized equations of motion of a sys- tem have only stable solutions by assessing the nature of the roots of the characteristic polynomial of the matrix associated with the linearization about the equilibrium point of interest. Consider a polynomial with real coefficients of the form:

$$p(\lambda) = a_0\lambda^n + a_1\lambda^{n-1} + ... + a_{n-1}\lambda + a_n, \quad a_i \in \mathbb{R}, \quad a_0 \neq 0. \tag{2.8}$$

The Routh table associated with the polynomial (2.8) is given by:

a_0	a_2	a_4	a_6	. . .
a_1	a_3	a_5	a_7	. . .
$r3,1$	$r3,2$	$r3,3$	$r3,4$	. . .
$r4,1$	$r4,2$	$r4,3$	$r4,4$	. . .
.	.	.	.	
.	.	.	.	
.	.	.	.	. . .
$r_{n+1,1}$	$r_{n+1,2}$	$r_{n+1,3}$	$r_{n+1,4}$	. . .

where,

$$(r_{i,1} \quad r_{i,2}...) \equiv (r_{i-2,2} \quad r_{i-2,3}...) - \frac{r_{i-2,1}}{r_{i-1,1}}(r_{i-1,2} \quad r_{i-1,3}...), \quad i > 2.$$

Theorem 5. *(Routh-Hurwitz Test) All of the roots of the polynomial* (2.8) *have real parts strictly less than zero if and only if all n+1 elements in the first column of the Routh table are nonzero and have the same sign.*

Hence, it follows that the equilibrium point is locally stable if all the roots of the characteristic polynomial are less than zero.

2.1.5 Next generation method

The next generation method is a linearisation method that is used to establish the local asymptotic stability of the disease-free equilibrium (DFE)and the basic reproduction number($\mathcal{R}_0$).This technique was developed first by Diekmann et al. (1990) and later developed by Van den Driessche and Watmough (2002) for finite dimensional systems .The method by van den Driessche and Watmough is going to be presented.In this method $\mathcal{R}_0$ is defined as the spectral radius of the Next Generation Operator. The determination of the operation involves the distribution into two compartments, the compartment of infected (latent, infectious, e.t.c) and the compartment of uninfected individuals. Consider an epidemiological model with no classes or with homogeneous compartments. The vector x represents the state of the system and x_j is the number of individuals in compartment j.For clarity the compartments are sorted such that the first k compartments correspond to infected individuals while the others are the infected compartments.

Set the vector $x = x_j, \quad j = 1, ..., n$ where x_j is the number of individuals in compartment j.

Let $\mathcal{F}_j(x)$ be the rate of appearance of new infections in compartment i ,$\mathcal{V}_i^+(x)$ be the rate of transfer of individuals into compartment i by all other means, and $\mathcal{V}_j^-(x)$, the rate of transfer of individuals out

of compartment j.It is assumed that each function is continuously differentiable at least twice in each variable.The dynamics of the compartment is defined by

$$\dot{x}_j = F_j(x) + V_j^+(x) - V_j^-(x)$$

If we put $V_j(x) = V_j^+(x) - V_j^-(x)$ the previous system becomes

$$\dot{x}_j = F_j(x) + V_j(x). \tag{2.9}$$

At the DFE, x_0 , the infected compartments are empty ie $j > k, (x_0)_j = 0$.Since each function represents a directed transfer of individuals, they are all non-negative.Thus we have the following hypothesis:

1. $x \geq 0$, then $\mathcal{F}_i$,$\mathcal{V}_i^+$,$\mathcal{V}_i^- \geq 0$ for $i = 1, \ . \ . \ . \ , n$.For biological reasons all the functions are non-negative.If a compartment is empty, then there can be no transfer of individuals out of the compartment by death, infection, nor any other means. Thus,

2. If $x_i = 0$ then $\mathcal{V}_j^-(x) = 0$. In particular, we if set $X_s = \{x \geq 0; x_j = 0, i = 1, ..., n\}$ and if $x \in X_s$, then $\mathcal{V}_j^-(x) = 0$.In other words, there can be no transfer from an empty compartment.

3. $\mathcal{F}_i = 0$ if $i > k$.The condition arises from the simple fact that the incidence of infection for uninfected compartments is zero.That is, there is no immigration of infectives from the uninfected compartment.

4. If x_0 is the disease free state then $\mathcal{F}_j(x_0) = 0$ and for $j \geq k$, $\mathcal{V}_j^+(x_0) = 0$.This ensures that the disease free subspace is invariant, if the population is free of disease then introduction of a few infected individual will not result in an epidemic ,the population will remain free of disease.

   The remaining condition is based on the derivatives of f near a DFE. For our purposes, we define a DFE of (3.8) to be a (locally asymptotically) stable equilibrium solution of the disease free model, i.e., (3.8) restricted to X_s. Note that we need not assume that the model has a unique DFE. Consider a population near the DFE x_0. If the population remains near the DFE then the population will return to the DFE according to the linearized system

   $$\dot{x} = Df(x_0)(x - x_0), \tag{2.10}$$

   where $Df(x_0)$ is the Jacobian matrix of f evaluated at the DFE, x_0.

5. If $\mathcal{F}(x)$ is set to zero, then all eigenvalues of $Df(x_0)$ have negative real parts.

The conditions listed above allow us to partition the matrix $Df(x_0)$ as shown by the following lemma.

Lemma 1. *If x_0 is a DFE of* (3.8) *and $f_i(x)$ satisfies all the conditions*(1-5)*, then the derivatives $D\mathcal{F}(x_0)$ and $D\mathcal{V}(x_0)$ are partitioned as*

$$D\mathcal{F}(x_0) = \begin{pmatrix} F & 0 \\ 0 & 0 \end{pmatrix}, \quad D\mathcal{V}(x_0) = \begin{pmatrix} V & 0 \\ J_3 & J_4 \end{pmatrix},$$

where F and V are the $k \times m$ matrices defined by :
$F = \left[\dfrac{\partial \mathcal{F}_i}{\partial x_j}(x_0)\right]$ *and* $V = \left[\dfrac{\partial \mathcal{V}_i}{\partial x_j}(x_0)\right]$ *with* $1 \leq i, j \leq k$.

Further, F is non-negative, V is non-singular and J_3 and J_4 are matrices of the transition terms and all eigenvalues of J_4 have positive real parts.The matrix FV^{-1} is called the Second Generation Matrix.

Definition 11. *(Basic Reproduction Number, $\mathcal{R}_0$). The basic reproduction number, $\mathcal{R}_0$ is the spectral radius of the second generation matrix, namely*

$$\mathcal{R}_0 = \rho(-FV^{-1})$$

Theorem 6. *Consider the disease transmission model given by* (3.8) *with $f(x)$ satisfying conditions* (1–5)*. If x_0 is a DFE of the model, then x_0 is locally asymptotically stable if $\mathcal{R}_0 < 1$, but unstable if $\mathcal{R}_0 > 1$.*

2.2 Epidemiological preliminaries

2.2.1 Definition of some basic terms

The following definitions are common in the epidemiology literature. References used here are (Mishra et al., 2011) and (Takeuchi et al., 2007).

- *Epidemiology* is the study of the distribution and determinants of health related states or events in specified populations and the application of this study to the control of health problems.

- *Susceptible*:Group of individuals in a given population who are not infectious by the disease under consideration but can become infected as a result of their interactions with infected individuals or by having contacts with infected objects. Their susceptibility is dependent on the disease under consideration; entering into the susceptible compartment can occur at birth, onset of sexual maturity (e.g., for sexual transmitted diseases), or loss of protective immunity.

- *Exposed (Latently infected)*:Group of individuals who have been infected with the disease, but have not started transmitting the disease due to incubation. Incubation is the time from the time of exposure to an infectious disease until on set of the disease symptoms.

- *Infectious*: Group of individuals who are infected with the disease and are capable of transmitting the infection to uninfected individuals. Transmission could be directly to other individuals or through other means such as vectors or the environment.

- *Recovered /removed*:Group of individuals who are no longer susceptible to the infection at that time. Recovered individuals are individuals who were once infected with the infection and have developed immunity against it. The recovery can be temporary, that is, individuals can be reinfected, or permanent (no reinfection). Removed individuals do not affect the transmission dynamics of the infection. The removal could be through isolation from the rest of the population, through immunization against the infection, through recovery from the disease with full immunity against reinfection or through death caused by the disease.

- *Vertical transmission*:Process in which an infected mother transfers the infection to her child during delivery or through breast feeding.

- *Horizontal transmission*:Transmission of infection through body contact or through contact with infected equipment or materials.

- *Force of infection*:The transmission dynamics of an infection depends on the per capita incidence rate of the infection $\lambda(t)$in relation to susceptible individuals,$\lambda(t)$ forms the basis for the transmission dynamics in the model. The force of infection accounts for the transmission process between infectious and susceptible individuals and depends on the prevalence of infection in the population, $I(t) \,/\, N(t)$, where $I(t)$ is the number of the infectious individuals at time t and $N(t)$ is the total population at time t . Assuming homogeneous mixing assumption $\lambda(t) = \beta c I(t) \,/\, N(t)$ where c represents the contact rate and β is the transmission probability per contact. Transmission between the infected and the susceptible depends on how the contact structure is expected to change with the total population.

  The transmission dynamics could follow any of the two ways:

  1. *Density-dependent (standard incidence) transmission*In this case, contacts are assumed to be proportional to the total population density ie: $c = cN \approx N$ and $\lambda(t) = \beta I(t)$. The number of newly infected individuals is obtained from $\lambda(t)S(t)$, which depends on the number of infectious individuals and susceptible individuals in the population, if random mixing is assumed.

2. *Frequency-dependent (mass action) transmission*:This is the case in which the number of contacts is assumed to be independent of the total population.The type of contacts required for the transmission depends on the mode of transmission of the infection (e.g, physical contact for directly transmitted infection such as influenza, chickenpox, or physical contact for sexually transmitted infection such as gonorrhoea and HIV).

- *Incidence* is the number of new cases of illness (infection) occurring in a population during a given time period.
- *Prevalence* is the number or proportion of cases of illness present in a given population at a specific point in time.
- *Endemic* :refers to the constant presence of a disease or infectious agent within a given geographic area or population group; may also refer to the usual prevalence of a given disease within such area or group.
- *Epidemic*:the occurrence of more cases of disease, in a given area or among a specific group of people over a particular period of time, than what is expected.
- *Pandemic:*An epidemic occurring over a very wide area and usually affecting a large proportion of the population such as several countries or continents.
- *Disease free equilibrium* is the state where the population is completely free from infection; the implication is that all infected compartments are zero and the total population comprises only susceptible or immune individuals.
- *Endemic equilibrium*is the state where the infection remains in the population, so there is a positive number of infectious individuals at equilibrium.

2.2.2 The basic reproduction number

The basic reproduction number, denoted by $\mathcal{R}_0$, is the expected number of secondary cases produced, in a completely susceptible population, by one infective individual during his/her entire period of infectiousness(Diekmann et al., 1990).Mathematical epidemic models, exhibit a threshold behaviour.If $\mathcal{R}_0 < 1$, then an infected individual produces on average less than one new infected individual during the course of their infectiousness, and the infection cannot grow.Conversely, if $\mathcal{R}_0 > 1$, then each infected individual produces more than one new infected individual, and the disease can spread in the population.For the case of a single infected compartment, $\mathcal{R}_0$ is simply the product of the infection rate and the mean duration of the infection. However, for more complicated models with several infected compartments this simple definition of $\mathcal{R}_0$ is insufficient(Van den Driessche and Watmough, 2002).

The disease outbreak could progress rapidly enough such that demographic effects in the population could be ignored but the disease will still die out if $\mathcal{R}_0$ is less than one, and if it exceeds unity, there will be an epidemic. In either case, the disease will die out if $\mathcal{R}_0$ is less than one, and if it exceeds unity, there will be an epidemic.Mathematically, if $\mathcal{R}_0 < 0$, the disease-free equilibrium is approached by solutions of the model describing the situation and if $\mathcal{R}_0 > 0$, the disease-free equilibrium is unstable and solutions move away from it. Furthermore, there is an endemic equilibrium with a positive number of infective individuals. In this case, the disease remains endemic in the population however, with more than one stable equilibrium when $\mathcal{R}_0$ is less than one, the situation may be different(Hethcote, 2000).

Chapter 3

Literature review

3.1 Review on universal test and treat approach

The Joint United Nations Program on HIV and AIDS (UNAIDS) set the 90-90-90 targets in 2013 with the goal of ending AIDS by the year 2030 (UNAIDS, 2014).These goals states that by the year 2020, 90% of all HIV-positive persons will know their HIV status, 90% of those with a diagnosis of HIV infection will receive sustained ART, and 90% of persons receiving ART will have attained viral suppression.In addition, the WHO reviewed ART guidelines in 2015 to allow an expanded access to ART such that all those who test HIV positive are immediately initiated on treatment regardless of their cd4 count otherwise referred to as the universal test and treat approach (UTT)(WHO, 2015).Since the inception of these new ART guidelines several intervention studies have demonstrated an increased level of viral suppression and reduced incidence of HIV infections in communities under UTT approach.In a community-randomized trial in 30 rural and peri urban communities in Botswana from 2013 to 2018 , those who where under UTT had a significantly higher viral load suppression compared to those receiving standard of care (Makhema et al., 2019).Also, a 30% reduction in HIV incidence was observed in the communities under UTT approach compared to those who where not.Similar findings where recorded by Khan et al. (2018) in a randomised controlled trial (RCT) which assessed the impact of UTT in 14 real-world service delivery sites, among people enrolling in HIV care in the Kingdom of eSwatini, from 2014 to 2017.Six months after enrolling in HIV care, patients enrolling under UTT approach were seven times more likely to be retained in care with viral suppression than those enrolling under the standard of care condition.

However, in some studies UTT did not result in a significantly lower incidence of HIV infection than standard care.A cluster randomised trial of 22 communities in rural KwaZulu-Natal, South Africa reported the absence of a lowering of HIV incidence in UTT clusters which was attributed to poor linkage to care although follow-up was too short to evaluate the role of ART adherence and retention on treatment on these findings (Iwuji et al.,

2018).In a randomised trial by Havlir et al. (2019) in rural communities in Uganda and Kenya there was no significant difference in the incidence of HIV infection between the groups though the percentage of HIV-infected persons with viral suppression for the UTT groups was 15% higher than the control groups.Among other possible explanations for the absence of a difference in HIV incidence Havlir and coworkers highlighted the presence of infection sources from a small subgroup of persons who had unsuppressed viral load.These subgroups may include those who are experiencing treatment failure , those that are not adhering to treatment and those that have completely stopped taking their medication.

Those individuals who drop out of ART are referred to here as treatment dropouts.ART dropouts are a serious challenge to the success of HIV/AIDS treatment with drop out rates as high as 30–50 % at 1 year in Sub-Saharan Africa(Koole et al., 2014; Fox and Rosen, 2010).Reasons and predictors of treatment dropout vary with set-up but may include but not limited to being young,adverse drug side effects,baseline CD4 counts,distance from health center ,mental health problems , death and loss to follow-up. However, the majority of treatment dropouts are due to loss to follow-up (Fox and Rosen, 2010).Those lost to follow up can stop their treatment leading to further disease progression and continued HIV transmission hence negating the population benefits of UTT.In addition treatment dropout of patients receiving ART is one of the reason for treatment failure due to poor adherence and drug resistance(Taiwo, 2009).As a result treatment dropout indirectly leads to treatment failure.

With expanded access to ART the problem of treatment dropouts is expected to occur at a larger scale since we now have more people starting ART at higher cd4 counts and will be on HIV treatment for longer hence increased potential for intermittent adherence.Consequently those who start ART at higher cd4 place themselves at higher risk for the emergence of ART resistance and treatment failure because they do not have clinical symptoms of AIDS and may take ART intermittently because they feel healthy and are less motivated to adher.In an observational study on effects of high CD4 cell counts on attrition among HIV patients receiving antiretroviral treatment by Tang et al. (2017), those with cd4 counts greater than 500 $cells/mm^3$ had a significantly higher ART attrition rate compared to those with cd4 counts less than 350 $cells/mm^3$.Similar findings of suboptimal adherence at higher baseline cd4 counts at initiation of ART where reported by Pasternak et al. (2015).However, a retrospective cohort study on retention on ART during UTT implementation in a Malawian district showed mildly increased retention on ART in general though certain groups remained at higher risk of attrition before and during UTT(Alhaj et al., 2019).Despite several studies having shown reduced morbidity and mortality with UTT approach, there is limited understanding of the possible negating effects of treatment failure and treatment dropouts on the overall success of ART programs over long durations especially in the era of UTT approach.

3.2 Mathematical modelling of epidemics

Mathematical modelling involves the use of mathematical tools to project how infectious diseases progress in populations and to show the likely outcome of an epidemic and help inform public health interventions.A better understanding of the transmission characteristics of infectious diseases in communities, regions, and countries can lead to better approaches in the management of these diseases. Mathematical models can either be *deterministic* or *stochastic* .Examples of deterministic models are compartmental mathematical models which use ordinary differential equations to describe the transition rates from one compartment to another and each compartment represents a specific stage of the epidemic.Stochastic models possess some inherent randomness that describes the transmission of infection between two individuals hence,closely resembles the real natural world situation.This dissertation will only consider a deterministic model .Mathematical modelling begun with Daniel Bernoulli in 1766 when he modelled the effects of smallpox variolation on life expectancy after which he was able to show that variolation would increase life expectancy .Ronald Ross also investigated intervention strategies for malaria for their effectiveness using mathematical models (Ross, 1910).Of much importance to this dissertation is the work by Kermack and McKendrick who were the first to describe the dynamics of disease transmission in terms of a system of differential equations (Kermack, 1927).We are going to use this model as a basis for our research.

The Kermack–McKendrick epidemic model splits the population into three nonintersecting classes, when a disease spreads in a population.The classes are named S,I and R.The class of individuals who are healthy but can contract the disease is denoted S and are called *susceptible individuals* or *susceptibles*.Those who have contracted the disease and are now sick with it make the class of *infected individuals* denoted by I .In this model, it is assumed that infected individuals are also infectious.The class of individuals who have recovered and cannot contract the disease again are called *removed/recovered individuals* denoted by R.In this model it is assumed that if someone is recovered, this person has become immune to that infection. The transmission model diagram is shown in Figure 3.1.

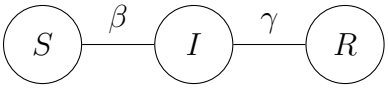

Figure 3.1: Flowchart of the Kermack–McKendrick SIR epidemic model

The number of individuals in each compartment changes with time hence, $S(t)$, $I(t)$ and $R(t)$ are functions of time, t. The total population size N is the sum of the sizes of these three classes:

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

This model gives rise to the following system of differential equations:

$$\begin{aligned} \frac{dS}{dt} &= -\beta SI \\ \frac{dI}{dt} &= \beta SI - \gamma I \\ \frac{dR}{dt} &= \gamma I \end{aligned}$$

Here $\gamma \geq 0$, is the recovery rate and $\beta \geq 0$ is the rate at which susceptibles get infected.The constant β in the first equation stands for b/N, where b is the number of susceptibles that each infected person transmits the pathogen to in a (small) time interval.The term βI is referred to as the force of infection.Many variations on this basic SIR model have been considered such as: i) the SI model which is used to describe the dynamics of a contagious and incurable disease such as HIV where there is no recovery from infection ii) models that incoperate temporary immunity ($SIRS$) or no immunity (SIS) iii)the($SEIR$)model is another variattion in which an infected individual has a latent period before becoming infectious iv) SIR models with vertical ttransmission and with stratified populations (Allen et al., 2008).

3.3 Review of some mathematical models of HIV/AIDS

Mathematical models have been used to describe the dynamics of HIV/AIDS epidemic and identify possible prevention strategies and some have revealed real impact of mathematical modelling on the war against the infection.From the initial model of Anderson et al. (1986) several modifications of the modelling structure have been presented.In particular, May and Anderson (1988) presented a simple HIV transmission model to help clarify the effects of various factors on the overall pattern of the HIV/AIDS epidemic.Also, Hyman et al. (1999) used two simple models to study the impact of variations in infectiousness in HIV infected individuals.They then derived and compared threshold conditions for the two models and explicit formulas of their endemic equilibria.

In 2001, Greenhalgh and colleagues examined the impact of condom use on the sexual transmission of HIV/AIDS amongst a homogeneously mixing male homosexual population(Greenhalgh et al., 2001).They derived a multigroup SIR model of HIV/AIDS transmission where the population of homosexuals is split into classes according to frequency of condom use.Analysis of this model showed that if $\mathcal{R}_0$ is greater than unity then there is a unique DFE which is locally unstable and a unique endemic equilibrium. However,the model exhibited unusual behaviour in that when $\mathcal{R}_0$ is less than unity two endemic equilibrium solutions can also co-exist simultaneously with the disease free solution which is locally stable.This unusual behaviour meant that reducing $\mathcal{R}_0$ to less than unity no longer

guarantees eradication of the disease, which findings could have important implications for control of the disease.

Mukandavire and Garira (2007) formulated a sex-structured model of HIV/AIDS aiming to investigate the effects of educational campaigns and the role of sex workers on the spread of HIV/AIDS among heterosexuals.In their model the population is divided into three subgroups: susceptibles, infectives and AIDS cases. The subgroups are further divided into two classes, consisting of individuals involved in high-risk sexual activities and individuals involved in low-risk sexual activities.It is assumed in this model that public health educational campaigns lead to movement of individuals from high to low sexual activity groups.They concluded that the presence of sex workers enlarges $\mathcal{R}_0$, thus fuels the epidemic among the heterosexuals. In addition they showed that public health educational campaigns among the high-risk heterosexual population reduces $\mathcal{R}_0$ and hence can slow or eradicate the spread of the disease.

A highly simplified deterministic model that incorporates the joint dynamics of Tuberculosis(TB) and HIV was formulated and analysed by(Roeger et al., 2009).The basic reproduction numbers of each of the diseases $\mathcal{R}_1$ (TB), $\mathcal{R}_2$ (HIV) and both diseases $\mathcal{R} = \max(\mathcal{R}_1; \mathcal{R}_2)$ were found and the model was qualitatively analysed.From their analytical results they found the disease free equilibrium for the full model to be locally asymptotically stable when $\mathcal{R} < 1$ and the disease free equilibrium point for TB-only model to be locally asymptotically stable when $\mathcal{R}_1 > 1$ and $\mathcal{R}_2 < 1$.They also showed that if $\mathcal{R}_1 < 1$ and$\mathcal{R}_2 < 1$ it does not guarantee a stable HIV-only equilibrium and there is possibility of TB coexisting with HIV when $\mathcal{R}_2 > 1$.Numerical simulation showed increase in the rate at which TB progresses from latent to active form in individuals that are co-infected with both HIV and TB therefore contributed greatly to the rise in prevalence of TB.Their results suggested that investing more in reducing the prevalence of HIV could be an effective way to reduce the impact of TB.

Nyabadza and Mukandavire (2011) proposed a deterministic HIV/AIDS model that incorporates condom use , screening through HIV counselling and testing (HCT), regular testing and treatment as intervention strategies.They aimed to assess the effectiveness of HCT on the incidence and predicting the long-term dynamics of the epidemic.The model was analyzed and fitted to the South African prevalence data.They showed that the classical requirement for the basic reproduction number to be below unity, though necessary, is not sufficient for disease control in this case due to the presence of bifurcation.They concluded that the future of the epidemic largely depends on changes in behaviour.Similar results where obtained in a study by Bhunu et al. (2011) in which they mathematically analysed a deterministic HIV/AIDS model to assess the impact of educational programs and abstinence in Sub-Saharan Africa.Bhunu *et al* showed that effective counselling and

testing have a great potential to partially control the epidemic (especially when HIV positive individuals either willingly withdraw from risky sexual activities or disclose their status beforehand) even in the absence ART.

3.4 A model for HIV/AIDS with screening and treatment in a population

In this section we will review an article by (Safiel et al., 2012) , on modelling the effect of screening and treatment on transmission of HIV/AIDS infection in a population.Our model is a direct modification of this model.Safiel and colleagues proposed a non linear mathematical model that subdivides the population of interest into five sub population compartments depending on the HIV status of individuals.The five subclasses are the susceptibles , unaware infectives, screened infectives , treated class and full blown AIDS class .According to their model the susceptibles are HIV negative individuals ; the unaware infectives are individuals that have contracted the infection but have not been tested ; the screened infectives are HIV positive individuals who have a confirmatory test of their status, treated class are those individuals who have been enrolled on ART and are taking their life long medication .Some of their assumptions in formulating this model include but not limited to i) Unaware infectives, screened infectives and treated class will move to full blown AIDS at different rates.ii) Unaware infectives, screened infectives and treated class can infect susceptibles class at different rates.

The authors analysed qualitatively the model system .The effective reproduction number $\mathcal{R}_e$ of the normalised model system was obtained using the next generation operator method and the formula for it was presented in the paper.The model showed that the DFE is locally stable by using Routh Hurwitz criteria when $\mathcal{R}_e < 1$ and unstable when $\mathcal{R}_e > 1$ but, globally the DFE is not stable due existence of forward bifurcation at threshold parameter equal to unity.In addition, the model analysis showed the existence of unique endemic equilibrium that is locally stable under certain conditions when $\mathcal{R}_e > 1$.They also used the Lyapunov method to show that the endemic equilibrium is globally stable under certain conditions.The normalized forward sensitivity index method was used to determine the sensitivity of $\mathcal{R}_e$ to the parameters in the model.Numerical simulations of the model showed that the screening of unaware HIV infectives and treatment of screened HIV infectives have the effect of reducing the spread of the infection.Furthermore, they observed that when the screened infectives and treated infectives do not participate in the transmission of the infection, the AIDS population is significantly reduced in comparison to the case where there is no screening and treatment.

The model by Safiel et al. (2012) did not consider the current approach of universal test

and treat where everyone who tests HIV positive is immediately initiated on ART and is assumed to be on treatment.In their model some of those who test positive for HIV can even progress to full blown AIDS before they receive treatment.Also, the model only captures treatment failure with no inclusion of a subgroup of treatment dropouts.

3.5 Review of some models of UTT approach in HIV/AIDS

Research advances on antiretroviral drugs for HIV/AIDS has led a number of researchers to develop and analyze mathematical models to study the impact of HIV treatment at population level.In this section we review some of the studies which mathematically modelled the impact of UTT under different settings .

The very first test-and-treat model was developed by Granich and his colleagues (Granich et al., 2009).In this study they proposed a staged progression compartmental transmission model for HIV infection and antiretroviral therapy(ART) provision.A test case community was employed in which everyone was tested for HIV every year and starting people on ART immediately after they are diagnosed HIV positive. A stochastic model was used to explore the effect of various treatment strategies and model parameters on $\mathcal{R}_0$ and a deterministic transmission model was used to explore the effect of various HIV testing and treatment strategies on the long term dynamics of the epidemic.The stochastic model showed that testing all adolescents and adults at least 15 years old once a year, on average, and starting individuals on ART as soon as they test positive for HIV would reduce $\mathcal{R}_0$ below unity and eventually eliminate HIV.Also it was seen that scaling up of universal voluntary HIV testing with immediate initiation of ART could stop transmission and eliminate HIV in a high prevalence setting.

Thereafter, Dodd et al. (2010) investigated the test and treat intervention in HIV/AIDS under a range of contexts, and using a different mathematical model.Unlike the Granich model ,their model incorporated updated information such as variation in sexual risk behaviour , changes in HIV transmissibility over the course of infection and observed HIV survival rates from an African setting.The modelling approach broadly confirmed initial findings by Granich and coworkers.However, the model analysis highlighted important aspects of UTT that need to be considered such as the crucial dependence of the approach on the epidemiological context (under some circumstances, the effect was as large as estimated by Granich *et al.*, but in others, the effect was much less).Also,from numerical simulations they found that failing to achieve sufficiently high coverage levels or failing to test frequently enough, was associated with a dramatic spiralling of treatment costs and from their model, the most cost-efficient strategy could be testing everyone 3-5 years instead of every year.

Another UTT model constructed by Kretzschmar et al. (2013) was a direct extention of the model by Granich et al. (2009).It allowed for an arbitrary number of stages of infection and variable infectivity was taken into account.The model also described progression through n stages of infection, background mortality, additional mortality from HIV infection, and the uptake and dropping out of treatment.The basic reproduction number of the model was analysed using the next generation method . After incorporating these more realistic assumptions the authors found that elimination of HIV by UTT is only feasible for populations with very low reproduction numbers or if the reproduction number is lowered significantly as a result of additional interventions.In particular for South Africa they predicted that, if the basic reproduction number is 2.62, elimination will be very hard to achieve taking into account the high annual treatment uptake of at least 80% and low treatment dropout rate needed, which correspond to a coverage of more than 90%.Though some aspects of treatment dropout where considered in this model, there still remain a question on how the inclusion of treatment failure and reinitiation of dropouts affects the overall dynamics of the disease.

Mathematical models have also been used to investigate the effect of expanding ART on HIV/AIDS epidemic for men who have sex with men (MSM) .In particular, Sood et al. (2013) formulated a compartmental HIV model for MSM in Los Angeles County.The model focused on UTT in MSM and incoperated multiple drug resistance(MDR) in order to explicitly address potential effects of UTT policies on the spread of MDR.A 1-way sensitivity analysis was conducted to determine how the model results were impacted by each parameter individually.The results from this model showed that the UTT policy can generate substantial reductions in new infections, death, and new AIDS cases.However, this model showed that HIV elimination is not possible from even the most aggressive UTT policy because benefits of test and treat are counterbalanced by large MDR increases.Similar findings where reported by Blower and Volberding (2002), in a modelling study on the impact of expanding ART coverage in the presence of transmitted and acquired drug resistance and showed that expanding ART coverage can substantially reduce the overall incidence of HIV while simultaneously increasing the incidence of drug-resistant strains. Sensetivity analysis by Sood et al. (2013) reviewed that new infections are most sensitive to the parameters that represent sexual behavior (ie, the transmissibility parameters and number of partners) and for MDR, results where most sensitive to the rate of resistance parameter.Similar findings of modest UTT policy benefits where reported by (Charlebois et al., 2011; Sorensen et al., 2012) , in mathematical models of comprehensive test-and-treat services and HIV incidence among MSM in the United States.

Nah et al. (2017) proposed a simple mathematical model to understand how UTT influences the population dynamics of HIV/AIDS .Their model divides the population into susceptible individuals, infected individuals without AIDS (H) and those who have been

diagnosed as AIDS (A). Population H and A are further divided into undiagnosed(A_u and H_u) and diagnosed groups(A_d and H_d). For this model the authors assumed that all diagnosed individuals are brought to be under ART.They also assumed that ART reduces one's infectiousness on a whole from β to $\xi\beta$ where parameter ξ takes a value between zero and one, and the value $1-\xi$ represents the relative reduction in the transmissibility.This model found that early removal from (undiagnosed) infectious state plays an important part in the population impact of test and treat strategy.Graphs from numerical simulations showed that if the rate of diagnosis is greater than a certain threshold UTT successfully controls the HIV epidemic.However, several realistic aspects of HIV treatment such as treatment failure and the issue of treatment dropouts where not captured by this model.

Lastly, we will consider a recent model by Omondi et al. (2018) of the impact of testing,treatment and control of HIV transmission in Kenya.In their study the authors employed a deterministic model to describe the transmission dynamics of HIV and the impact of testing and treatment on the disease transmission .The model comprises of susceptible class and infection class which is further divided into four compartments.Surveillance data was used to describe the spread of HIV and they assumed a scenario of UTT.Stability analysis of the model equilibria was carried out by constructing suitable Lyapunov function.Sensitivity analysis was done using the normalised forward sensitivity index method in order to determine the relative importance of model parameters on disease transmission .The next-generation matrix method was used to deduce the reproduction number $\mathcal{R}_0$.They showed that the disease-free equilibrium of the system is globally asymptotically stable if $\mathcal{R}_0 \leq 1$ and unstable otherwise.Furthermore, they showed that there exists a unique endemic equilibrium of the system and is globally asymptotically stable whenever $\mathcal{R}_0 > 0$.The results of sensitivity analysis showed that the model system is most sensitive to infection contact rates, testing and counselling rates and treatment rates.However, this study and the rest of the studies on UTT presented, did not investigate the potential impact of the combination of treatment failure and treatment dropouts on the success of this approach.

Chapter 4

The model

4.1 Model formulation

A system of non linear ordinary differential equations will be used to model the transmission dynamics of HIV/AIDS in a population.The proposed model subdivides the total human population $N(t)$ at time t into five classes, namely, the susceptible class ($S(t)$), unaware infectives ($I_1(t)$), treatment class ($I_T(t)$), treatment dropout class ($I_2(t)$), AIDS class ($A(t)$), so that

$$N(t) = S(t) + I_1(t) + I_T(t) + I_2(t) + A(t).$$

The susceptibles are individuals that have not contracted the HIV infection but can become infected due to interaction with the infectious groups. The unaware infectives are all HIV infected individuals(primary, asymptomatic and chronic HIV stages) who are ignorant of their HIV-positive status. The treatment class are those infected individuals who have been screened for HIV and are immediately put on ART. Treatment dropouts class are those individuals who where previously on ART and have since stopped taking their medication and the AIDS class consists of those individuals infected with HIV and have clinical symptoms of AIDS.

The susceptible population is replenished by the recruitment of individuals into the sexually active population at a rate π.These individuals contract HIV infection, following effective contact with infectives in classes I_1, I_2 and I_T with force of infection ϕ, where

$$\phi = \frac{\beta_1 I_1 + \beta_2 I_2 + \beta_3 I_T}{N}$$

with β_1, β_2 and β_3 representing the transmission parameters for each class respectively. Natural deaths results in a decrease of the population in all the compartments at the rate

μ.The rate of change for the susceptible individuals is given by

$$\frac{dS}{dt} = \pi - \frac{\beta_1 I_1}{N} - \frac{\beta_2 I_2}{N} - \frac{\beta_3 I_T}{N} - \mu S.$$

The unaware infectives class increases due to infection of the susceptible group at a rate ϕ .It is decreased due to natural death and movement to the treatment class of those who would have been screened and tested positive to HIV at a rate ρ_1.Also, it is decreased by the progression to full blown AIDS of unaware infectives who are not screened at a rate λ_1.Hence, the rate of change of unaware infectives is given by

$$\frac{dI_1}{dt} = \frac{\beta_1 I_1}{N} + \frac{\beta_2 I_2}{N} + \frac{\beta_3 I_T}{N} - (\rho_1 + \lambda_1 + \mu) I_1.$$

The population of individuals in the treatment class is increased by the enrolment into ART of unaware infectives, treatment dropouts and those in the AIDS class at rates ρ_1,ρ_2 and ρ_3 respectively.The treatment class is decreased as result of progression of individuals on ART to the AIDS class due to treatment failure at a rate θ.In addition the decrease is due to treatment dropouts at a rate ε and natural death.So that

$$\frac{dI_T}{dt} = \rho_1 I_1 + \rho_2 I_2 - (\theta + \varepsilon + \mu) I_T.$$

The treatment dropouts class increases as individuals in the treatment class stop ART at a rate ε.This population decreases due to enrolment back to treatment of those who would have stopped ART at a rate ρ_2, progression to AIDS at a rate λ_2 and natural death.This gives

$$\frac{dI_2}{dt} = \varepsilon I_T - (\rho_2 + \lambda_2 + \mu) I_2.$$

The population of individuals infected with AIDS is increased by the progression of unaware infectives and treatment dropouts to full blown AIDS at a rate λ_1 and λ_2 respectively.In addition the class grows as some those in the treatment class experience treatment failure and proceed to AIDS at the rate θ.This class is reduced by natural death and due to AIDS related death at a rate σ.Also, the AIDS class is reduced as some of the patients are initiated on treatment and respond to treatment such that they move to the infective class I_T at a rate ρ_3 .Therefore, the rate of change for the AIDS class is given by

$$\frac{dA}{dt} = \lambda_1 I_1 + \lambda_2 I_2 + \theta I_T - (\rho_3 + \sigma + \mu) A.$$

The schematic diagram of the model is as shown in Figure 4.1.

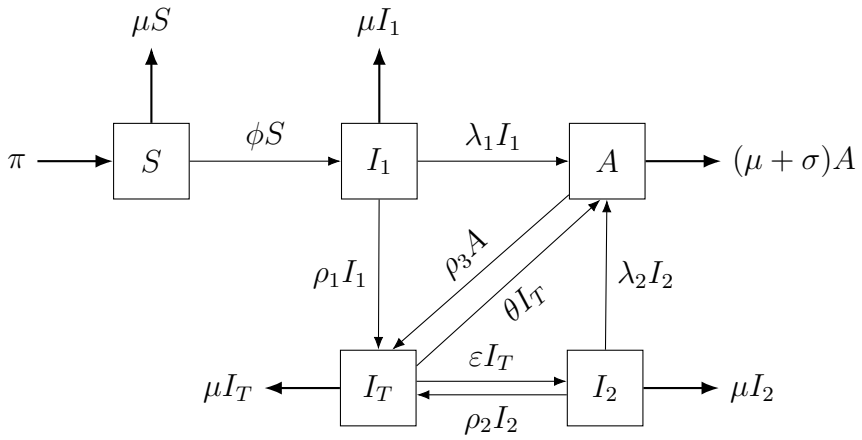

Figure 4.1: A compartmental flow diagram for universal test and treatment model of HIV/AIDS with demography.

Model assumptions

The following are some of the assumptions made in the construction of the HIV/AIDS model:

- The population is considered to be homogeneously mixed and hence there is uniform interaction of individuals in all the compartments.
- Though some susceptible individuals may have some level of immunity to infection due to genetic reasons or due to pre exposure prophylaxis , we assume each susceptible individual has an equal chance of acquiring HIV infection when they get into contact with infectives.
- There is no vertical transmission of the infection, meaning there is no infection from mother to the unborn baby.
- This is a varying population model where susceptible individuals are recruited into the population at a constant rate π.
- Unaware infectives, treatment dropouts and those in the treatment class progress to the AIDS class at different rates λ_1,λ_2 and θ respectively.
- Since it is possible for treatment failure to be diagnosed and averted before an infected individual who is on ART proceeds to full blown AIDS, in this model we have assumed that all cases of treatment failure lead to AIDS.
- In this model we assume that those in the AIDS class are sexually inactive and do not contribute to any new infections.

- The level of infectivity of the infectious groups I_1, I_T and I_2 are different with rates β_1 , β_3 and β_2 respectively, where $\beta_3 < \beta_2 < \beta_1$.Those in the treatment class have the lowest infectivity as a result of reduced viral load due to the effect of ART.Treatment dropouts are considered to have lower infectivity compared to unaware infectives since they at least know that they are HIV positive hence their sexual behaviour is assumed to have changed.

- The model considers only heterosexual transmission of HIV infection.

Based on the assumptions above and the model diagram, the model representing the dynamics of HIV/AIDS is governed by the following system of non linear ordinary differential equations:

$$\begin{aligned}
\tfrac{dS}{dt} &= \pi - \phi S - \mu S, \\
\tfrac{dI_1}{dt} &= \phi S - (\rho_1 + \lambda_1 + \mu) I_1, \\
\tfrac{dI_T}{dt} &= \rho_1 I_1 + \rho_2 I_2 + \rho_3 A - (\theta + \varepsilon + \mu) I_T, \\
\tfrac{dI_2}{dt} &= \varepsilon I_T - (\rho_2 + \lambda_2 + \mu) I_2, \\
\tfrac{dA}{dt} &= \lambda_1 I_1 + \lambda_2 I_2 + \theta I_T - (\rho_3 + \mu + \sigma) A,
\end{aligned} \tag{4.1}$$

subject to the following initial conditions

$$S(0) > 0, \quad I_1(0) \geq 0, \quad I_T(0) \geq 0, \quad I_2(0) \geq 0, \quad A(0) \geq 0. \tag{4.2}$$

4.2 Basic properties of the model

Feasible Solution

This epidemiological model deals with a population of humans and therefore it is important to consider non negative populations.Hence, the model should be considered in (feasible) regions where such property of non-negativity is preserved.

Lemma 2. *Let the feasible region Ω be defined by*

$$\Omega = \left\{ (S, I_1, I_T, I_2, A) \in \mathbb{R}^5_+ : 0 \leq N \leq \frac{\pi}{\mu} \right\},$$

with the initial conditions as given in (4.2)*. The region Ω is positively invariant with respect to the system* (4.1) *for all $t > 0$.*

Proof. By adding the equations of system 4.1, we obtain

$$\frac{dN}{dt} = \pi - \mu N - \sigma A$$

Thus, it follows that

$$\frac{dN}{dt} \leq \pi - \mu N \tag{4.3}$$

We then get the general solution of equation (4.3) as,

$$N \leq \frac{\pi}{\mu} + C\mathrm{e}^{-\mu t}$$

Applying the initial conditions in (4.2), we get $C = N(0) - \frac{\pi}{\mu}$. So that

$$N = \frac{\pi}{\mu} + \left(N(0) - \frac{\pi}{\mu}\right)\mathrm{e}^{-\mu t} \tag{4.4}$$

From equation (4.4) we can deduce that as $t \to \infty$ the population reaches its limiting value $\frac{\pi}{\mu}$.Thus, all the feasible solutions of system (4.1) enter the region Ω and stay inside it. Hence the region Ω is positively invariant.Therefore, we have proven that the system is well-posed epidemiologically and hence it is sufficient to study the system (4.1) in the region Ω.

Positivity of solutions

Since the model (4.1) describes changes in the human population it is important to show that all the state variables (S, I_1, I_T, I_2 and A) are non-negative for all time.

Lemma 3. *The solutions $S(t), I(t)_1, I(t)_T, I(t)_2$ and $A(t)$ of the system* (4.1) *are positive $\forall t \geq 0$, given the initial conditions* (4.2).

Proof. From the first equation of system (4.1) we have

$$\frac{dS}{dt} \geq -(\Phi + \mu)S.$$

By integrating both sides we have,

$$\begin{aligned}
\int \frac{dS}{S} &\geq -\int (\Phi + \mu)dt \\
\ln S &\geq B - \left(\mu t + \int \Phi dt\right) \\
S &\geq C\mathrm{e}^{-\left(\mu t + \int \Phi dt\right)}.
\end{aligned}$$

Applying the initial conditions we get,

$$S(t) \geq S(0)\mathrm{e}^{-\left(\mu t + \int \Phi dt\right)}.$$

Since $e^{-\left(\mu t+\int \Phi dt\right)} > 0$, this implies that $S(t)$ is always positive.

Similarly, from the second equation of system (4.1) we have

$$\begin{aligned} \frac{dI_1}{dt} &\geq -(\rho_1+\lambda_1+\mu_1)I_1 \\ \int \frac{dI_1}{I_1} &\geq -\int(\rho_1+\lambda_1+\mu_1) \\ \ln I_1 &\geq B-(\rho_1+\lambda_1+\mu_1)t \\ I_1 &\geq Ce^{-(\rho_1+\lambda_1+\mu_1)t}. \end{aligned}$$

Applying initial conditions we have,

$$I_1(t) \geq I(0)e^{-(\rho_1+\lambda_1+\mu_1)t}.$$

Since $e^{-(\rho_1+\lambda_1+\mu_1)t} > 0$ this means $I_1 \geq 0$ for all $t \geq 0$.It can also be shown using the same method for the remaining equations of system (4.1) that $I_T(t) \geq 0$, $I_2(t) \geq 0$ and $A(t) \geq 0$ for all $t \geq 0$.

Chapter 5

Model Analysis

5.1 Disease free equilibrium(DFE)

The DFE point is a steady state solution where there is no HIV infection and AIDS disease in the population therefore,

$$I_1 = I_T = I_2 = A = 0. \tag{5.1}$$

To obtain the DFE (E_0) we set the right-hand side of the equations in system (4.1) to zero and apply equation (5.1) and then solve for S, I_1, I_T, I_2 and A.Hence,

$$E_0 = (S, I_1, I_T, I_2, A) = \left(\frac{\pi}{\mu}, 0, 0, 0, 0\right).$$

5.1.1 Reproduction number and the local stability of the DFE

The basic reproduction number $\mathcal{R}_0$ is defined as the number of secondary infections produced by an infectious individual for the duration of infectiousness in a totally susceptible population.We are going to use the next generation operator method on system (4.1) following Van den Driessche and Watmough (2002) to determine the model $\mathcal{R}_0$.The infected compartments are I_1, I_T, I_2 and A.Let $\mathcal{F}(x)$ represent the rate of appearance of new infections in the infected compartments and let $\mathcal{V}(x)$ represent rate at which the population in each compartment changes due to transfers between compartments.The matrices showing these movements are given by,

$$\mathcal{F}(x) = \begin{pmatrix} \frac{\beta_1 I_1 + \beta_2 I_T + \beta_3 I_2}{N} S \\ 0 \\ 0 \\ 0 \\ 0 \end{pmatrix},$$

$$\mathcal{V}(x) = \begin{pmatrix} (\rho_1 + \lambda_1 + \mu) I_1 \\ (\theta + \varepsilon + \mu) I_T - \rho_1 I_1 - \rho_2 I_2 - \rho_3 A \\ (\rho_2 + \lambda_2 + \mu) I_2 - \varepsilon I_T \\ (\rho_3 + \mu + \sigma) A - \lambda_1 I_1 - \lambda_2 I_2 - \theta I_T \end{pmatrix}$$

The Jacobian matrix of $\mathcal{F}(x)$ evaluated at the disease free equilibrium point E_0 is given by,

$$F = \frac{\partial \mathcal{F}(E_0)}{\partial x} = \begin{pmatrix} \beta_1 & \beta_3 & \beta_2 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{pmatrix}$$

The Jacobian matrix of $\mathcal{V}(x)$ evaluated at the DFE is given by

$$V = \frac{\partial \mathcal{V}(E_0)}{\partial x} = \begin{pmatrix} \rho_1 + \lambda_1 + \mu & 0 & 0 & 0 \\ -\rho_1 & \theta + \varepsilon + \mu & -\rho_2 & -\rho_3 \\ 0 & -\varepsilon & \rho_2 + \lambda_2 + \mu & 0 \\ -\lambda_1 & -\theta & -\lambda_2 & \rho_3 + \mu + \sigma \end{pmatrix}$$

If we let ,

$$\begin{aligned} k_1 &= \rho_1 + \lambda_1 + \mu \\ k_2 &= \theta + \varepsilon + \mu \\ k_3 &= \rho_2 + \lambda_2 + \mu \\ k_4 &= \rho_3 + \mu + \sigma \\ k_5 &= \mu + \phi \end{aligned}$$

then V^{-1} exists and is given by

$$V^{-1} = \begin{pmatrix} \frac{1}{k_1} & 0 & 0 & 0 \\ \frac{k_3k_4\rho_1+k_3\lambda_1\rho_3}{detV} & \frac{k_3k_4}{detV} & \frac{k_4\rho_2+\lambda_2\rho_3}{detV} & \frac{k_3\rho_3}{detV} \\ \frac{k_4\rho_1\varepsilon+\lambda_1\rho_3\varepsilon}{detV} & \frac{k_4\varepsilon}{detV} & \frac{k_2k_4-\rho_3\theta}{detV} & \frac{\rho_3\varepsilon}{detV} \\ \frac{k_2k_3\lambda_1+k_3\rho_1\theta-\lambda_1\rho_2\varepsilon+\lambda_2\rho_1\varepsilon}{detV} & \frac{k_3\theta+\lambda_2\varepsilon}{detV} & \frac{k_2\lambda_2+\rho_2\theta}{detV} & \frac{k_2k_3-\rho_2\varepsilon}{detV} \end{pmatrix}$$

where $detV$ is the determinant of matrix V computed as

$$k_1(k_3\rho_3\theta - k_2k_3k_4 + k_4\rho_2\varepsilon + \lambda_2\rho_3\varepsilon).$$

Using a computer software(Matlab 2018a) the next generation matrix FV^{-1} is given by

$$\begin{pmatrix} \frac{\beta_1}{k_1} + \frac{\beta_2(k_4\rho_1\varepsilon+\lambda_1\rho_3\varepsilon)}{detV} + \frac{\beta_3(k_3k_4\rho_1+k_3\lambda_1\rho_3)}{detV} & -\frac{\beta_2k_4\varepsilon}{M} - \frac{\beta_3k_3k_4}{M} & \frac{\beta_2(\rho_3\theta-k_2k_4)}{M} - \frac{\beta_3(k_4\rho_2+\lambda_2\rho_3)}{M} & -\frac{\beta_2\rho_3\varepsilon}{M} - \frac{\beta_3k_3\rho_3}{M} \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{pmatrix}$$

where $M = k_3\rho_3\theta - k_2k_3k_4 + k_4\rho_2\varepsilon + \lambda_2\rho_3\varepsilon$.

Therefore, the basic reproduction number $\mathcal{R}_0$ is given by

$$\mathcal{R}_0 = \rho(FV^{-1}) = \frac{\beta_1}{k_1} + \frac{\beta_2(k_4\rho_1\varepsilon + \lambda_1\rho_3\varepsilon)}{k_1(k_3\rho_3\theta - k_2k_3k_4 + k_4\rho_2\varepsilon + \lambda_2\rho_3\varepsilon)} + \frac{\beta_3(k_3k_4\rho_1 + k_3\lambda_1\rho_3)}{k_1(k_3\rho_3\theta - k_2k_3k_4 + k_4\rho_2\varepsilon + \lambda_2\rho_3\varepsilon)},$$

where ρ is the spectral radius of the next generation matrix FV^{-1}.

From the expression for $\mathcal{R}_0$ it can be seen that the first, second and third terms represent the contribution of unaware infectives, treatment dropouts and those in the treatment class to the overall model reproduction number, respectively.This result mean that the number of secondary infections produced by one infectious individuals during their entire period of infectiousness is influenced not only by unaware infectives but by the contribution of those on treatment and treatment dropouts.Therefore, current strategies to reduce transmission of the infection such as promoting condom use and contact tracing should also focus on these groups in order to curb the epidemic.

We are going to use results from **Theorem 9** as discussed in Chapter 3 to assess the local stability of E_0.The disease free equilibrium point E_0 is locally asymptotically stable

if $\mathcal{R}_0 < 1$.This implies that HIV/AIDS can be effectively controlled in the population (given $\mathcal{R}_0 < 1$) if the initial sizes of the sub populations of model (4.1) are near the disease free equilibrium point, E_0.If $\mathcal{R}_0 > 1$ then the DFE becomes unstable and the endemic equilibrium because locally stable meaning that a single infected individual will lead to more than one secondary cases during their entire course of infectiousness in a completely susceptible population.

5.2 The endemic equilibrium (EE) and its local stability

The EE can be computed by equating the right-hand side of equations in system(4.1) to zero and solving them in terms of the force of infection, ϕ. At equilibria,

$$\pi - \phi S^* - \mu S^* = 0, \tag{5.2}$$
$$\phi S^* - (\rho_1 + \lambda_1 + \mu) I_1^* = 0, \tag{5.3}$$
$$\rho_1 I_1^* + \rho_2 I_2^* + \rho_3 A^* - (\theta + \varepsilon + \mu) I_T^* = 0, \tag{5.4}$$
$$\varepsilon I_T^* - (\rho_2 + \lambda_2 + \mu) I_2^* = 0, \tag{5.5}$$
$$\lambda_1 I_1^* + \lambda_2 I_2^* + \theta I_T^* - (\rho_3 + \mu + \sigma) A^* = 0, \tag{5.6}$$

From equation (5.2), we have

$$S^* = \frac{\pi}{K_5}. \tag{5.7}$$

Substituting equation (5.7) in equation (5.3), gives

$$I_1^* = \frac{\phi \pi}{k_1 k_5} \tag{5.8}$$

From equation (5.5),

$$I_2^* = \frac{\varepsilon I_T}{k_3} \tag{5.9}$$

Substituting equations (5.8) and (5.9) in equations (5.4) and (5.6) , we get the following simultaneous equations

$$\begin{array}{l} \frac{\rho_1 \phi \pi}{k_1 k_5} + \frac{(\rho_2 \varepsilon - k_2 k_3)}{k_3} I_T^* + \rho_3 A^* = 0 \\ \frac{\lambda_1 \phi \pi}{k_1 k_5} + \frac{(\lambda_2 \varepsilon + \theta k_3)}{k_3} I_T^* - k_4 A^* = 0 \end{array} \tag{5.10}$$

From (5.10)

$$I_T^* = \frac{k_3 \phi \pi (k_4 \rho_1 + \rho_3 \lambda_1)}{k_1 k_4 k_5 (k_2 k_3 - \rho_2 \varepsilon) - k_1 k_5 \rho_3 (\lambda_2 \varepsilon + k_3 \theta)}, \tag{5.11}$$

$$A^* = \frac{k_3 \lambda_1 \phi \pi + k_1 k_5 (\lambda_2 \varepsilon + k_3 \theta) I_T^*}{k_1 k_3 k_4 k_5}, \tag{5.12}$$

and from (5.9),

$$I_2^* = \frac{k_3\phi\pi\varepsilon(k_4\rho_1 + \rho_3\lambda_1)}{k_3[k_1k_4k_5(k_2k_3 - \rho_2\varepsilon) - k_1k_5\rho_3(\lambda_2\varepsilon + k_3\theta)]}. \tag{5.13}$$

Therefore a unique endemic equilibrium point exists given by $E_1 = (S^*, I_1^*, I_T^*, I_2^*, A^*)$.

To investigate the local stability of E_1 we will consider the signs of the eigenvalues of the Jacobian matrix of system (4.1) evaluated at the endemic equilibrium point, E_1.At the endemic equilibrium point the Jacobian matrix of this system is given by

$$J_{E_1} = \begin{pmatrix} -(\phi_1 + \mu) & -\phi_2 & -\phi_3 & -\phi_4 & 0 \\ \phi_1 & \phi_2 - k_1 & \phi_3 & \phi_4 & 0 \\ 0 & \rho_1 & -k_2 & \rho_2 & \rho_3 \\ 0 & 0 & \varepsilon & -k_3 & 0 \\ 0 & \lambda_1 & \theta & \lambda_2 & -k_4 \end{pmatrix},$$

where

$$\begin{aligned} \phi_1 &= \frac{\beta_1 I_1^* + \beta_2 I_2^* + \beta_3 I_T^*}{N}, \\ \phi_2 &= \frac{\beta_1 S^*}{N}, \\ \phi_3 &= \frac{\beta_3 S^*}{N}, \\ \phi_4 &= \frac{\beta_2 S^*}{N}. \end{aligned}$$

The characteristic equation corresponding to J_{E_1} is given by,

$$P(\psi) = \psi^5 + a_1\psi^4 + a_2\psi^3 + a_3\psi^2 + a_4\psi + a_5 = 0,$$

where

$$
\begin{aligned}
a_1 &= \phi_1 - \phi_2 + k_1 + k_2 + k_3 + k_4 + \mu, \\
a_2 &= \phi_1(k_1 + k_2 + k_3 + k4) + \phi_2(k_3 - k_2 - k_4 - \mu) - \phi_3\rho_1 - \varepsilon\rho_2 + k_1(k_2 + k_3 + k4 + \mu) \\
&+ k_2(k_3 + k4 + \mu) + k_3(k_4 + \mu) + k_4\mu - \rho_3\theta, \\
a_3 &= \varepsilon\rho_2(\phi_2 - \phi_1) - \phi_3(\lambda_1\rho_3 + k_3\rho_1 + k_4\rho_1 + \mu\rho_1) - \phi_4\varepsilon\rho_1 + \phi_1(k_1k_2 + k_1k_3 + k_1k_4 + k_2k_3 + k_2k_4 \\
&+ k_3k_4 - \rho_3\theta) - \phi_2(k_2k_3 + k_2k_4 + k_3k_4 + k_2\mu + k_3\mu + k_4\mu - \rho_3\theta) + \mu(k_1k_2 + k_1k_3 + k_1k_4 + k_2k_3 \\
&+ k_2k_4 + k_3k_4) - \varepsilon(\rho_2\mu + \lambda_2\rho_3 + k_1\rho_2 + k_4\rho_2) - \rho_3\theta(k_1 + k_3 + \mu) \\
&+ k_1k_3(k_2 + k_4) + k_2k_4(k_1 + k_3), \\
a_4 &= \phi_1(k_1k_2k_3 + k_1k_2k_4 + k_1k_3k_4 + k_2k_3k_4) - \phi_1\varepsilon(\lambda_2\rho_3 + k_1\rho_2 + k_4\rho_2) - \phi_1\theta\rho_3(k_1 + k_3) + \phi_2\mu(\rho_3\theta \\
&+ \varepsilon\rho_2 - k_2k_3 - k_2k_4 - k_3k_4) + \phi_2(\lambda_2\varepsilon\rho_3 + \varepsilon k_4\rho_2 - k_2k_3k_4 + k_3\rho_3\theta) - \phi_3\mu(k_4\rho_1 + k_3\rho_1 + \lambda_1\rho_3) \\
&- \phi_3k_3(\lambda_1\rho_3 + k_4\rho_1) - \phi_4\varepsilon(\lambda_1\rho_3 + k_4\rho_1 + \mu\rho_1) - \varepsilon\mu(\lambda_2\rho_3 + k_1\rho_2 + k_4\rho_2) - \theta\rho_3(\mu k_1 + \mu k_3 \\
&+ k_1k_3) + \mu(k_1k_2k_3 + k_1k_2k_4 + k_1k_3k_4 + k_2k_3k_4) - \varepsilon k_1(k_4\rho_2 + \lambda_2\rho_3) + k_1k_2k_3k_4, \\
a_5 &= \phi_1k_1(k_2k_3k_4 - \varepsilon k_4\rho_2 - \lambda_2\varepsilon\rho_3 - k_3\rho_3\theta) + \phi_2\mu(\lambda_2\varepsilon\rho_3 + \varepsilon k_4\rho_2 - k_2k_3k_4 + k_3\rho_3\theta) - \phi_3k_3\mu(\lambda_1\rho_3 \\
&+ k_4\rho_1) - \phi_4\varepsilon\mu(\lambda_1\rho_3 + k_4\rho_1) - \varepsilon k_1\mu(\lambda_2\rho_3 + k_4\rho_2) + k_1k_3\mu(k_2k_4 - \rho_3\theta).
\end{aligned}
$$

The system has a locally asymptotically stable endemic equilibrium point E_1 if all the eigenvalues of J_{E_1} are either negative or have negative real parts.From the Routh-Hurwitz stability criterion for a fifth order polynomial, all the eigenvalues are negative or have negative real parts if the following conditions are satisfied:

$a_i > 0$ where $i = 1, 2, 3, 4, 5$, $a_1a_2a_3 > a_3^2 + a_1^2a_4$ and
$(a_1a_4 - a_5)(a_1a_2a_3 - a_3^2 - a_1^2a_4) > a_5(a_1a_2 - a_3)^2 + a_1a_5^2$.

5.3 Numerical simulations

In this section, we present analytical results of the numerical simulations of model (4.1) using Matlab 2018a.The simulations are done for a hypothetical population, $N = 100,000$ and the initial conditions of the state variables considered

$$S(0) = 10,000, \quad I_1(0) = 300, \quad I_T(0) = 30, \quad I_2(0) = 5, \quad A(0) = 5. \tag{5.14}$$

This population size would suit an averagely sized district in Zimbambwe and we have assumed the initial conditions in (5.14). The parameter values used in the numerical simulations of model (4.1) are presented in Table 5.1.

Parameter	Value (per unit time)	Reference
π	10	Mahato et al. (2014)
μ	0.02	Omondi et al. (2018)
σ	0.8	Mahato et al. (2014)
λ_1	0.9	Mahato et al. (2014)
λ_2	0.01	Safiel et al. (2012)
ρ_1	0.88	Omondi et al. (2018)
ρ_2	0.2	Estimated
ρ_3	0.1	Safiel et al. (2012)
β_1	2.58	Safiel et al. (2012)
β_2	0.1	Safiel et al. (2012)
β_3	0.01	Safiel et al. (2012)
θ	0.01	Omondi et al. (2018)
ε	0.25	Mutasa-Apollo et al. (2014)

Table 5.1: *Parameters used in the numerical simulations of model (4.1).*

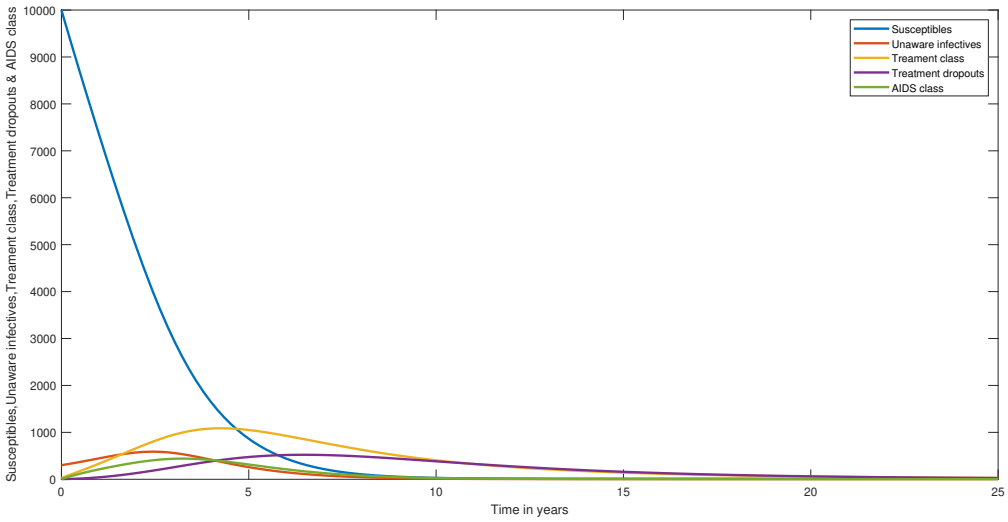

Figure 5.1: textitTime series of population in different classes.

As shown in Figure 5.1., as the number of infected individuals who are on treatment increases the size of the susceptible population decreases over time then reaches zero.Also the increase in the treatment class results in an increase in the treatment dropouts and AIDS populations.

5.3.1 Effects of treatment failure on the dynamics of system 4.1

The possible effects of increasing treatment failure on the dynamics of the HIV/AIDS population are shown in Figure 5.2.

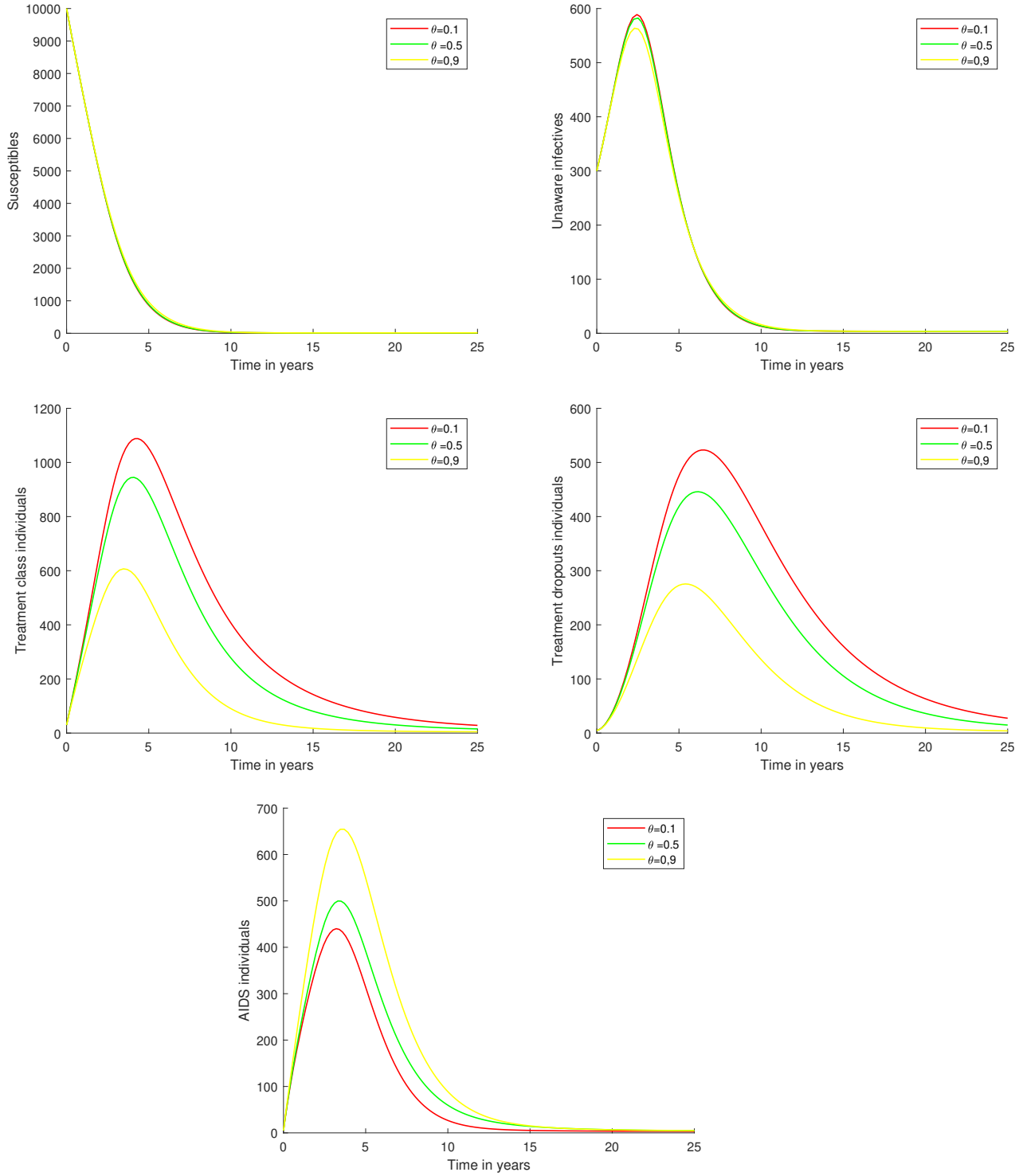

Figure 5.2: *Simulation results showing the dynamics of all individual populations of system (4.1) for different values of θ, the treatment failure rate.Initial conditions are as given in (5.14) and parameter values are as presented in Table 5.1.*

Figure 5.2 shows that an increase in the rate of treatment failure results in an increase in the maximum population of full blown AIDS individuals.However, the AIDS population decreases to zero overtime and this can be due to treatment with second and third line

ART which lowers the viral load and increases their cd4 counts.Also, the AIDS population decreases due to death as a result of AIDS related conditions.Moreover, the length of time it takes for the AIDS population to reach zero increases as the rate of treatment failure increases.It is seen also that increased treatment failure causes a decrease in the maximum population of treatment and treatment dropouts classes.Changes in the rate of treatment failure do not change the susceptibles and unaware infectives populations.

5.3.2 Effects of treatment dropouts on the dynamics of system 4.1

The effect of treatment dropouts on the population dynamics of HIV/AIDS is presented in Figure 5.3.

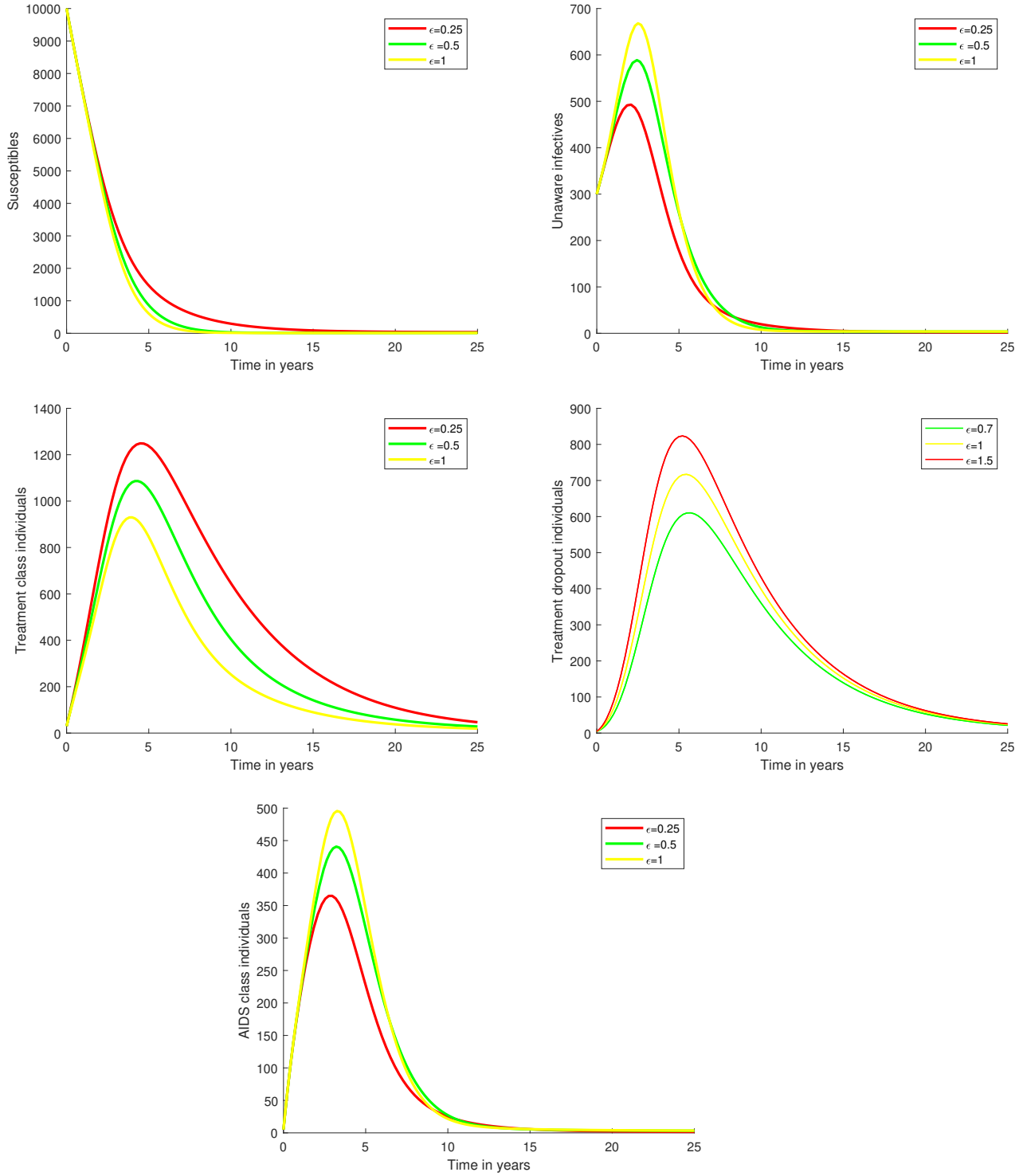

Figure 5.3: *Simulation results showing the dynamics of all individual populations of system (4.1) for different values of ε, the treatment dropout rate.Initial conditions are as given in (5.14) and parameter values are as presented in Table 5.1.*

Figure 5.3 shows that increasing the rate of treatment dropouts results in an increased maximum populations of treatment dropouts, unaware infectives and AIDS classes. The observed increase in the maximum population of AIDS individuals can be due to an

increase in the viral load of those who would have stopped treatment resulting in their cd4 count dropping leading to deterioration of their disease condition.Also, the maximum population of unaware infectives is greatest for higher rates of treatment dropouts and this can be explained by the fact that stopping treatment increases the level of infectivity and therefore treatment dropouts continue to spread the infection at a higher rate of infectivity than those on treatment.However, the length of time it takes for the treatment dropouts, unaware infectives and AIDS populations to reach zero is fairly the same for different rates of treatment dropout.

5.3.3 Effects of re initiation of treatment dropouts back to ART on the dynamics of system 4.1

The results of the effects of treatment dropouts obtained by varying ρ_2 is explored in Figure 5.4.

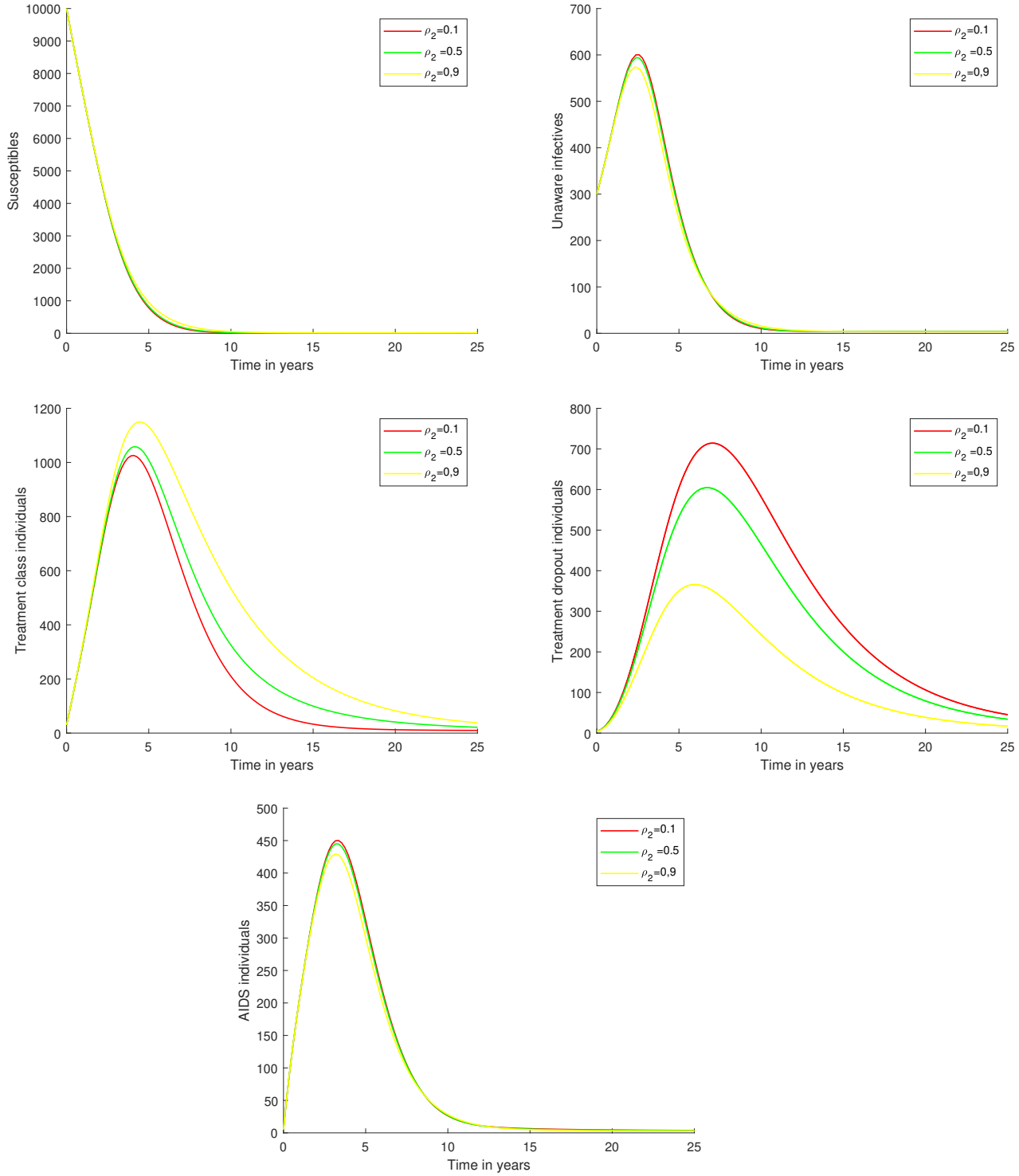

Figure 5.4: *Simulation results showing the dynamics of all individual populations of system (4.1) for different values of ρ_2, the rate of enrolment into ART of treatment dropouts.Initial conditions are as given in (5.14) and parameter values are as presented in Table 5.1.*

The simulation results in Figure 5.4 illustrate that an increase in the rate at which treatment dropouts are enrolled back into ART results in a decrease in the maximum pop-

ulation of treatment dropouts and a moderate decrease in the the AIDS and unaware infectives population.This result highlights the potential benefits of increasing efforts of finding and enrolling back to ART of those who would have stopped their treatment.How ever, increased enrolment back to ART results in the treatment class growing bigger and hence the need for more resources for ART programmes.

5.3.4 Effects of treatment failure on $\mathcal{R}_0$

We present the effects of treatment failure on $\mathcal{R}_0$ in Figure 5.5, obtained by varying the rate of treatment failure, θ.

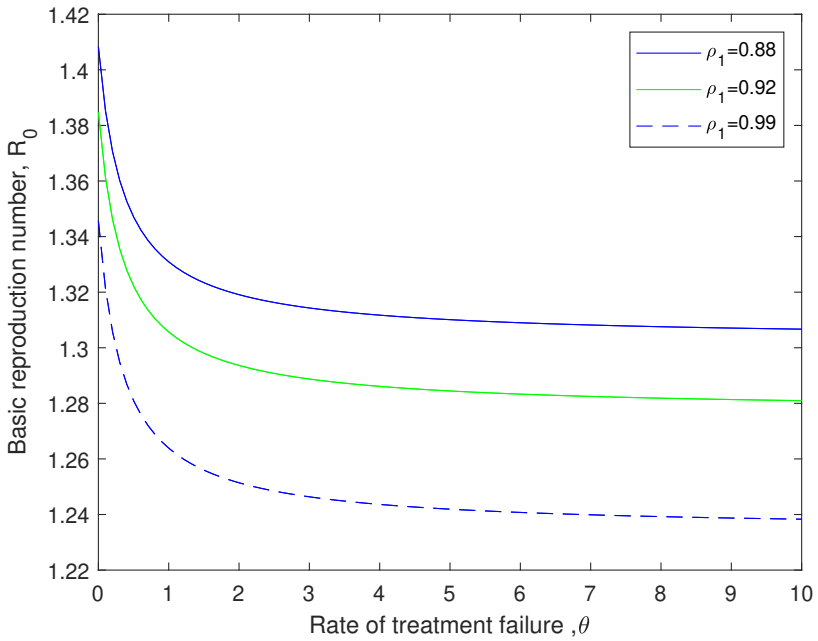

Figure 5.5: *Effects of treatment failure on $\mathcal{R}_0$.Other parameter values are as presented in Table 5.1.*

It can be seen from Figure 5.5 that an increase in treatment failure results in a reduction of $\mathcal{R}_0$.This result cannot be used as an intervention strategy against the HIV/AIDS epidemic because the observed reduction of $\mathcal{R}_0$ is due to increased progression to the AIDS class as a result of increased treatment failure.Since those who are in the AIDS class do not contribute to new infections due to morbidity and they are removed from the population at a higher rate as a result of the effect of both natural death and disease related death which explains the observed reduction in the $\mathcal{R}_0$ .However, this finding highlights the possible confounding effect of treatment failure on researches that report a reduction of $\mathcal{R}_0$ of HIV/AIDS due to treatment interventions.

5.3.5 Effects of treatment dropouts on $\mathcal{R}_0$

Numerical simulations for assessing the effects treatment dropouts on $\mathcal{R}_0$ is presented in Figure 5.6.

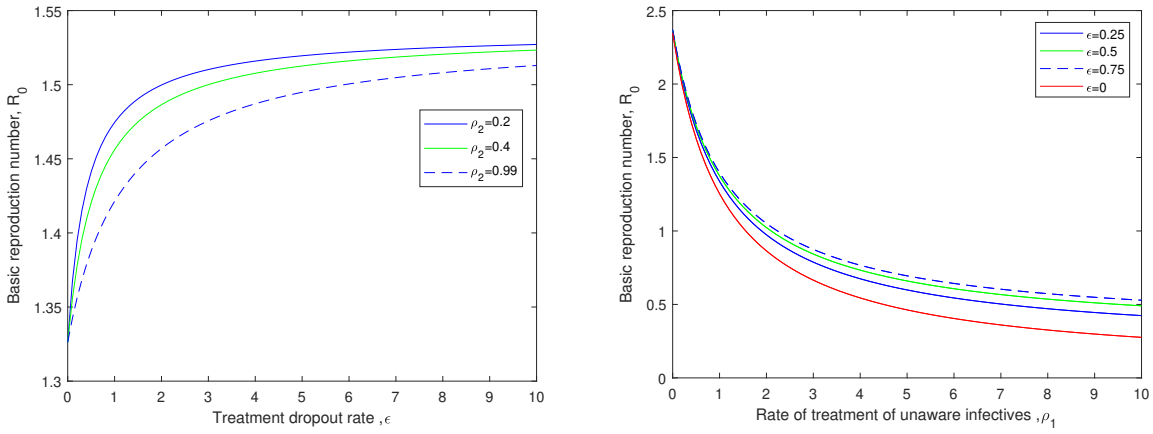

Figure 5.6: *Effects of treatment dropouts on $\mathcal{R}_0$.Other parameter values are as presented in Table 5.1.*

From the left graph in Figure 5.6 the simulation results show that as the rate of people stopping treatment increases, $\mathcal{R}_0$ increases upto an equilibrium point.This is so because we have more people transmitting the disease at a much higher level of infectivity than those still adhering to treatment.In addition the graph shows that increasing the rate of re introduction to ART of treatment dropouts(ρ_2) reduces the maximum value of $\mathcal{R}_0$ that can be attained though the value of $\mathcal{R}_0$ still remains above unit.We also note that even in the absence of treatment dropouts(when ε=0), $\mathcal{R}_0$ is still greater than unit meaning the disease will still persist in the population in the absence of other control measures.The graph on the right side indicates that treatment of unaware infectives only can bring a stop to the spread of the infection however higher rates of treatment(ρ_1) must be achieved to bring $\mathcal{R}_0$ below unit in the presence of treatment dropouts than in its absence(when $\varepsilon = 0$).

5.3.6 Model data fitting

To predict the expected changes in the various sub populations of model 4.1 we used data from the National AIDS Council of Zimbabwe for Midlands Province.The anaysis is done using R software version 3.6.1 and the results of this analysis are as shown in Fig 5.7.

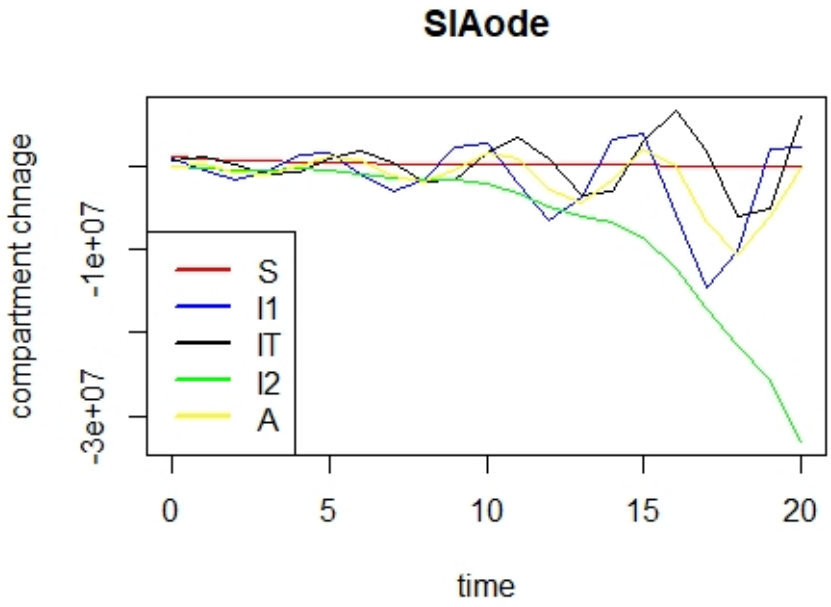

Figure 5.7: *Predicted changes in the sub populations of model 4.1 over time(in years).*

It is seen from Fig 5.7 that the number of susceptibles will remain constant and the unaware infectives, treatment class and AIDS class will fluctuate over time.However, the class of treatment dropouts will initially remain constant but will gradually start to decrease.This result suggest that, with the current strategies to retain and maintain individuals on ART, marked decreases in the rate of treatment dropouts can only be expected to drop after close to a decade from now highlighting the need to increase efforts against the issue of treatment dropouts.

Chapter 6

Discussion and conclusion

In this dissertation we considered a mathematical model of HIV/AIDS to study the possible effects of treatment failure and treatment dropouts on the population dynamics of the infection.The model incorporated a UTT scenario and a separate sub population of treatment dropout individuals. The basic reproduction number $\mathcal{R}_0$ and the model equilibria is computed.Analysis of the model shows that the disease free equilibrium is locally stable if $\mathcal{R}_0 < 1$ and unstable otherwise.Practical application of this result is that keeping the reproduction number below unity may be necessary to end the spread of HIV.If $\mathcal{R}_0 > 0$ the disease free equilibrium loses its stability and there exists an endemic equilibrium and the disease persists in the population.The conditions for the local stability of the endemic equilibrium where also given.

Numerical simulations where conducted to show the effects of treatment failure and treatment dropout on the dynamics of the HIV/AIDS epidemic.According to the numerical results, we conclude that increasing treatment dropouts results in increased transmission of HIV in a population and an increase in efforts to enrol treatment dropouts back on ART reduces the spread of the infection.However, we note that even in the absence of treatment dropouts and maximum efforts to enrol treatment dropouts the basic reproduction number remains above unity suggest that preventing treatment dropouts alone is not enough in the fight against the epidemic.This observation aligns with findings by Bhunu et al. (2011) in which a single intervention strategy could not be relied on for effectively controlling or eradicating HIV/AIDS.Also the study showed that an increase in treatment failure results in a decrease in the transmission of the infection however controlling treatment failure alone does not bring $\mathcal{R}_0$ below unit.Though, this finding can not be applied in real practice it points to the need to scrutinize any observed reduction of the basic reproduction number in studies of UTT for this possible effects of treatment failure on the basic reproduction number.Hence, this model highlights the need to focus on increasing efforts of reducing treatment dropouts in combination with other intervention strategies, through monitoring adherence and identifying and enrolling back to ART of treatment

dropouts.Also there is need to improve on early diagnosis of treatment failure such that those on treatment do not progress to AIDS before they are put on second or third line ART.

The main limitation of this study is that simulations where not based on empirical data and where purely qualitative.In addition the model did not consider immigration of infected individuals into the system and other modes of transmission .Also the model did not incorporate differential sucseptibility due to the current strategy of the use of ART as pre exposure prophylaxis which reduces the probability of getting infected.Incorporating these aspects in future work will improve in understanding the dynamics of the infection.

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