AN IMMUNOEPIDEMIOLOGICAL MODEL FOR HIV INCORPORATING VIRAL AND CELLULAR TRANSMISSION WITH ANTIRETROVIRAL TREATMENT

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DECLARATION

This research is my original work prepared with no other than the indicated sources and support and has not been presented elsewhere for a degree or any other award.

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CERTIFICATION

The undersigned certify that they have read and hereby recommend for acceptance of Masinde Muliro University of Science and Technology a thesis entitled "An immunoepidemiological model For HIV incorporating viral and cellular transmission with antiretroviral treatment".

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To my children your infinite love is forever memorable.

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ABSTRACT

Mathematicians have made various attempts to understand the dynamical behaviour of HIV and AIDS using within-and between-host transmission models. Since the mechanism of HIV and AIDS transmission is an intricate process, treating these processes separately may not comprehensively unravel the many properties that can emerge as a result of the interdependence of the two transmission processes. Hence a paradigm shift on modelling is fundamental in generating new predictions and strategies for controlling HIV spread. In view of this, multiscale models for HIV and AIDS are key in addressing this gap. Existing immuno-epidemiological models for HIV and AIDS however do not incorporate treatment in the viral and cellular transmission paths. This study focused on developing an immuno-epidemiological model for HIV and AIDS, incorporating viral and cellular transmission with antiretroviral treatment. Using ordinary differential equations, the two transmission subsystems were coupled in which the transmission rate at the population was expressed as a function of the viral load, while the within-host infection rates were modelled as functions of the number of infectives. The basic reproduction number, R_{0C} of the coupled model was found to be a maximum of the two reproduction numbers R_{0B} and R_{0W} corresponding to the between host and within host subsystems respectively. Stability analysis revealed that the disease free equilibrium is globally asymptotically stable whenever $R_{0B} < 1$ and $R_{0W} < 1$. Theoretically this means that the disease is wiped out. Using the center manifold Theorem, the endemic equilibrium was found to be locally asymptotically stable if $R_{0C} > 1$ and unstable otherwise. This reveals that the high transmissibility of HIV caused by high viral load at the within host level will lead to disease persistence in the population. Numerical simulation shows that an increase in viral load at the within host level leads to proportional increase in the number of infectives at the population level. The effectiveness of ARV treatment in combating the spread of HIV and AIDS depends on the efficacy levels of both RTI and PI. Consequently the study recommends the administration of ARVs with high treatment efficacy for both RTI and PI levels.

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

AIDS	:	Acquired Immunodeficiency Syndrome
ARV	:	Antiretroviral
$CD4^{+}$	:	Cluster of Differentiation 4 (glycoprotein found on the surface of immune cells)
CD8	:	Cluster of Differentiation 8
CTL	:	Cytotoxic T Lymphocytes
DFE	:	Disease Free Equilibrium
DNA	:	Deoxyribonucleic Acids
EE	:	Endemic Equilibrium
GAS	:	Globally Asymptotically Stable
HIV	:	Human Immunodeficiency Virus
IFE	:	Infection Free Equlibrium
ODE	:	Ordinary Differential Equations
PI	:	Protease Inhibitors
PDEs	:	Partial Differential Equations
RNA	:	Ribonucleic Acids
RTI	:	Reserve Transcription Transmission
SEIR	:	Susceptible Exposed Infected Recovered
SIA	:	Susceptible Infected Aids
UNAIDS	:	United Nations Acquired Immunodefiency Syndrome

List of Tables

List of Figures

CHAPTER ONE

INTRODUCTION

1.1 Background of the study

Since its discovery over three decades ago, HIV/AIDS still remains a major threat to human life and resource. Human resource is a major recipe for economic and industrial development. HIV and AIDS has greatly affected and/or depleted this important resource and exerted great economic burden globally especially in sub-Saharan countries, where its prevalence has always been high. According to UNAIDS global HIV and AIDS statistics of 2019 , 37.9 million people globally were living with HIV while 770000 people died from AIDS related illnesses. In many Sub-Saharan countries, for example, Kenya and Uganda, the effects of HIV and AIDS on the economy has been adverse due to the high cost of treatment and management. Thus enormous resources are being channeled to research and management.

HIV is a virus belonging to the genus lentivirus, which is a family of retrovirus whose genome is in form of RNA that transfers their genomic material through a process of reverse transcription, via viral enzyme called Reverse transcriptase [24]. This is in contrast to other living cells in which their genome sequence information flow as a result of replication. HIV mainly infects various immune cells such as microphage and lymphocyte T cells, which are part of the white blood cells. T cells can further be categorised into CD8 and $CD4^{+}T$ cells. HIV targets mainly the $CD4^{+}T$ cells. Besides attacking $CD4^{+}T$ cells, HIV also attack other body organs such as kidney, heart and the brain. This may lead to acute renal failure, cardiomyopathy and dementia. The reverse transcription process of viral RNA alters the function and genomic structure of $CD4^{+}T$ cells. These changes

damage the immune system leading to low $CD4^+T$ cell count. When the $CD4^+T$ cell count declines below a critical level (with the loss of cell mediated immunity), the overall immune system fails to hinder the growth of HIV and the body becomes progressively more susceptible to opportunistic diseases.

Tremendous research work has been conducted on how to contain or eradicate HIV and AIDS among the human population. This has been done by researchers from diverse fields such as biology, medicine and mathematics. Mathematicians through mathematical modelling of viral infections, have enhanced greater understanding of virus dynamics. This achievement has largely been realised by studying HIV infection and transmission dynamics at two levels namely; Within-host infection (immunological models) and Between-host transmission (epidemiological models) dynamics.

The between-host HIV transmission models (epidemiological models) seek to investigate how HIV spreads in the population through; sexual contact, intravenous drug use, blood transfusion and mother to child vertical transmission. Specifically the between host models describes HIV and AIDS progression among susceptibles, S (people who are vulnerable to infection), the asymptomatically infected, I (those who are infected without symptoms) and the symptomatically infected, A (the AIDS class) population. In the recent past, mathematical modelling of HIV and AIDS epidemiology has incorporated dynamics such as the impact of awareness, screening and counselling of infectives [17], adherence to ART treatment [35], vertical transmission and time delay [23] and HIV dynamics with treatment and vertical transmission [40] among others.

The immunological models, basically model the dynamics of HIV and target immune cells-$CD4^+T$ cells. These models can further be classified into viral and cellular infection models. Virus-to-cell models of infection describes the binding of a virus to a receptor on the surface of target $CD4^+T$ cells, replication and transcription into a provirus. Early

models of within host HIV infection such as those by [24] and [25] were successful in numerically describing dynamics of HIV infection and thus provided standard viral infection models that are the basis for current modelling of viral disease dynamics. Recent studies have however revealed that a high virus-to-cell infection rate is likely to lead to a transfer of multiple virions to target cells, hence the virus induced cell-to-cell transmission of viruses. The inclusion of cell-to-cell transmission in viral modelling has gained considerable attention in the recent past, this has greatly enhanced understanding of the HIV and AIDS infection in vivo. It has also opened new strategies in designing antiretroviral treatment, provided new insights into the pathogenisis of HIV as well as improve diagnosis.

The fight against the spread of HIV/AIDS pandemic has intensified over the years through ARV treatment and preventive programmes such as public awareness campaigns. Antiretroviral treatment can be done based on the two levels of infection, that is; virus-to-cell and cell-to-cell infection. Reverse Transcriptase Inhibitors (RTIs) form of treatment prevent virus-to-cell transmission by preventing reverse transcription of viral RNA into DNA, hence serves to reduce the rate of infection of activated $CD4^{+}T$ cells. While Protease Inhibitors (PIs) prevent cell-to-cell transmission by preventing HIV-1 protease from clearing the HIV polyprotein into functional units, thereby causing infected cells to produce immature virus particles that are not capable of infecting additional cells.

Since the mechanisms of HIV and AIDS transmission is an intricate process of interrelated and interconnected components such as viral replication, immune response system and other transmission pathways, a paradigm shift on HIV and AIDS modelling is fundamental in generating new predictions and strategies for HIV control. This may involve, for instance, for the inclusion of both viral-cell and cell-to-cell transmission treatment in the within host models. Standard HIV models have over time focused on either within host (viral and cellular interactions) or the between host (epidemiological) dynamics. However, for such biological phenomena, it is biologically feasible to study them together. Hence

the multiscale modelling framework that couple within-host and between-host processes of HIV transmission is crucial.

1.2 Statement of the problem

The within host immune viral dynamics and between host transmission dynamics of HIV can be modelled as an immmunoepidemiological model. These models factor the HIV transmission dynamics at the population level as a function of within host immune viral responses at the individual level. Existing immunoepidemiological models however do not incorporate treatment in the viral and cellular transmission paths. This is critical as it would determine the viral load as well as transmission at the population level.

1.3 Objectives of the study

1.3.1 General Objective

The main objective of our study is to develop and analyse a coupled immunoepidemiological model for HIV with viral and cellular transmission incorporating antiretroviral treatment.

1.3.2 Specific Objective

The specific objectives of this study are

(i) To develop and analyze a within host HIV infection model incorporating viral and cellular transmission with combined antiretroviral treatment.

(ii) To develop and analyse between host HIV transmission model with a saturated incidence rate incorporating antiretroviral treatment efficacy.

(iii) To develop and analyse a coupled within and between host model for HIV transmission incorporating viral and cellular transmission with antiretroviral treatment.

(iv) Numerically simulate the effect of treatment efficacy of the two treatment strategies namely the reverse transcriptase inhibitors (RTIs) and the protease inhibitors (PIs) in controlling the spread of HIV and AIDS.

1.4 Justification of the Study

HIV is one of the most researched virus, yet it still remains a threat to human life. Even with the existence of ARTs, the high level prevalence of HIV among the population, imply that the transmission rate within an individual as well as between individuals remains high. The fight against the spread of HIV requires an understanding of the immunoepidemiological transmission dynamics and the effects of ART drugs. An immunoepidemiological transmission model incorporating drug efficacy is therefore crucial in enhancing efforts towards the reduction of HIV prevalence and subsequent eradication of the virus.

1.5 Significance of the Study

Mathematical modelling of viral infection is a very important component in clinical and public health understanding of HIV prognosis, transmission risk and intervention effectiveness. By using ODEs we quantitatively represent a coupled immunoepidiemological model of within host and between host transmission with ART treatment. Furthermore the study will help open new strategies in designing antiretroviral treatment as a key component in figting HIV spread among the human population. In addition the results obtained from the analysis of this model will have a significant impact on future research on the evolutionary dynamics of HIV.

1.6 Outline of the study

To achieve the objectives of the study we shall;

(i) Formulate a within host dynamics model in which the $CD4^+$ T-cells are classified as uninfected ($T(t)$) and infected ($T^\star(t)$). The third compartment for the model

are the free virus cells ($V(t)$). The rates of change of the population of these cells are modelled by a system of ordinary differential equations. Efficacy of treatment is incorporated in the transmission terms for both viral to cell and cell to cell transmission.

(ii) Formulate between host model in which the population is compartmentalized as susceptible ($S(t)$), asymptomatically infected ($I(t)$), and symptomatically infected ($A(t)$). This model captures the transmission dynamics between individuals in a given population.

(iii) Bridge the two scales or coupling to produce the immunoepidemiological model, this is done by modelling the transmission rate for the population level model as a function of viral load V. This functional relationship may be linear, logistic or saturated type, For example,

- linear function

$$\beta(V) = rV \tag{1.1}$$

- logistic function

$$\beta(V) = rV(1 - \frac{V}{V_{max}}) \tag{1.2}$$

- saturated function

$$\beta(V) = \frac{rV}{V + \pi} \tag{1.3}$$

where the parameter r is the rate of transmission due to viral load. The parameter π is a threshold of the viral load that a host may need to cross to transmit the infection.

(iv) In order to investigate the theoretical results and determine the qualitative behaviour of the solutions, numerical simulations using MATLAB were performed. This was done by varying parameter values under different initial conditions and illustrating the results graphically and making various conclusions on the dynamical behaviour of transmission in the population.

CHAPTER TWO

LITERATURE REVIEW

2.1 Introduction

The use of sophisticated mathematical techniques has increasingly been embraced in unravelling various scientific and technological problems for many years. In particular mathematical modelling has been applied in complex biomedical processes such as viral infections. This has enhanced greater understanding of viral disease dynamics and helped in predicting and controlling the spread of diseases such as HIV and AIDS, dengue fever, Cholera and Ebola virus.

HIV and AIDS is one of the most widely studied viral disease, since its discovery over thirty years ago. This is largely due to its complex infection dynamics and its devastating effect on human life. This has prompted both biologists, biomedical researchers and mathematicians to adopt an interdisciplinary approach as an essential tool in studying the spread of HIV and AIDS in the human population. Mathematical modelling has emerged as a key component in this endeavour, as it logically and quantitatively describes the biological mechanisms governing HIV transmission. Also mathematical models have reliably been used to make predictions on the dynamics of HIV and AIDS. This section provides a literary journey of some of the main mathematical models that have made significant contribution in the fight against the spread and devastating effect of HIV and AIDS pandemic.

2.2 Within-host mathematical models

One of the early mathematical models of HIV infection was developed by [24] and [27], who came up with model (2.1) which was a basic three component model representing

HIV interaction with the body's immune system. The model sought to describe the dynamics of HIV progression from the onset of infection through the asymptomatic stage and finally into the symptomatic stage. They however did not include key dynamics like cellular infection. Though basic, the model provides a basis for future modelling for HIV and AIDS dynamics.

$$\begin{aligned} \dot{x} &= \lambda - dx - \beta xy \\ \dot{y} &= \beta xy - ay \\ \dot{v} &= ky - uv \end{aligned} \tag{2.1}$$

where

x: is the population of uninfected cells

y: the infected cells

v: free virus particles

β: rate of infection of uninfected cells

λ: rate at which uninfected cells are produced

d: death rate of uninfected cells

k: rate at which infected cells produce free virus

a: death rate of Infected cells

u: rate at which free virus particles are removed from the system.

In an effort to provide deeper insight on the various aspects of HIV, [26] developed a mathematical model of partial differential equations to study the spatial dependence on infection dynamics. In order to investigate the impact of spatial dynamics in a simple mathematical model of HIV infection they extended the standard three component model of in host viral dynamics to include spatially random diffusion and spatially dependent T cells supply rate. Model (2.2) was formulated and a mathematical analysis of the spatial viral dynamics was conducted. Basic results of well-posedness of smooth solutions and longtime asymptotic behaviour was determined. By denoting T as uninfected target cells, I as infected cells and V as free virions, the model assumed that target cells are supplied at constant rate of λ, and removed either through infection via contact with virions at

a rate of k per virion or through natural cell death with per capita rate μ_T. Similarly μ_I represents the per capita rate at which infected cells are destroyed, while μ_V the per capita at which virions are cleared from the body. N represents burst rate of the virus.

$$\begin{aligned} \partial_t T - D_T \Delta T &= \lambda(x) - \mu_T T - \kappa TV \\ \partial_t I - D_I &= \kappa TV - \mu_I I \\ \partial_t - D_V \Delta V &= N\mu_I I - \mu_V V \end{aligned} \tag{2.2}$$

A study by [30] focused on the analysis of the global and local stability of the within host virus models incorporating the mechanisms of direct cell to cell viral transmission and the viral co-infection (absorption of free virions into already infected cells). They proposed three dimensional system with both virus-to-cell and cell-to-cell transmission model (2.3), where T, $T^\star$ and V denote the concentrations of the uninfected host cells, infected host cells and free virus particles, respectively. Parameters k_1, is the contact rate of between uninfected cells and viruses, while k_2 is the contact rate between uninfected cells and infected cells. The parameters β and γ represent the death rate of infected cells and virus particles respectively. N is the average number of virus particles produced by either infected cells in its entire lifetime or by lytic virions through bursting. K_3 models rate of absorption of free virions into healthy cells during the infection process, while K_4 models the absorption of free virions into already infected cells. By analyzing the system they showed that the model demonstrates a global threshold dynamics. Model (2.3), as proposed by [30] sought to expand the standard model by including the additional cell to cell infection mechanism. Further [30] focused on the global stability dynamics of the two levels. Treatment at both levels of infection was not incorporated.

$$\begin{aligned} \dot{T}(t) &= f(T) - k_1 VT - k_2 TT^* \\ \dot{T}^*(t) &= k_1 VT + k_2 TT^* - \beta T^* \\ \dot{V}(t) &= N\beta T^* - \gamma V - k_3 VT - k_4 VT^* \end{aligned} \tag{2.3}$$

An investigation into the dynamical behaviour of a viral disease infection model using

general contact rate between free virus particles and healthy susceptible cells was done by [10]. They proposed model (2.4), which is a modified version of the basic viral infection model proposed by [24]. In the model susceptible host cells are produced at a constant rate, r, die at the rate of mx, and become infected with the rate of βxv. Infected host cells are produced at the rate of βxv and die at the rate of ay. Free virus particles are released from infected host cells at the rate of uv. To meet more biological practices the constant contact rate β was replaced with the general rate $f(v)$ between susceptible cells and virus particles. However Model (2.4) did not include cellular infection which is a significant component in a within host HIV infection dynamics.

$$\begin{aligned} \frac{dx}{dt} &= r - mx - f(x)xv \\ \frac{dy}{dt} &= f(v)xv - ay \\ \frac{dv}{dt} &= ky - uv \end{aligned} \tag{2.4}$$

The analysis of this model revealed that the value of the basic reproductive ratio determines the endemicity of the disease. This study focused on a general viral infection and therefore did not consider a specific disease like HIV and AIDS. Also various dynamics like role of treatment on disease spread was not incorporated in the study.

A study on the dynamical behaviour of HIV transmission with treatment parameters and delayed immune response was conducted by [15]. They proposed model (2.5), in which x, y, v and z represent uninfected $CD4^+$ T cells, infected $CD4^+$ T cells, virus and CTL(Cytotoxic T Lymphocytes) respectively. Uninfected T cell produced at rate s, dies at a rate dx and become infected at a rate kxv. Infected $CD4^+$ T cells die at a rate βy, and are lysed by CTL at a rate pyz. On average each productively infected cells produces N virions during its lifetime. Free virus particles decay at a rate av. The CTL expands at a rate cy and decays at a rate bz. v_i are infectious virus and v_n noninfectious virus. $(1-\sigma_1)$ and $(1-\sigma_2)$ represent the effectiveness of the RTI and PI treatments respectively.

$$\dot{x} = s - dx + rx(1 - \frac{x}{x_{max}}) - kv$$

$$\begin{aligned}
\dot{y} &= \sigma_1 k x v_i - \beta y - zpy \\
\dot{v_i} &= \sigma_2 N \beta y - a v_i \\
\dot{v_n} &= (1-\sigma_2) N \beta y - a v_n \\
\dot{z} &= C y(t-\tau) z(t-\tau) - bz
\end{aligned} \tag{2.5}$$

Their main findings were that if the Protease Inhibitors (σ_1) and Reverse Transcriptase Inhibitors (σ_2) satisfy the conditions $0 \leq \sigma_1 \leq 1$ and $0 \leq \sigma_2 \leq 1$ respectively, then the uninfected steady state is a unique equilibrium and the point is globally asymptotically stable, and if treatment is not effective enough then the equilibrium becomes unstable and HIV infection persists. They also analyzed time delays and its impact on the stability of the immune exhausted equilibrium and infected equilibrium. Although their study incorporated treatment, the effect of various levels of RTI and PI treatment on the population of $CD4^+$ T-cells, infected cells and virions were not elucidated, hence the gap on the role of efficacy of ART treatment of HIV.

The use of delay differential equations in modelling infection dynamics of HIV was utilized by [11], in which model (2.6) was developed and analyzed. The model (2.6) incorporated distributed time delays and humoral immune response in a cellular and viral nonlinear equations. Their analysis established that time delays play key role in virion clearance from the human body a role similar to the one played by the use of antiretroviral treatment. Despite this novel result, the study did not incorporate treatment in their analysis.

$$\begin{aligned}
\dot{T}(t) &= \lambda - dT(t) - \beta_1 T(t) V(t) - \beta_2 T(t) T^*(t) \\
\dot{T^*}(t) &= \int_0^\infty f_1(\tau) e^{-\delta_1 \tau} (\beta_1 T(t-\tau) V(t-\tau) + \beta_2 T(t-\tau) T^*(t-\tau)) d\tau - \mu T^*(t) \\
\dot{V}(t) &= b \int_0^\infty f_2(\tau) e^{-\delta_2 \tau} T^*(t-\tau) d\tau - cV(t) - aV(t) W(t), \\
\dot{W}(t) &= rV(t) W(t) - mW(t)
\end{aligned} \tag{2.6}$$

where $T(t)$, $T^\star$) and $V(t)$ are the concentrations(the number of cells or viruses per unit volume) of the uninfected cells, infected cells and free virus particles at a time t, respectively. The assumptions are as follows: The uninfected cells are replenished at a rate

λ, die at rate αT and become infected at rate $\beta_1 T(t)V(t) + \beta_2 T^{\star}(t)V(t)$ where β_1 is the virus-target incidence rate constant and β_2 is the infected-target incidence rate constant. μ and c are death rate constants of the infected cells and free virus particles, respectively. b is the average number of virus particles that bud out from an infected cell. The virus or infected cell contacts an uninfected target cell at time $t - \tau$, the cell becomes infected at time t, where τ is a random variable taken from a probability distribution $f_1(\tau)$. The term $e^{-\delta_1 \tau}$ modelling the decay of survival of the contacted cell in the time interval of the decay, where δ_1, is a positive constant. In addition the model assumed that, a cell infected at time $t - \tau$ starts to generate new infective virus particles at time t, where τ is taken from a probability distribution $f_2(\tau)$. The term $e^{-\delta_2 \tau}$ modelling decay of survival of the infected cell in the time interval of the decay, where δ_2 is a positive constant.

Studies by [28], [30], [31], [32] and [33] add to the list of researchers who have factored various dynamics in the within host infection models in the recent past. For instance [28] examined a model on the interaction of HIV with $CD4^{+}T$ cells, involving T cells , latently infected T cells, actively infected T cells and free virus. The effects of AZT treatment on viral growth and T cell population were highlighted, but was not included in the mathematical model. In addition only one level of treatment (RTI) was discussed while cellular infection was not considered. [30] on the other hand sought to expand the standard models by [24] and [28] by including the additional cell to cell infection mechanisms and mainly focused on global stability dynamics of their model. [31] investigated stability analysis in delayed within host viral dynamics with both viral and cellular infections while, [32] studied viral mutation rates with a focus on the role of within-host viral dynamics and the trade off between replication fidelity and speed. [33] in his study , modelled within host HIV-1 dynamics and the evolution of drug resistance.
Our study seeks to explicitly incorporate both viral and cellular levels of treatment on the within-host model for HIV infection dynamics, in particular the treatment efficacy of both treatment levels will be analysed.

2.3 Between-host mathematical models

Between host models focus on modelling transmission dynamics in the population. For instance [42], studied the dynamics of a general epidemic model using an SEIR framework given in model (2.7), with a saturated incidence rate and a continually differentiable treatment function $h(I) = \frac{rI}{1+kI}$ to characterise the saturation phenomenon of limited medical resources. The results of their study showed that improved efficiency and enlarged treatment capacity are important in the fight against the spread of an epidemic disease. The study focused on the general transmission dynamics of an epidemic model with saturated treatment and therefore did not specifically apply to any particular epidemic such as HIV and AIDS. Furthermore the efficacy of treatment as an important aspect in control of disease transmission were not elucidated. In view of this, our study in chapter four focuses on the between-host transmission dynamics of HIV and AIDS in the population with saturated incidence and combined treatment efficacy. In addition, the study by [42] did not address how the within host dynamics impacts on the transmission dynamics in the population for a specific epidemic disease such as HIV/AIDS.

$$\begin{aligned} S'(t) &= A - \frac{\beta SI}{1+\alpha I} - ds \\ E'(t) &= \frac{\beta SI}{1+\alpha I} - (d+\varepsilon)E \\ I'(t) &= \varepsilon E - (d+\mu+v)I - \frac{rI}{1+kI} \\ R'(t) &= vI - dR + \frac{rI}{1+kI} \end{aligned} \tag{2.7}$$

where $S(t)$, $E(t)$, $I(t)$ and $R(t)$, denote the number of susceptible, exposed but not infectious, infected and recovered individuals respectively. while A is the recruitment rate of the population, α the saturation factor that measures the inhibitory effect, β is the transmission or contact rate, d is the natural death rate of the population, ε is the rate of transformation from incubation period individuals to infective individuals, μ is the disease rated mortality, v is the natural recovery rate of the infective individuals, r is the maximal medical resources supplied per unit time and k is the saturation factor that measures the

effect of infected being delayed for treatment. $S(t), E(t), I(t), R(t) > 0$ while β, d, ε, μ, v and r are all positive, and α and k nonnegative.

In a study on the stability analysis of an HIV/AIDS epidemic model with treatment, [4] formulated a treatment model using ordinary differential equations, in which individuals infected with HIV, move from symptomatic stage to the asymptomatic stage. They also investigated the effect of discrete time delay and found that the delay model exhibits a Hopf bifurcations. Among their key results was that the behaviour of the solutions of the model can be determined by its basic reproductive number R_0, in which $R_0 \leq 1$ imply that the disease free equilibrium is globally asymptotically stable while $R_0 > 1$ imply that HIV persists in the population and the unique endemic equilibrium is globally asymptotically stable. Whereas this study provided significant insights in epidemic modelling with treatment, it did not put into account how treatment efficacy impacts HIV spread in the population and at what point of the infection process it is introduced. Chapter four of our study investigates the effect of treatment efficacy for both the asymptomatic and symptomatically infected classes. Subsequently our study in chapter five, investigates how the within host viral dynamics of HIV interrelates with the between host viral transmission dynamics. Thus nesting of both within and between host HIV viral mechanisms will be vital in modelling HIV and AIDS transmission with treatment.

The impact of awareness, screening and counselling of infectives in the transmission dynamics of HIV in a homogenous population with constant immigration of susceptibles was investigated by [17]. They postulated that an increase in screening decreases the equilibrium level of infectives and AIDS patients while an increase in awareness decrease the basic reproduction number below one which forces the system towards the disease free equilibrium point. Their results further suggested that general awareness and screening of HIV infectives are crucial in reducing the transmission of HIV. It is however acknowledged that awareness, screening and counselling alone cannot effectively combat the spread of

HIV and AIDS, hence the inclusion of treatment in modelling HIV spread in the population is crucial. Chapter four of our study seeks to address this gap.

A study on the stability analysis of HIV/AIDS epidemic model with nonlinear incidence and treatment was done by [16], in which both analytic and numerical results indicated that a change in the susceptible behaviours' sexual habits significantly reduces both incidence and prevalence of HIV/AIDS. Even though this study was successful in mathematically analysing the stability of HIV and AIDS epidemic with treatment, emerging solution behaviour of HIV and AIDS epidemic model can be unravelled if within-host models are coupled with between-host models. Furthermore the aspect of HIV treatment efficacy can be investigated effectively when incorporated in a coupled multiscale model.

2.4 Immunoepidemiological models

Infectious disease dynamics are governed by various interrelated processes, that is , from complex within host infection processes to between-host transmission dynamics [2]. As a result, mathematical modelling has become an important tool in understanding these processes. Over the years, various disease models have focused on the two transmission scales namely: within-host, involving cellular interactions: and between-host, focusing on population transmission independently.

For instance viral models by [22, 25, 26, 29, 30] consider the within host dynamics independent of the interaction at the population level, whereas epidemic models of population dynamics such as [1, 3, 4] consider the interaction between susceptible and infected hosts without an explicit link to the viral dynamics of the within host system. Although when the two processes are decoupled, the mathematical models are generally easier to analyse, there are however very insightful questions that can only be answered by coupled models, such as: (i). What is the impact within-host dynamics on population level quantities such as R_o and prevalence?, (ii). What is the effect of population dynamics of disease

transmission on the viral dynamics at the individual level [14, 21], hence the rationale for multiscale models in mathematical disease modelling.

A multi-scale model linking the two levels of transmission, that is, the immunological and epidemiological viral infection levels by [2] suggested that the link between the two levels can be done by considering transmission at the population level as a function of viral load of the transmitting individual. Consequently, stability and bifurcation analysis were conducted using the coupling of the two basic reproduction numbers R_0^W and R_0^B for both subsystems respectively. In the study the derivation of R_0^B as a general increasing function of R_0^W was their main result. The study also focused on a general approach towards coupling of an infectious disease, however this novel idea can be applied in modelling HIV and AIDS transmission dynamics, which we seek to investigate in our research. Further the model considered only within host dynamics influencing between host processes and not vice versa.

A coupled model that explicitly links the epidemiological and immunological dynamics was proposed by [14]. The model aimed at establishing new properties and complex dynamics that can be deduced from the coupled system. In their analysis of the coupled model two threshold quantities were used, that is, R_V and R_H which denotes the within- and between-host threshold values respectively, and it was shown that the magnitudes of these quantities can jointly determine the disease prevalence. Also as a direct consequence of coupling of the within- and between-host processes, multiple endemic equilibria and bi-stability was observed. The model by [14], successfully bridged the two scales by incorporating the dependence of epidemics on the viral dynamics, as well as the dependence of the within host dynamics on the between host dynamics. However [14] only considered a general infectious disease dynamics. Our study seeks to extend these ideas in developing a coupled immunoepidemiological model incorporating viral and cellular infection dynamics of HIV with treatment.

A nested mathematical model for within-host and between-host transmission dynamics in the progression of HIV/AIDS in China was formulated and analysed by [20] . They carried out a model linkage in the rate of transmission of an infection as an increasing function of viral load. By assuming that the rate of transmission $\beta(\tau)$ is proportional to the Hill function of viral load $V(\tau)$, at a given age-since-infection τ, they came up with equation (2.8) . The analysis of the stabilities of the equilibria was done by use of the reproductive ratio R_0. Through numerical simulations they established that the within-host dynamics does influence the between host dynamics, and that the nesting of within-host and between host play an important role in the HIV/AIDS evolution.

$$\beta(\tau) = \beta_o(V(\tau)) = \beta_O(\frac{V(\tau)}{V(\tau)} + \Omega) \tag{2.8}$$

Also [20], divides host population into; susceptible, the infected without receiving treatment and the infected receiving treatment in accordance with "Chinese-Four-Free-one-Care policy". It is worth noting that [20] focused on a model that considered only within-host dynamics influencing between host processes and not vice versa. On treatment [20] did not explicitly investigate the efficacy of the two levels of treatment (RTI and PI) on viral and cellular transmission. In our study we endeavour to explore this gap.

A review of the literature on immunoepidemiological modelling as well as the main insights these models have created, was done by [21]. They categorised the modelling approaches for coupling into Network models, ODE immunoepidemiological models, size structured PDE immunoepidemiological models and nested models. The study by [21] did not investigate the various transmission dynamics, such as viral and cellular infection dynamics at the within host level or effect of virulence on between host transmission for the case of coupled models. In particular their study did not focus on any specific disease such as HIV and AIDS.

The global stability of an infection-age structured HIV-1 model linking within-and between-host dynamics was investigated by [34] . In their study the different disease progression stages were formulated as age since infection in the form of PDEs, they argued that the transmission rates at different stages are treated as saturated functions of viral load, hence adopted a saturation function to describe the relationship between viral load and the transmission rate in each disease progression stage. The model by [34], however did not incorporate viral and cellular infections in their multiscale model linkage, in addition RTI and PI treatment regimes of HIV-1 was not included in their study. Hence our study seeks to address this gap. From the above literature we observe that most of the proposed models on HIV and AIDS, focused on the two processes of HIV transmission separately. Despite great strides that have been made in capturing the many HIV dynamics, it is clear that treating these processes separately may not comprehensively unravel the many properties that can emerge from the interdependence of the two transmission processes. For example, the functional relationship between viral load and rates of transmission at the population level. Hence there is need to explore a new approach that can elucidate this phenomena.

This study sought to address this gap by applying the new approach that couples the two dynamic processes. Specifically this research investigated the behaviour of HIV viral transmission by formulating a multiscale model that couples the two subsystems, that is, from early viremia (within host) to the epidemic level (between host). In addition the study investigated the effect of ART treatment on a within and between host viral infection dynamics on the human population.

The remaining part of this research is organised as follows; In chapter three, a mathematical model of within host HIV infection dynamics in vivo, with combined treatment is formulated and analysed. Numerical simulation of the theoretical results are done and graphically represented. In chapter four, the between host model with saturated incidence is presented. Chapter five seeks to couple the within and between host models discussed

in chapter three and four respectively. The analysis is done using the centre manifold theorem, whose results are numerically simulated and deductions made. Conclusion and recommendations are made in chapter six.

CHAPTER THREE

DYNAMICS OF THE WITHIN HOST HIV INFECTION MODEL UNDER COMBINED ANTIRETROVIRAL TREATMENT

3.1 Introduction

In this chapter we formulate a mathematical model for the within host HIV infection model, incorporating viral and cellular infection dynamics with combined antiretroviral treatment. Specifically, the chapter analyses both local and global stability for the within host model, as well as numerically investigate , the effect of RTI and PI treatment regimes on the viral load and the population of uninfected $CD4^+$ T cells.

3.2 Model Formulation

In order to conduct a thorough analysis of the dynamics of the in-vivo HIV infection with combined ART treatment, it is imperative to formulate a mathematical model describing the interaction between HIV, actively infectious cells and the immune system. This interaction involves free virus particles $V(t)$, actively infected $T^\star(t)$ and the healthy susceptible $CD4^+$ T cells $T(t)$. The susceptible $CD4^+$ T cells $T(t)$ are recruited at a constant rate r from the thymus glands and have a natural mortality rate of μ_W. It assumed that the growth of $CD4^+$ T cells is logistic, this is represented by the logistic term $(1 - \frac{T}{T_{max}})$. This means that total number of T cells in the body remains bounded, Hence the growth of T cell population approaches the carrying capacity T_{max}. When HIV enters the body, it infects the healthy $CD4^+$ T cells at a rate βVT, thus the susceptible $CD4^+$ T cells become actively infected, this makes them infectious and upon interaction with other healthy $CD4^+$ T cells, will infect them at the rate $\alpha_W TT^\star$. The actively infected cells die at a constant per capita rate κ. The free virions regenerate at a rate $\omega\kappa T^\star$, where ω

is the bust rate of actively infectious cells. The free virions die at a constant per capita rate of c.

Viral and cellular infection can be inhibited by using combined ART treatment. Therefore HIV viral load in the human blood is a function of the combined ART treatment efficacy. The use of RTI prevents HIV from entering the $CD4^+$ T cell and its efficacy is represented by parameter ρ. On the other hand the PI prevents the infected cells from reproducing infectious virions or to become activated into infectious cells and are rendered immature noninfectious virions, its efficacy is represented by parameter ϑ. The effectiveness of treatment for both RTI and PI ranges between zero and one. For example $\rho, \vartheta = 0.2$ imply low treatment efficacy, while $\rho, \vartheta = 0.8$ is considered highly effective treatment. The within host infection host dynamics can be illustrated diagrammatically by Figure (3.1) below.

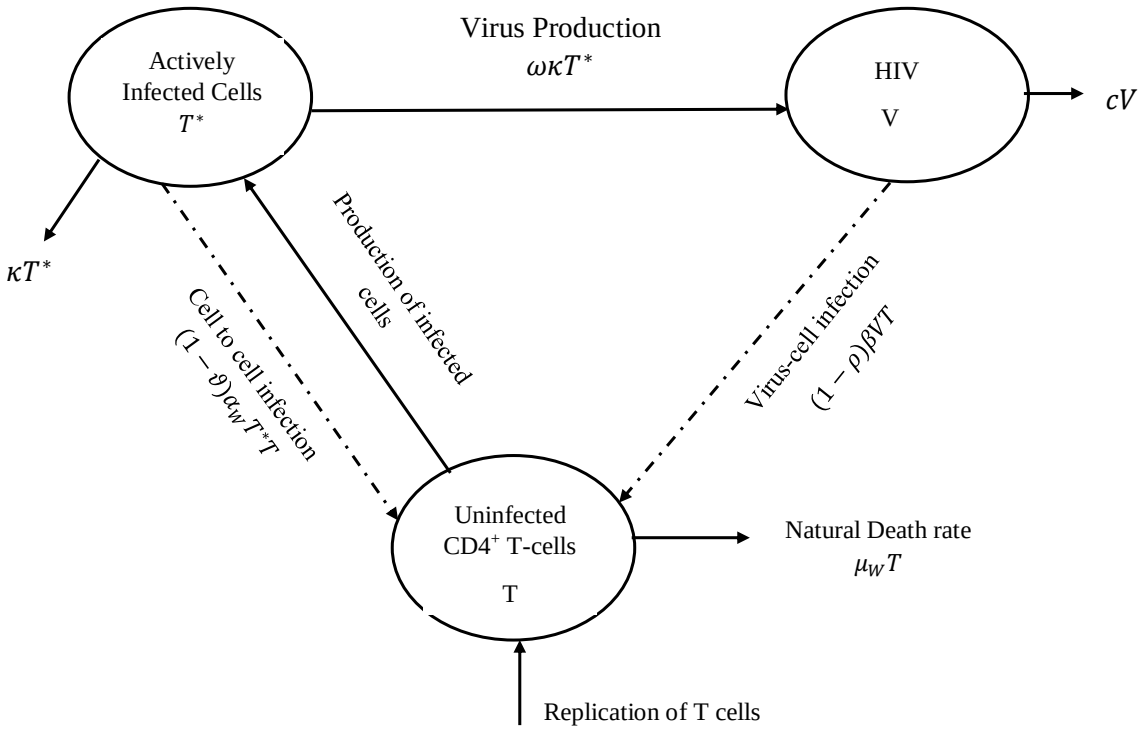

Figure 3.1: Flow chart of the within-host HIV transmission

From the description and definitions made, the infection dynamics are summarized by the

following system of ODEs:

$$\begin{aligned}
\frac{dT}{dt} &= rT(1-\frac{T}{T_{max}}) - (1-\rho)\beta VT - (1-\vartheta)\alpha_W TT^\star - \mu_W T \\
\frac{dT^\star}{dt} &= (1-\rho)\beta VT + (1-\vartheta)\alpha_W TT^\star - \kappa T^\star \\
\frac{dV}{dt} &= \omega\kappa T^\star - cV
\end{aligned} \tag{3.1}$$

With initial conditions

$$T(0) = T_0 > 0, T^\star(0) = T_0^\star \geq 0, V(0) = V_0 > 0 \tag{3.2}$$

3.3 Positivity of solutions

Model (3.1) describes cell and virus population whose values will never be negative. We therefore assume that all variables and parameters are non-negative for all time, $t \geq 0$. Thus positivity of solutions of model (3.1) can be established using the following lemma.

Lemma 3.3.1. *Let $T(t), T^\star(t)$ and $V(t)$ be the solutions of model (3.1) satisfying the initial conditions (3.2), the solutions of model (3.1) will remain positive and bounded in the feasible region* $\Gamma = \{(T, T^\star, V) \in \mathbb{R}^3_+ : T + T^\star + V \leq T_{max}(1 - \frac{\mu_W}{r})\}, \forall t \geq 0$

Proof. From the third equation of model (3.1), that is

$\frac{dV}{dt} = \omega\kappa T^\star - cV$

we have

$$\frac{dV}{dt} = \omega\kappa T^\star - cV \geq -cV \tag{3.3}$$

we can solve (3.3) by separation of variables method, thus

$$\int \frac{dv}{V} = \int -cdt \tag{3.4}$$

to obtain

$$V(t) \geq V(0)e^{-ct} > 0, \forall t \geq 0 \tag{3.5}$$

Similarly, for the infected T-cell population,

$$\frac{dT^\star}{dt} = (1-\rho)\beta VT + (1-\vartheta)\alpha_W TT^\star - \kappa T^\star \geq -T^\star(\kappa - (1-\vartheta)\alpha_W T) \tag{3.6}$$

Integrating (3.6) yields

$$T^\star(t) \geq T^\star(0)e^{-(\kappa-(1-\vartheta)\alpha_W T)t} > 0 \tag{3.7}$$

Since $\kappa - (1-\vartheta)\alpha_W T > 0$ □

Applying the same procedure, it can be shown that the positivity of the uninfected T-cell population is also positive. Hence each solution of model (3.1) with initial conditions (3.2) is positive for all $t \geq 0$.

3.3.1 Basic Reproduction Number

The basic reproduction number R_{0W} is defined as the average number of secondary infections produced by one infectious virion and one infected cell over the course of their infectious period in uninfected $CD4^+$ T cell population. The basic reproduction number, R_{0W}, for model (3.1) is computed using the next generation matrix method as used in [7, 38]. Model (3.1) has two infected compartments $T^\star$ and V. Let f_i be the rate of appearance of new infections in compartment i and ν_i as the transfer of individuals out of compartment i for the two compartments respectively, and are given in partitioned form as follows:

$$\mathcal{F} = \begin{pmatrix} (1-\rho)\beta VT + \alpha_W(1-\vartheta)TT^\star \\ \\ 0 \end{pmatrix} \tag{3.8}$$

and

$$\mathcal{V} = \begin{pmatrix} \kappa T^\star \\ \\ -\omega\kappa T^\star + cV \end{pmatrix} \tag{3.9}$$

The Jacobian of $\mathcal{F}$ and $\mathcal{V}$ evaluated at the Infection Free Equilibrium $E_0 = (T_{max}(1-\frac{\mu_W}{r}), 0, 0)$ yields ;

$$F = \begin{pmatrix} \alpha_W(1-\vartheta)T_0 & \beta(1-\rho)T_0 \\ \\ 0 & 0 \end{pmatrix} \tag{3.10}$$

$$V = \begin{pmatrix} \kappa & 0 \\ -\omega\kappa & c \end{pmatrix} \tag{3.11}$$

where F is nonnegative and V is nonsingular. The inverse of V is

$$V^{-1} = \frac{1}{\kappa c}\begin{pmatrix} c & 0 \\ \omega\kappa & \kappa \end{pmatrix} \tag{3.12}$$

hence

$$FV^{-1} = \begin{pmatrix} \alpha_W(\frac{1}{\varphi}-1)T_0 & \beta(1-\rho)T_0 \\ 0 & 0 \end{pmatrix}\begin{pmatrix} \frac{1}{\kappa} & 0 \\ \frac{\omega}{\kappa} & \frac{1}{c} \end{pmatrix} \tag{3.13}$$

$$FV^{-1} = \begin{pmatrix} \frac{\alpha_W}{\kappa}(\frac{1}{\varphi}-1)T_{max}(1-\frac{\mu_W}{r}) + \frac{\omega\beta}{c}T_{max}(1-\rho)(1-\frac{\mu_W}{r}) & \frac{\beta}{c}T_{max}(1-\rho)(1-\frac{\mu_W}{r}) \\ 0 & 0 \end{pmatrix} \tag{3.14}$$

The basic reproduction number is thus given by $R_{0W} = \rho(FV^{-1})$, where $\rho(FV^{-1})$ is the spectral radius of the matrix FV^{-1}. Thus

$$R_{0W} = T_{max}(1-\frac{\mu_W}{r})(1-\vartheta)\frac{\alpha_W}{\kappa} + T_{max}(1-\frac{\mu_W}{r})\frac{\omega\beta}{c}(1-\rho) \tag{3.15}$$

3.4 Analysis of the Infection Free Equilibrium

3.4.1 Local Stability Analysis

Since the model is nonlinear, the local stability properties of the infection free equilibrium can be determined by approximating the nonlinear system of the differential equations (3.1) with the linear system at the infection free equilibrium $E_0 = (T_{max}(1-\frac{\mu_W}{r}), 0, 0)$.

Theorem 3.4.1. *The infection free equilibrium E_0 is locally asymptotically stable if and only if $R_{0W} < 1$*

Proof. Evaluating the Jacobian of model (3.1) at E_0 we obtain

$$J(E_0) = \begin{pmatrix} \mu_W - r & -\alpha_W T_{max}(1-\frac{\mu_W}{r})(1-\vartheta) & -\beta T_{max}(1-\frac{\mu_W}{r})(1-\rho) \\ 0 & \alpha_W T_{max}(1-\frac{\mu_W}{r})(1-\vartheta) - \kappa & \beta T_{max}(1-\frac{\mu_W}{r})(1-\rho) \\ 0 & \omega\kappa & -c \end{pmatrix} \tag{3.16}$$

clearly

$$\lambda_1 = \mu_W - r \tag{3.17}$$

is one of the eigenvalues of the matrix in equation (3.16). The eigenvalue λ_1 is negative since for any population whose growth in numbers is positive; the production rate (birth rate) is greater than the mortality rate, that is, $r > \mu_W$.

To determine the nature of the remaining roots of equation (3.16) consider the reduced matrix,A, below;

$$A = \begin{pmatrix} \alpha_W T_{max}(1 - \frac{\mu_W}{r})(1 - \vartheta) - \kappa & \beta T_{max}(1 - \frac{\mu_W}{r})(1 - \rho) \\ \omega\kappa & -c \end{pmatrix} \tag{3.18}$$

Applying the Routh-Hurwitz technique for stability analysis, then matrix A in equation (3.18) will have negative real roots if and only if the $tr(A) < 0$ and $det(A) > 0$, thus

$$tr(A) = (R_{0W} - 1) - T_{max}(1 - \frac{\mu_W}{r})(1 - \rho)\frac{\beta\omega}{c} - \frac{c}{k} \tag{3.19}$$

and

$$det(A) = -[\frac{\alpha_W}{\kappa} T_{max}(1 - \frac{\mu_W}{r})(1 - \vartheta) + \frac{\beta\omega}{c} T_{max}(1 - \frac{\mu_W}{r})(1 - \rho)] + 1 \tag{3.20}$$

Using equation (3.15), equation (3.20) reduces to

$$det(A) = 1 - R_{0W} \tag{3.21}$$

From equations (3.19) and (3.21), $tr(A) < 0$ and $det(A) > 0$ if and only if $R_{0W} < 1$. Thus E_0 is locally asymptotically stable whenever $R_{0W} < 1$, and unstable otherwise. □

Biologically this implies that if a few free virion enters the blood stream, then there is a high chance of infecting less than one susceptible cell in its entire period of infectivity, whenever $R_{0W} < 1$. Theoretically this can be interpreted to mean viral clearance from the human body if $R_{0W} < 1$.

3.4.2 Global Stability Analysis of the Infection Free Equilibrium

In this section the global stability of the Virus Free Equilibrium of Model (3.1), can be studied by using the theorem ascribable to [7]. This is done by rewriting Model (3.1) as follows

$$\frac{dX}{dt} = H(X, Z)$$

$$\frac{dZ}{dt} = G(X, Z), G(X, 0) = 0 \tag{3.22}$$

where $X \in \mathbb{R}$ denotes the number of susceptible cells and $Z \in \mathbb{R}^2$ denotes the number of actively infected cells and free virions respectively. The Infection Free Equilibrium (IFE) assumes the following notation

$$U_0 = (X^0, 0), X^0 = T_{max}(1 - \frac{\mu_W}{r}) \tag{3.23}$$

The conditions $H_1$and H_2 given below must be met in order to guarantee global asymptotic stability:

- (H_1): For $\frac{dX}{dt} = H(X, 0), X^0$ is Globally Asymptotically Stable (GAS)
- (H_2):$G(X, Z) = PZ - \hat{G}(X, Z), \hat{G}(X, Z) \geq 0$, for $(X, Z) \in \Omega$

where $P = D_Z G(X^0, 0)$ is an M- matrix (the off diagonal elements of P are nonnegative) and Ω is the region where the model makes biological sense. If system (3.22) satisfies conditions H_1 and H_2, then the following theorem (3.4.2) holds:

Theorem 3.4.2. *The fixed point $U_0 = (X^0, 0)$ is Globally Asymptotically Stable equilibrium of (3.22) provided that $R_{0W} < 1$ and that assumptions (H_1) and (H_2) are satisfied.*

Proof. Let $X(t) = T(t)$, $Z = (T^\star(t), V(t))$, $H(X, 0) = \begin{pmatrix} rT(1 - \frac{T}{T_{max}}) - \mu_W T \\ 0 \end{pmatrix}$ and $G(X, Z) = PZ - \hat{G}(X, Z)$ where

$$P = \begin{pmatrix} \alpha_W T_{max}(1 - \vartheta) - \kappa & \beta T_{max}(1 - \rho) \\ \omega\kappa & -c \end{pmatrix} \tag{3.24}$$

$$\hat{G}(X,Z) = \begin{pmatrix} \hat{G}_1(X,Z) \\ \\ \hat{G}_2(X,Z) \end{pmatrix} = \begin{pmatrix} 0 \\ \\ 0 \end{pmatrix} \tag{3.25}$$

From equation (3.25) $\hat{G}_1(X,Z) = \hat{G}_2(X,Z) = 0$ this implies that $\hat{G}(X,Z) \geq 0$. Therefore, E_0 is globally asymptotically stable when $R_{0W} < 1$ □

This means that any perturbation of the equilibrium point by the introduction of free virus particles, the model solutions will always converge to the IFE, whenever $R_{0W} < 1$.

3.5 Endemic Equilibrium (EE)

3.5.1 Existence of the Endemic Equilibrium (EE) for the Within Host HIV infection model

Theorem 3.5.1. *A positive Endemic equilibrium EE exists provided* $R_{0W} > 1$, $T_e^\star \neq 0$ *and* $V_e \neq 0$

Proof. The endemic equilibrium $EE = (T_e, T_e^\star, V_e)$ satisfies:

$$rT_e(1 - \frac{T_e}{T_{max}}) - (1-\rho)\beta V_e T_e - \alpha_W(1-\vartheta)T_e T_e^\star - \mu_W T_e = 0 \tag{3.26}$$

$$(1-\rho)\beta V_e T_e + \alpha_W(1-\vartheta)T_e T_e^\star - \kappa T_e^\star = 0 \tag{3.27}$$

$$\omega\kappa T_e^\star - cV_e = 0 \tag{3.28}$$

From equation (3.28) we have

$$V_e = \frac{\omega\kappa T_e^\star}{c} \tag{3.29}$$

Substituting equation (3.29) in equation (3.27) we get

$$T_e \;\; = \;\; \frac{1}{(1-\rho)\frac{\beta\omega}{c} + (1-\vartheta)\frac{\alpha_W}{\kappa}} \tag{3.30}$$

Using equation (3.15) equation (3.30) becomes

$$T_e = \frac{T_{max}(1 - \frac{\mu_W}{r})}{R_{0W}} \tag{3.31}$$

Substituting V_e and T_e in equation (3.26) we obtain

$$T_e^\star = \frac{T_{max}(1-\frac{\mu_W}{r})(R_{0W}-1)(r-\mu_W)}{\kappa R_{0W}^2} \tag{3.32}$$

The endemic equilibrium (EE) is given as

$$EE = (\frac{T_{max}(1-\frac{\mu_W}{r})}{R_{0W}}, \frac{T_e(R_{0W}-1)(r-\mu_W)}{\kappa R_{0W}}, \frac{\omega\kappa T_e^\star}{c}) \tag{3.33}$$

Clearly $T_e^\star > 0$ if and only if $R_{0W} > 1$ □

3.5.2 Local Stability Analysis of the Endemic Equilibrium

Theorem 3.5.2. *The endemic equilibrium $EE = (T_e, T_e^\star, V_e)$ is locally asymptotically stable whenever $R_{0W} > 1$*

Proof. The local stability of model (3.1) can be analysed using the eigen values of the Jacobian matrix of model (3.1) at EE

$$J(EE) = \begin{pmatrix} \frac{(r-2)(r-\mu_W)}{rR_{0W}} & \frac{-\alpha_W(1-\vartheta)T_{max}(1-\frac{\mu_W}{r})}{R_{0W}} & \frac{-\beta(1-\rho)T_{max}(1-\frac{\mu_W}{r})}{R_{0W}} \\ \frac{(R_{0W}-1)(r-\mu_W)}{R_{0W}} & \frac{\alpha_W(1-\vartheta)T_{max}(1-\frac{\mu_W}{r})}{R_{0W}} - \kappa & \frac{(1-\rho)\beta T_{max}(1-\frac{\mu_W}{r})}{R_{0W}} \\ 0 & \omega\kappa & -c \end{pmatrix} \tag{3.34}$$

from equation (3.34) we obtain the characteristic equation in the form

$$\lambda^3 + a_0\lambda^2 + a_1\lambda + a_2 = 0 \tag{3.35}$$

where

$$a_0 = \kappa + c - \frac{\alpha_W(1-\vartheta)T_{max}(1-\frac{\mu_W}{r})}{R_{0W}} - \frac{(r-2)(r-\mu_W)}{rR_{0W}}$$

$$\begin{aligned} a_1 &= (\frac{(1-\vartheta)T_{max}(1-\frac{\mu_W}{r})}{R_{0W}})(\frac{(r-2)(r-\mu_W)}{rR_{0W}} + \frac{(R_{0W}-1)(r-\mu_W)}{R_{0W}}) \\ &+ (\frac{(r-2)(r-\mu_W)}{rR_0})(c-\kappa) + c\kappa - 1 \end{aligned}$$

$$a_2 = \frac{(R_{0W}-1)(r-\mu_W)}{R_{0W}} + \frac{(r-2)(r-\mu_W)}{rR_{0W}}(1-c\kappa)$$

The number of possible negative real roots of equation (3.35) depends on the signs of a_0, a_1 and a_2. This can be established by applying Descartes Rule of Signs as used in [36].

$$P(\lambda) = a_1\lambda^2 + a_2\lambda + a_3 \tag{3.36}$$

According to this rule the number of negative real zeros of $P(\lambda)$ is either equal to the number of sign changes of $P(-\lambda)$ or less by an even number, as shown in (3.1).

Table 3.1: Roots of characteristic equation (3.36)

cases	a_0	a_1	a_2	$R_{0W} > 1$	no. of sign changes	no. of real -ve roots
1	-	+	-	$R_{0W} > 1$	2	2,0
2	-	-	-	$R_{0W} > 1$	0	0
3	+	+	-	$R_{0W} > 1$	1	0
4	+	-	-	$R_{0W} > 1$	1	0
5	-	+	+	$R_{0W} > 1$	1	0
6	-	-	+	$R_{0W} > 1$	1	0
7	+	+	+	$R_{0W} > 1$	0	0
8	+	-	+	$R_{0W} > 1$	2	2,0

From Table (3.1) the maximum number of sign changes in $P(-\lambda)$ is 2, hence the characteristic polynomial (3.36) has two negative roots. Thus

$$P(-\lambda) = -\lambda^3 + a_0\lambda^2 - a_1\lambda + a_2 = 0 \tag{3.37}$$

has negative real roots. Hence for $r > \mu_W$ and if cases 1 to 8 are satisfied then the endemic equilibrium EE is locally asymptotically stable. □

Therefore if $R_{0W} > 1$ and given a small number of free virus particles, each virus, in the entire period of its infectivity, will produce on average more than one infected cell, implying viral persistence.

3.5.3 Global Stability Analysis of the Endemic Equilibrium

In this section the global stability of the endemic equilibrium using geometric approach, as developed by [18] is investigated. Consider the autonomous dynamical system

$$y' = f(x) \tag{3.38}$$

where $f : \Omega \longrightarrow \mathbb{R}^n$, $\Omega \subset \mathbb{R}^n$ is an open set and is simply connected and $y \in \Omega$, $y \mapsto f(x) \in \mathbb{R}^n$, $f(x) \in C'(\Omega)$. Let $y^\star$ be an equilibrium point, then $y^\star$ is said to be globally stable in Ω if it is locally stable in Ω and that all trajectories in Ω, converge to $y^\star$. In this method the equilibrium $y^\star$ is locally asymptotically stable provided the following conditions hold;

- (H1) Ω is simply connected
- (H2) There exist a compact absorbing set $K \subset \Omega$
- (H3) Equation (3.38) has a unique equilibrium $y^\star$ in Ω

Let $P(y)$ be a $\binom{n}{2} \times \binom{n}{2}$ matrix-valued function that is C' on Ω and consider

$B = P_f P^{-1} + P\frac{\partial f^2}{\partial y}P^{-1}$ where the matrix P_f is $\frac{\partial P^\star_{ij}}{\partial y} f = \frac{dP_{ij}}{dt}$ and let the matrix $J^{(2)}$ be

the second additive compound matrix of the Jacobian matrix J, that is, $J_{(y)}=(J_{ij})$, $J^{(2)}$ is a $\binom{n}{2} \times \binom{n}{2}$ matrix and in our case n=3 hence

$$J^{(2)}=\begin{pmatrix} J_{11}+J_{22} & J_{23} & -J_{13} \\ J_{32} & J_{11}+J_{33} & J_{12} \\ -J_{31} & J_{21} & J_{22}+J_{33} \end{pmatrix}$$

Consider the Lonziskii measure μ of B with respect to a vector norm $|\cdot|$ in $\mathbb{R}^N$ where $N = \binom{n}{2}$

$$\mu(B) = \lim_{t\to 0^+} \frac{\| I + hB \| -1}{h} \tag{3.39}$$

where $\|\cdot\|$ is a matrix norm defined by $\| A \| = \sup_{x<1} | Ax |$. It is proved in [18] that if (H1), (H2) and (H3) hold and condition

$$\bar{q} = \limsup_{t\to\infty} \sup_{y_0\in K} \frac{1}{t} \int_0^t \mu_W(B(x(s,x_0)))ds < 0 \tag{3.40}$$

is satisfied, then the unique equilibrium $y^\star$ is globally asymptotically stable

Theorem 3.5.3. *The endemic equilibrium EE is globally asymptotically stable in* Ω *if* $R_{0W} > 1$

Proof. Consider the Jacobian of model (3.1)

$$J = \begin{pmatrix} r - \frac{2rT}{T_{max}} - (1-\rho)\beta V - (1-\vartheta)\alpha_W T^\star - \mu_W & -(1-\vartheta)\alpha_W T & -(1-\rho)\beta T \\ (1-\rho)\beta V + (1-\vartheta)\alpha_W T^\star & (1-\vartheta)\alpha_W T - \kappa & (1-\rho)\beta T \\ 0 & \omega\kappa & -c \end{pmatrix} \tag{3.41}$$

the second compound additive matrix of (3.41) is given as

$$J^{(2)} = \begin{pmatrix} a+b-\kappa & d & d \\ \omega\kappa & a-c & -b \\ 0 & e & b-\kappa-c \end{pmatrix} \tag{3.42}$$

where

$$\begin{aligned} a &= r - \frac{2rT}{T_{max}} - (1-\rho)\beta V - \alpha_W(1-\vartheta)T^\star - \mu_W \\ b &= \alpha_W T(1-\vartheta) \\ d &= (1-\rho)\beta T \\ e &= (1-\rho)\beta V + \alpha_W T^\star(1-\vartheta) \end{aligned}$$

We define an auxiliary matrix function Q on Ω as

$$Q = diag\left(\frac{1}{T^\star}, \frac{1}{V}, \frac{1}{V}\right) \tag{3.43}$$

setting $T^\star, V > 0$ everywhere in Ω, Q is smooth and nonsingular. Q_f and $Q_f Q^{-1}$ are given as

$$Q_f = diag\left(-\frac{\dot{T^\star}}{(T^\star)^2}, -\frac{\dot{V}}{V^2}, -\frac{\dot{V}}{V^2}\right) \tag{3.44}$$

$$Q_f Q^{-1} = diag\left(-\frac{\dot{T^\star}}{T^\star}, -\frac{\dot{V}}{V}, -\frac{\dot{V}}{V}\right) \tag{3.45}$$

where $\dot{T^\star} = \frac{dT^\star}{dt}$ and $\dot{V} = \frac{dV}{dt}$. Matrix $QJ^{(2)}Q^{-1}$ is given as

$$QJ^{(2)}Q^{-1} = \begin{pmatrix} a+b-\kappa & \frac{dV}{T^\star} & \frac{dV}{T^\star} \\ \frac{\omega\kappa T^\star}{V} & a-c & -b \\ 0 & e & b-\kappa-c \end{pmatrix} \tag{3.46}$$

Thus the matrix $M = Q_f Q^{-1} + QJ^{(2)}Q^{-1}$ as defined in equation (4.4) of [18] can be written in block form as:

$$M = \begin{pmatrix} m_{11} & m_{12} \\ m_{21} & m_{22} \end{pmatrix} \tag{3.47}$$

Where

$$m_{11} = a + b - \kappa - \frac{\dot{T}\star}{T^\star}$$

$$m_{12} = \frac{dV}{T^\star}, \frac{dV}{T^\star}$$

$$m_{21} = \begin{pmatrix} \frac{\omega\kappa T^\star}{V} \\ \\ 0 \end{pmatrix}$$

and

$$m_{22} = \begin{pmatrix} a - c - \frac{\dot{V}}{V} & -b \\ \\ e & b - c - \kappa - \frac{\dot{V}}{V} \end{pmatrix}$$

Let the vector norm $|\cdot|$ in $\mathbb{R}^3 \cong \mathbb{R}\begin{pmatrix} 3 \\ \\ 2 \end{pmatrix}$ be chosen as

$$|(u, v, w)| = \sup\{|u|, |v| + |w|\} \tag{3.48}$$

The Lozinskii measure $\mu(M)$ with respect to $|\cdot|$ can be estimated as follows

$$\mu(M) \leq \sup\{g_1, g_2\} \tag{3.49}$$

where

$$g_1 = \mu_1(m_{11}) + \parallel m_{12} \parallel \tag{3.50}$$

$$g_2 = \mu_1(m_{22}) + \parallel m_{21} \parallel \tag{3.51}$$

$\parallel m_{12} \parallel$ and $\parallel m_{21} \parallel$ are operator norms associated to the linear mappings $m_{12} : \mathbb{R}^2 \to \mathbb{R}$ and $m_{12} : \mathbb{R} \to \mathbb{R}^2$ respectively, where $\mathbb{R}$ is endowed with the ℓ_1 vector norm in both cases. Specifically $\mu_1(m_{11}) = a + b - \kappa - \frac{\dot{T^\star}}{T^\star}$, $\parallel m_{12} \parallel = \frac{dV}{T^\star}$, $\parallel m_{21} \parallel = \sup\{\frac{\omega\kappa T^\star}{V}, 0\}$ and $\mu_1(m_{22}) = -c - \frac{\dot{V}}{V} + \sup\{a + e, -\kappa\}$. From model (3.1) we have

$$\frac{\dot{T^\star}}{T^\star} = (1 - \rho)\beta V T + (1 - \vartheta)\alpha_W T - \kappa \tag{3.52}$$

$$\frac{\dot{V}}{V} = \frac{\omega\kappa T^\star}{V} - c \tag{3.53}$$

and recalling expressions for a, b, d and e we obtain

$$g_1 = r - \frac{2rT}{T_{max}} - (1 - \rho)\beta V - (1 - \vartheta)\alpha_W T^\star - \mu_W \tag{3.54}$$

$$g_2 = \sup\{r - \frac{2rT}{T_{max}} - \mu_W, -\kappa\} \tag{3.55}$$

Since $r - \frac{2rT}{T_{max}} - (1-\rho)\beta V - (1-\vartheta)\alpha_W T^\star - \mu_W \leq \sup\{r - \frac{2rT}{T_{max}} - \mu_W, -\kappa\}$, we have that $g_1 \leq g_2$, and thus equation (3.49) implies that $\mu(M) \leq g_2$, hence

$$\mu(M) \quad \leq \quad r - \frac{2rT}{T_{max}} - \mu_W + \sup\{-(1-\rho)\beta V - (1-\vartheta)\alpha_W T^\star, 0\} \tag{3.56}$$

$$\mu(M) \quad \leq \quad r - \frac{2rT}{T_{max}} - \mu_W \tag{3.57}$$

Since T_{max} is the limiting value of $T(t)$ then this implies that $\limsup_{t\to\infty} T(t) \leq T_{max}$, therefore the expression (3.57) reduces to

$$\mu(M) \leq r - 2r - \mu_W \tag{3.58}$$

Integrating (3.58) we obtain

$$\frac{1}{t}\int_0^t \mu(M)ds \leq \frac{1}{t}\int_0^t (-r - \mu_W)ds < 0 \tag{3.59}$$

using equation (3.40), equation (3.59) means that $\bar{q} < -(r - w)$, hence the endemic equilibrium (EE) is globally asymptotically stable whenever $R_{0W} > 1$. □

This implies that regardless of any starting solution, the solution of the model will converge to EE whenever $R_{0W} > 1$. Immunologically, it means that any perturbation of the equilibrium point as a result of the introduction of the free virus particles,the model solutions will converge to the endemic state.

3.6 Numerical simulations and discussion of the Within Host HIV Infection Model

In this section we illustrate the validity of our analytical results for model (3.1) by carrying out numerical simulations using MATLAB with the parameter values given in Table 3.2. The numerical simulation aims at analyzing the change in state of virus progression with time and also investigate the impact of the variation of treatment efficacy on the transmission dynamics of HIV. This is achieved by varying the parameter values ρ and ϑ while keeping the other parameters constant.

Table 3.2: Parameters values for model (3.1)

Parameters	units	Description	source
T_{max}	1500 cells mm^{-3}	Maximum $CD4+$ cell population level	12
r	0.03 cells day^{-1}	Production rate of uninfected T cells	12
μ_W	0.02 cells day^{-1}	Natural death rate of uninfected T cells	12
κ	0.24 cells day^{-1}	Death rate of actively infected T cells	12
c	2.4 day^{-1}	Shedding rate of virions	12
β	$2.4\times10^{-5}mm^{-3}$	Viral infection rate by free virions	12
α_W	$2.4 \times 10^{-5}mm^{-3}$	cellular infection rate	12
ω	varies: $\omega \geq 0$	Burst rate of actively infected T cells	-
ρ	varies: $0 < \rho < 1$	Efficacy of RT Inhibitor	-
ϑ	varies: $0 < \vartheta < 1$	efficacy of Protease Inhibitor	-

3.6.1 Effect of variations in RTI and PI treatment efficacy on the asymptotic behaviour of the equilibrium points

To investigate the role of ART treatment efficacy on the stability of equilibria, the parameter values in Table (3.2) were used. This was achieved by varying the parameters ρ and ϑ while keeping the other parameters constant. Although each class of ARV (RTI and PI) drug attacks HIV in a different way, in practice drugs from two (or sometime three) classes are combined to ensure a combined attack on HIV. Clinically doctors recommend a

combination or cocktail of at least two of them, an approach called antiretroviral therapy. For purposes of illustrating the efficacy of RTI and PI treatment our choice of values of ρ and ϑ will be uniformly done, based on this premise. Consequently we shall consider three scenarios; when efficacy is relatively low (0.1), moderate (0.5) and relatively high (0.9). Further with appropriate set of initial conditions listed below

- I_1: $T_1(t) = 1000$, $T_1^\star(t) = 0$, $V_1(t) = 10^{-3}$
- I_2: $T_2(t) = 800$, $T_2^\star(t) = 10$, $V_2(t) = 0.001$
- I_3: $T_3(t) = 900$, $T_3^\star(t) = 5$, $V_3(t) = 0.01$
- I_4: $T_4(t) = 1000$, $T_4^\star(t) = 1$, $V_4(t) = 0.1$

and based on Theorems (3.4.2) and (3.5.3), the corresponding stabilities of model (3.1) are;

- If $R_{0W} < 1$, the IFE is globally asymptotically stable.
- If $R_{0W} > 1$, the EE is globally asymptotically stable.

The following results were obtained

Scenario 1 : Setting $\rho = 0.1$ and $\vartheta = 0.1$, yields $R_{0W} = 4.545 > 1$, and by Theorem (3.5.3), the endemic equilibrium is globally asymptotically stable and the system converges to $EE = (110.011, 3.575, 357.53)$, for all initial conditions I_1 to I_4. This imply that the virus persists in the host and that the low treatment efficacy of 0.1 cannot effectively combat the virus. This is illustrated by Figures (3.2), (3.3) and (3.4).

Scenario 2 When $\rho = 0.5$ and $\vartheta = 0.5$, the value of R_{0W} is given as $R_{0W} = 2.525$, which is greater than one, and the system approaches $EE = (198.02, 4.98, 498.31)$ in accordance to Theorem (3.59). This shows that even with improved drug efficacy the virus will continue persisting in the host but with low virulence. The Figures (3.2), (3.3) and (3.4) clearly illustrates this scenario.

Scenario 3 The high treatment efficacy of $\rho = 0.9$ and $\vartheta = 0.9$ gives rise to $R_{0W} = 0.101 < 1$, in line with Theorem (3.4.2), in which the infection free steady state is GAS for all initial conditions I_1 to I_4. This is illustrated by Figures (3.2), (3.3) and (3.4.)
This clearly indicates that high efficacy levels for both forms of ART (RTI and PI) is crucial in fighting both viral and cellular infection of HIV within a given human host.

3.6.2 Impact of variations of parameters ρ and ϑ on the $CD4^+T$ cell count (T), number of infected cells ($T^\star$) and viral load (V)

From Figure (3.2), (3.3) and (3.4.) it can be deduced that the level of ART treatment efficacy has an impact on $CD4^+T$ cell count, the infected population as well as viral load. As can be observed from figure (3.2)(a) the $CD4^+T$ cell count undergoes a sharp decline as a result of low treatment efficacy of 0.1, for both RTI and PI. When ART treatment efficacy level increase to 0.5, the decline is moderate and takes a shorter time (40 days) to reduce to a minimum of approximately zero. The situation is however reversed when the efficacy level is high, that is 0.9, the immunity is boosted and therefore decline is mild and stabilized at approximately $700mm^{-3}$ as can be observed from Figure (3.2)(a). This is a clear indication that the CD4 T cell count is directly proportional to the efficacy of ART treatment.

Figures (3.2)(b) and (3.2)(c) depicts how ART treatment efficacy affects the number of infected cells and viral load respectively. It can be seen that with an efficacy level of 0.1, the number of infected cells rises to a pick of 519 infected cells, within a short period of time (17 days), and virions attain a maximum of 5.074×10^4 over the same period of time. However when the PI and RTI efficacy levels are high that is above 0.85, both infected cells and virus population experience remarkable decline to almost undetectable levels within the first 90 days. This clearly shows that viral replication and cellular infection within host can effectively be reduced by high efficacy of combined ART treatment.

Figures (3.2)(b) and (3.2)(c), illustrate the effect of treatment efficacy on the number

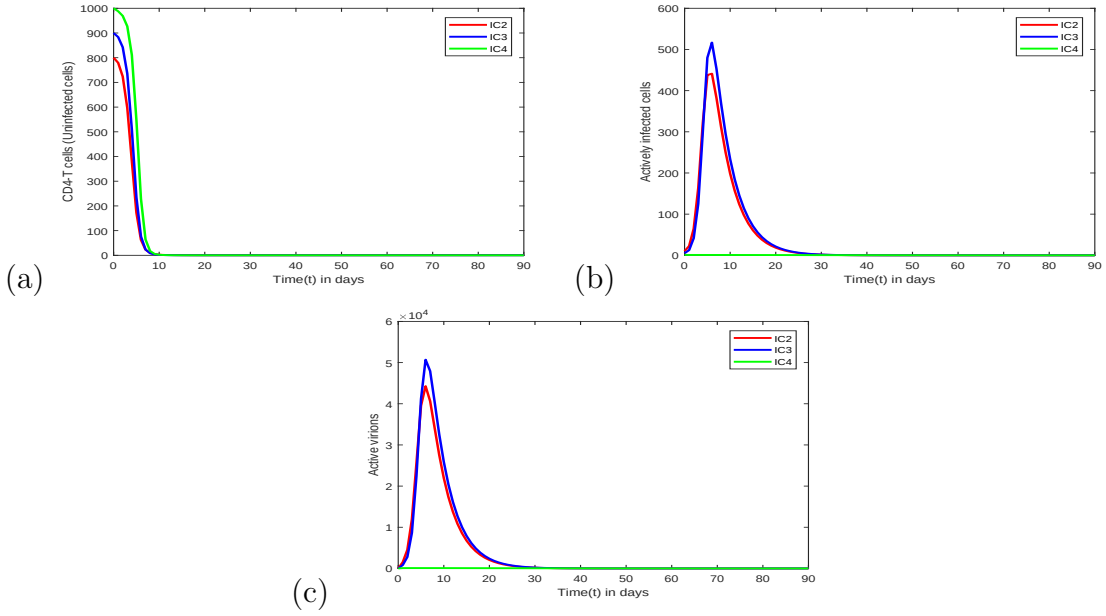

Figure 3.2: (a)-(c): The graph trajectory of $T(t)$,$T^{\star}(t)$ and $V(t)$ for $\rho = 0.1$ and $\vartheta = 0.1$ with the initial conditions IC2-IC4. $R_{0W} = 4.545$ and $EE = (110.011, 3.575, 357.53)$ is GAS.

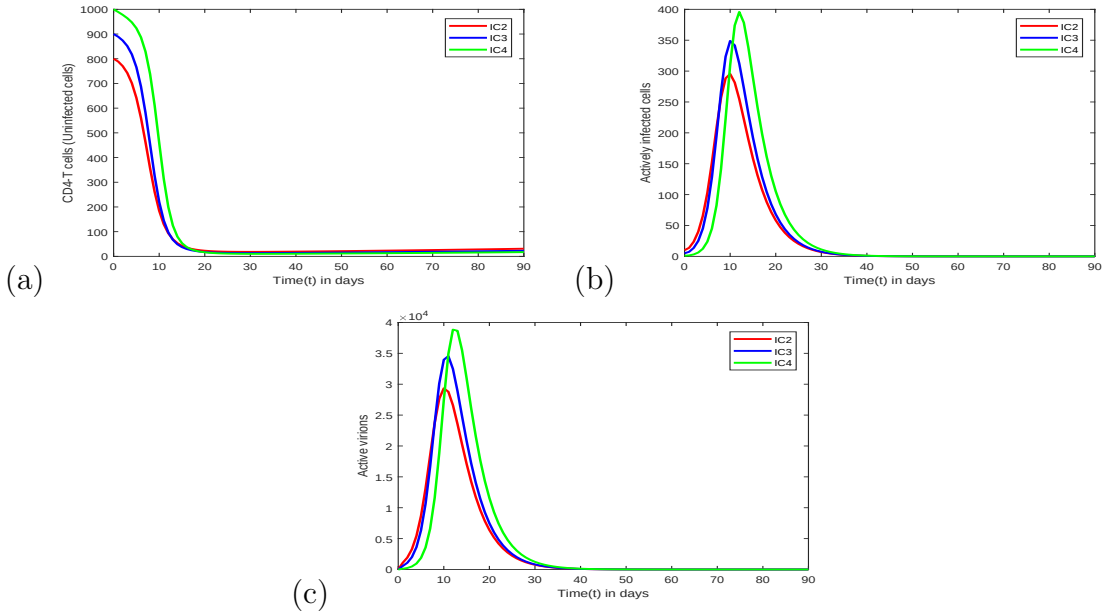

Figure 3.3: (a)-(c): The graph trajectory of $T(t)$,$T^{\star}(t)$ and $V(t)$ for $\rho = 0.15$ and $\vartheta = 0.5$ with the initial conditions IC2-IC4. $R_{0W} = 2.525 > 1$ and $EE = (198.02, 4.98, 498.31)$ is GAS

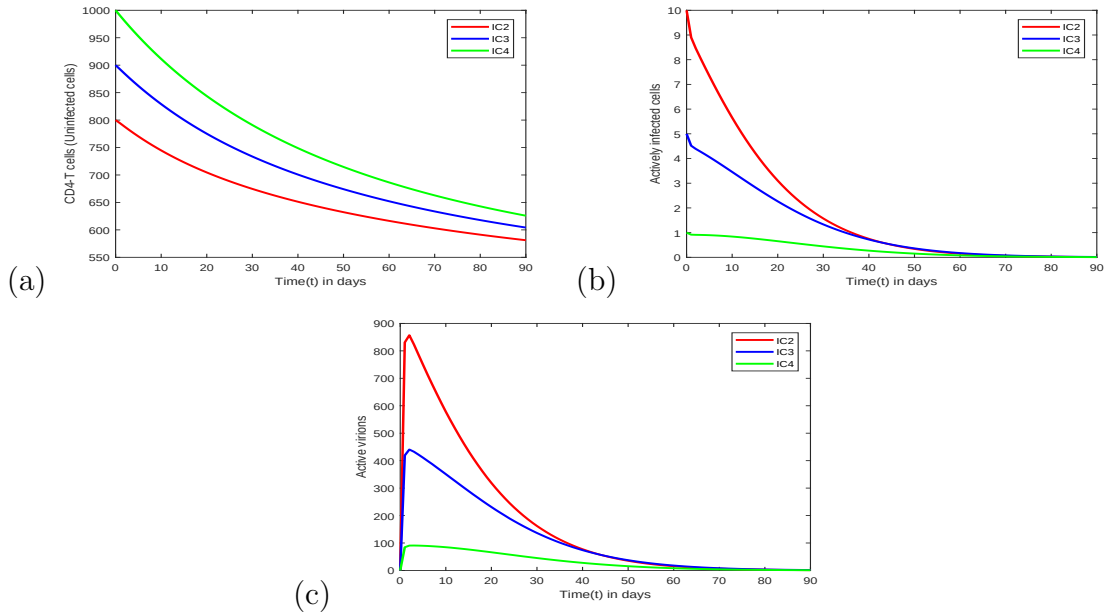

Figure 3.4: (a)-(c): The graph trajectory of $T(t)$,$T^{\star}(t)$ and $V(t)$ for $\rho = 0.9$ and $\vartheta = 0.9$ with the initial conditions IC2-IC4. $R_{0W} = 0.101 < 1$ and $E_0 = (1500, 0, 0)$ is globally asymptotically stable.

of actively infected cells and free virions respectively. It is clear that from the time of infection if treatment efficacy is kept at a minimum of 0.1, then both actively infected cells and free virions replicates rapidly attaining a primary peak of 519 infected cells within the first 17 days, while the virions reach a peak of 5.074×10^4 within the same period of time. With an increase in treatment efficacy both infected cells and viral replication rates are significantly reduced, for instance at 0.9 efficacy level the number of virus and infected cells approach zero within the first 90 days.

3.7 Conclusion

In this chapter, a mathematical model describing a within host HIV infection with viral and cellular infection incorporating treatment was formulated and analysed . The replenishment rate of $CD4^{+}T$ cells was represented by a logistic growth rate. The qualitative analysis of model (3.1) shows that the in-vivo HIV infection dynamics can best be described by the threshold value R_{0W}, in which for the value of $R_{0W} < 1$ the infection free equilibrium is globally asymptotically stable. This is theoretically interpreted to mean that HIV is cleared from the body, however in reality HIV is not completely eliminated but can be suppressed to undetectable levels. On the other hand when $R_{0W} > 1$, the endemic equilibrium is globally asymptotically stable. This scenario imply viral persistence. Furthermore the global asymptotic stability of IFE and EE were proved using the method by [7] and the geometric approach [18] respectively. With parameter values in table (3.2), numerical simulations were performed and the results graphically represented. The numerical results validated the theoretical results and further showed that treatment efficacy of combined ART leads to reduced viral replication and eventually low number of infected cells, this in turn leads to increased CD4 count. This observation is in agreement with the findings of [27] which showed that if $R_{0W} > 1$ before treatment then the virus will increase as would be the number of infected cells, but after treatment if $R_{0W} < 1$, then $T^{\star}$ and V would both decline.

CHAPTER FOUR

DYNAMICS OF THE BETWEEN HOST HIV TRANSMISSION MODEL WITH SATURATED INCIDENCE RATE AND TREATMENT EFFICACY

4.1 Introduction

In this chapter between-host mathematical model for HIV/AIDS transmission is developed and analysed. Under the SIA framework, the model takes into account the saturated incidence rate and treatment efficacy. This chapter is organised as follows; secction 4.2 deals with model description and formulation. In section 4.3 positivity and boundedness of solutions is determined, while the basic reproduction number is determined using the next generation matrix in section 4.4. Section 4.5 deals with the use of numerical simulations to validate the theoretical results obtained in section 4.4, in addition the effect of antiretroviral treatment on the number of infected individuals in the population is discussed. Finally the chapter is concluded in section 4.6.

4.2 Model Description and Formulation

A between host epidemiological model for HIV spread in the human population is formulated, in which it is compartmentalized as susceptible ($S(t)$), asymptomatically infected ($I(t)$), and symptomatically infected ($A(t)$), with a natural death rate of μ_B in all the compartments and t is the chronological time. It is assumed that the susceptibles are recruited into the population with approximately the same equilibrium level of healthy $CD4^{+}TCells$ at a constant rate Λ and become infected via sexual contact with infected individuals at the rate π. Depending on the viral count, the infected individuals join the AIDS class at a rate $\phi\sigma I$ and die at a rate δ. In this model we have introduced a saturated incidence rate $\frac{\pi SI}{1+\alpha I}$ as opposed to a bilinear incidence rate βSI which assumes

that contact rate is proportional to the size of the total population. The saturated incidence is reasonable due to the fact that as the infected individuals increase they reach a saturation point and hence may not exceed the carrying capacity. Due to psychological effect or inhibition effects from the behavioral changes of infected individuals or protective measures from susceptible individuals the number of infected individuals decreases as the susceptibles increase. It is therefore reasonable to consider a saturated incidence rate in order to prevent the unboundedness of the contact rate [5]. Bilinear incidence rates do not admit bi-stability or periodicity, as they have at most one endemic equilibrium, i.e, the disease will be eradicated if the basic reproductive number is less than one and will persist if otherwise, hence do not provide sufficient details of complexity in the population behavior [1]. Also considering the infected individuals as predators of the susceptible population, the incidence term will reflect a saturation effect of the infectives' infectious rate. This implies that infection is approximately a linear function of the susceptible population size for a small population size, but the transmission rate approaches a constant when the susceptible population size is large since the infected do not infect more and more susceptibles as the susceptible population increases [13]. From the foregoing the dynamics of between host transmission can be described by the system of ODEs, as shown below;

$$\begin{aligned} \frac{dS}{dt} &= \Lambda - \frac{\pi SI}{1+\alpha_B I} - \mu_B S \\ \frac{dI}{dt} &= \frac{\pi SI}{1+\alpha_B I} - (1-\phi)\sigma I - \mu_B I \\ \frac{dA}{dt} &= (1-\phi)\sigma I - \delta A - \mu_B A \end{aligned} \tag{4.1}$$

The initial conditions for (4.1) are ;

$$S(0) = S_0 > 0, I(0) = I_0 > 0, A(0) = A_0 \geq 0 \tag{4.2}$$

$N(t) = S(t) + I(t) + A(t)$

The descriptions of all parameters considered in model formulation are summarized in Table 4.1.

4.3 Positivity and boundedness

Since the model under consideration involves human population, it is henceforth assumed that all the associated model variables and parameters are non-negative. This result can be summarised in the following lemmas:

Lemma 4.3.1. *For all time $t \geq 0$, all solutions of the system (4.1) are eventually confined in the compact subset $\Omega = \{(S, I, A) \in \mathbb{R}^3_+ : N^+ = (S(t) + I(t) + A(t)) \leq \frac{\Lambda}{\mu_B}\}$; i.e the closed set Ω is positively invariant for the system (4.1)*

Proof. We show that the positive invariance of Ω, i.e all solutions of (4.1) which start in Ω remain in the region Ω. The rate of change of the population N, is calculated by adding the equations considered in the system (4.1), to obtain

$$\frac{dN^+}{dt} = \Lambda - \mu_B N - \delta A \tag{4.3}$$

It follows that whenever $N > \frac{\Lambda}{\mu_B}$, then $\frac{dN}{dt} < 0$ since $\frac{dN}{dt}$ is bounded by $\Lambda - \mu_B N$, therefore the standard comparison theorem [**?**] can be used to show that $N \leq \frac{\Lambda}{\mu_B}(1 - e^{-\mu_B t}) + N_0 e^{-\mu_B t}$ for $t \to \infty$, we have $\limsup_{t\to\infty} N \leq \frac{\Lambda}{\mu_B}$. In particular, $N(t) < \frac{\Lambda}{\mu_B}$ if $N(0) < \frac{\Lambda}{\mu_B}$. The feasible region for system (4.1) is thus

$$\Omega = (S, I, A) \mid S + I + A \leq \frac{\Lambda}{\mu_B}, S > 0, I \geq 0, A \geq 0 \tag{4.4}$$

Clearly it has been proved that all solutions of system (4.1) which start in $\mathbb{R}^3_+$ remain in the region Ω □

.

Lemma 4.3.2. *Let $\Omega = \{(S, I, A) \in \mathbb{R}^3_+ : (S_0 > 0, I_0 \geq 0, A_0 \geq 0)\}$ then the solutions $S(t), I(t), A(t)$ of system (4.1) are positive for $t \geq 0$*

Proof. From the first equation in system (4.1), that is $\frac{dS}{dt} = \Lambda - \frac{\pi SI}{1+\alpha_B I} - \mu_B S$, we have

$$\frac{dS}{dt} = \Lambda - \frac{\pi SI}{1 + \alpha_B I} - \mu_B S \geq -(\frac{\pi I}{1 + \alpha_B I} + \mu_B)S \tag{4.5}$$

Integrating (4.5) yields

$$S(t) \geq S_0 e^{-(\frac{\pi I}{1+\alpha_B I}+\mu)t} \geq 0 \tag{4.6}$$

since $\frac{\pi I}{1+\alpha_B I} + \mu_B > 0$ □

Applying the same procedure, we can show that the remaining variables are also positive $\forall t \geq 0$. Hence Ω is positively invariant and attracting. System (4.1) is therefore considered epidemiologically and mathematically well posed in the region Ω therefore it is sufficient to consider solutions in Ω.

4.4 Basic Reproduction Number

The basic reproduction number of an infection R_{0B} is defined as the expected number of new infections caused by each infected host per unit density of susceptible hosts. We obtain the basic reproduction number for system (4.1) using the next generation matrix method as used in [7] as follows, we define

$$\mathcal{F} = \begin{pmatrix} \frac{\pi SI}{1+\alpha_B I} \\ \\ 0 \end{pmatrix} \tag{4.7}$$

and

$$\mathcal{V} = \begin{pmatrix} (1-\phi)\sigma I + \mu_B I \\ \\ -(1-\phi)\sigma I + \delta A + \mu_B A \end{pmatrix} \tag{4.8}$$

The Jacobian of $\mathcal{F}$ and $\mathcal{V}$ evaluated at the DFE $E_0 = (\frac{\Lambda}{\mu_B}, 0, 0)$ yields

$$F = \begin{pmatrix} \frac{\pi\Lambda}{\mu_B} & 0 \\ \\ 0 & 0 \end{pmatrix} \tag{4.9}$$

and

$$V = \begin{pmatrix} (1-\phi)\sigma + \mu_B & 0 \\ \\ -(1-\phi)\sigma & \delta + \mu_B \end{pmatrix} \tag{4.10}$$

so that the next generation matrix is given as

$$FV^{-1} = \begin{pmatrix} \frac{\pi\Lambda}{\mu_B((1-\phi)\sigma+\mu_B)} & 0 \\ \\ 0 & 0 \end{pmatrix} \tag{4.11}$$

The basic reproduction number R_{0B} is defined as the spectral radius of FV^{-1} hence

$$R_{0B} = \frac{\pi\Lambda}{\mu_B((1-\phi)\sigma + \mu_B)} \tag{4.12}$$

4.4.1 Local Stability Analysis of the Disease Free Equilibrium (DFE)

The system (4.1) always has a disease free equilibrium $E_0 = (\frac{\Lambda}{\mu_B}, 0, 0)$. We examine the local stability of the disease free equilibrium (DFE) by analyzing the eigenvalues of the Jacobian matrix of system (4.1) at the DFE.

Theorem 4.4.1. *The disease free equilibrium E_0 is locally asymptotically stable when $R_{0B} < 1$ and unstable when $R_{0B} > 1$*

Proof. The Jacobian matrix of system (4.1) is as follows

$$J = \begin{pmatrix} \frac{-\pi I}{1+\alpha_B I} - \mu_B & \frac{-\pi S}{(1+\alpha_B I)^2} & 0 \\ \frac{\pi I}{(1+\alpha_B I)} & \frac{\pi S}{(1+\alpha_B I)^2} - (1-\phi)\sigma - \mu_B & 0 \\ 0 & (1-\phi)\sigma & -(\delta + \mu_B) \end{pmatrix} \tag{4.13}$$

and the jacobian matrix at E_0 is given by

$$J(E_0) = \begin{pmatrix} -\mu_B & \frac{-\pi\Lambda}{\mu_B} & 0 \\ 0 & \frac{\pi\Lambda}{\mu_B} - (1-\phi)\sigma - \mu_B & 0 \\ 0 & (1-\phi)\sigma & -(\delta + \mu_B) \end{pmatrix} \tag{4.14}$$

The corresponding characteristic equation is given as

$$\begin{vmatrix} -\mu_B & \frac{-\pi\Lambda}{\mu_B} & 0 \\ 0 & R_0 - 1 & 0 \\ 0 & (1-\phi)\sigma & -(\delta + \mu_B) \end{vmatrix} = 0 \tag{4.15}$$

clearly $\lambda_1 = -\mu_B$, $\lambda_2 = R_{0B} - 1$ and $\lambda_3 = -(\delta + \mu_B)$ are eigenvalues of (4.15). Thus the DFE is locally asymptotically stable if and only if $R_{0B} < 1$, otherwise the DFE is unstable. □

4.4.2 Global stability Analysis of Disease Free Equilibrium (DFE)

Our aim in this section is to establish the global stability of the disease free equilibrium of the between host infection model by employing the direct Lyapunov method and LaSalle invariance principle.

Theorem 4.4.2. *If $R_{0B} < 1$ then the DFE (E_0) is globally asymptotically stable and if $R_{0B} > 1$ then the DFE is unstable*

Proof. From the first equation of system (4.1) we have $\frac{ds}{dt} \leq \Lambda - \mu_B S$. A solution of the equation $\frac{dx}{dt} = \Lambda - \mu_B x$ is a maximal solution of $S(t)$. We note that $x \to \frac{\Lambda}{\mu_B}$ as $t \to \infty$, by comparison theorem, we see that $S(t) \leq \frac{\Lambda}{\mu_B}$, and from the set $\Omega = \{(S, I, A) \mid S + I + A \leq \frac{\Lambda}{\mu_B}, S > 0, I \geq 0, A \geq 0\}$ we have $I(t) \leq \frac{\Lambda}{\mu_B}$ Consider the following Lyapunov functional

$$U = (1-\phi)\sigma I + (\delta + \mu_B)A \tag{4.16}$$

evaluating $\dot{U}$ along the trajectories of system (4.1) we have

$$\begin{aligned}
\dot{U} &= (1-\phi)\sigma\dot{I} + (\delta+\mu_B)\dot{A} \\
&= (1-\phi)\sigma[\frac{\pi SI}{1+\alpha_B I} - (1-\phi)\sigma I - \mu_B I] + (\delta+\mu_B)((1-\phi)\sigma I - \delta A - \mu_B A) \\
&= ((1-\phi)\sigma I)[(\frac{\pi\Lambda}{\mu_B(1+\alpha_B I)((1-\phi)\sigma+\mu_B)} - 1) + (\delta+\mu_B)] - (\delta+\mu_B)^2 A \\
&\leq ((1-\phi)\sigma I)[(\frac{R_0}{1+\alpha_B I} - 1) + (\delta+\mu_B)] - (\delta+\mu_B)^2 A \leq 0
\end{aligned} \tag{4.17}$$

From (4.17) it is clear that $\dot{U} = 0$ if and only if $I = A = 0$, also $\dot{U} < 0$ if and only if $R_{0B} < 1$. Thus the largest compact invariant sets in $\{(S, I, A) \in \Omega, \dot{U} = 0\}$ are I_0 and A_0. Therefore by LaSalle -Lyapunov theorem, every solution that starts in Ω approaches (I_0, A_0) as $t \to \infty$, and the global stability of E_0 follows from the LaSalle invariance principle [19]. □

4.4.3 Existence of Endemic Equilibrium (EE)

We determine the endemic equilibrium (EE) for system (4.1)

Theorem 4.4.3. *A positive endemic equilibrium EE exists whenever* $I^\star > 0$

Proof. An endemic equilibrium $EE = (S^\star, I^\star, A^\star)$ always satisfies

$$\Lambda - \frac{\pi S^\star I^\star}{(1 + \alpha_B I^\star)} - \mu_B S^\star = 0 \tag{4.18}$$

$$\frac{\pi S^\star I^\star}{(1 + \alpha_B I^\star)} - (1 - \phi)\sigma I^\star - \mu_B I^\star = 0 \tag{4.19}$$

$$(1 - \phi)\sigma I^\star - (\delta + \mu_B)A^\star = 0 \tag{4.20}$$

From equation (4.18) we have

$$S^\star = \frac{\Lambda(1 + \alpha_B I^\star)}{\pi I^\star + \mu_B(1 + \alpha_B I^\star)} \tag{4.21}$$

substituting for $S^\star$ in equation (4.19) we have

$$\frac{\pi I^\star \Lambda}{\pi I^\star + \mu_B(1 + \alpha_B I^\star)} - ((1 - \phi)\sigma + \mu_B)I^\star = 0 \tag{4.22}$$

which reduces to

$$I^\star = \frac{(R_{0B} - 1)\mu_B}{\pi + \mu_B \alpha_B} \tag{4.23}$$

and the endemic equilibrium is given as

$$EE = (S^\star, I^\star, A^\star) = \left(\frac{\Lambda(\pi + \alpha_B \mu_B R_0)}{\mu_B R_{0B}(\pi + \alpha_B \mu_B)}, \frac{(R_{0B} - 1)\mu_B}{\pi + \alpha_B \mu_B}, \frac{(1 - \phi)\sigma \mu_B (R_{0B} - 1)}{(\pi + \alpha_B \mu_B)(\delta + \mu_B)}\right) \tag{4.24}$$

it is clear from equation (4.23) that $I^\star > 0$ if and only if $R_{0B} > 1$, hence there exists an endemic equilibrium for system (4.1) whenever $I^\star > 0$ □

4.4.4 Local Stability Analysis of the Endemic Equilibrium (EE)

Theorem 4.4.4. *When* $R_{0B} > 1$*, the endemic equilibrium* $EE = (S^\star, I^\star, A^\star)$ *is locally asymptotically stable*

Proof. The jacobian of the system (4.1) evaluated at EE is given as

$$J(EE) = \begin{pmatrix} -\frac{\pi\mu_B(R_{0B}-1)}{\pi+\alpha_B\mu_B R_{0B}} - \mu_B & \frac{-\pi\Lambda(\pi+\alpha_B\mu_B)}{\mu_B R_{0B}(\pi+\alpha_B\mu_B R_{0B})} & 0 \\ \frac{\pi\mu_B(R_{0B}-1)}{\pi+\alpha_B\mu_B R_{0B}} & \frac{\pi\Lambda(\pi+\alpha_B\mu_B)}{\mu_B R_{0B}(\pi+\alpha_B\mu_B R_{0B})} - (1-\phi)\sigma - \mu_B & 0 \\ 0 & (1-\phi)\sigma & -(\delta+\mu_B) \end{pmatrix} \quad (4.25)$$

The characteristic equation of the system (4.25) has one of its eigen values given by $\lambda_1 = -\delta - \mu_B < 0$. The remaining eigenvalues can be determined by expressing (4.25) as a 2×2 block matrix M defined by

$$M = \begin{pmatrix} \frac{-\pi\mu_B(R_{0B}-1)}{\pi+\alpha_B\mu_B R_{0B}} - \mu_B & \frac{-\pi\Lambda(\pi+\alpha_B\mu_B)}{\mu_B R_{0B}(\pi+\alpha_B\mu_B R_{0B})} \\ \frac{\pi\mu_B(R_{0B}-1)}{\pi+\alpha_B\mu_B R_{0B}} & \frac{\pi\Lambda(\pi+\alpha_B\mu_B)}{\mu_B R_{0B}(\pi+\alpha_B\mu_B R_{0B})} - (1-\phi)\sigma - \mu_B \end{pmatrix} \quad (4.26)$$

If $R_{0B} > 1$ and $\frac{\pi\mu_B(R_{0B}-1)}{\pi+\alpha_B\mu_B R_{0B}} > \frac{\pi\Lambda(\pi+\alpha_B\mu_B)}{\mu_B R_{0B}(\pi+\alpha_B\mu_B R_{0B})}$, then clearly the trace of M is negative. The determinant of matrix M is given as

$$\begin{aligned} DetM = {} & \frac{\pi^2\mu_B\Lambda(R_{0B}-1)(\pi+\alpha_B\mu_B)}{\mu_B R_{0B}(\pi+\alpha_B\mu_B R_{0B})^2} + \frac{(1-\phi)\sigma\pi\mu_B(R_{0B}-1)}{\pi+\alpha_B\mu_B R_{0B}} + \frac{\pi\mu_B^2(R_{0B}-1)}{\pi+\alpha_B\mu_B R_{0B}} \\ & +(1-\phi)\sigma\mu_B + \mu_B^2 - \frac{(\pi\mu_B)^2(R_{0B}-1)^2(\pi+\alpha_B\mu_B)}{(\pi+\alpha_B\mu_B R_{0B})^2} - \frac{\pi\mu_B^2(R_{0B}-1)(\pi+\alpha_B\mu_B)}{(\pi+\alpha_B\mu_B R_{0B})} \end{aligned} \quad (4.27)$$

From equation (4.27) if $R_{0B} > 1$, then $\frac{\pi^2\mu_B\Lambda(R_{0B}-1)(\pi+\alpha_B\mu_B)}{\mu_B R_{0B}(\pi+\alpha_B\mu_B R_{0B})^2} + \frac{(1-\phi)\sigma\pi\mu_B(R_{0B}-1)}{\pi+\alpha_B\mu_B R_{0B}} + \frac{\pi\mu_B^2(R_{0B}-1)}{\pi+\alpha_B\mu_B R_{0B}}$ $+ (1-\phi)\sigma\mu_B + \mu_B^2 > \frac{(\pi\mu_B)^2(R_{0B}-1)^2(\pi+\alpha_B\mu_B)}{(\pi+\alpha_B\mu_B R_{0B})^2} + \frac{\pi\mu_B^2(R_{0B}-1)(\pi+\alpha_B\mu_B)}{(\pi+\alpha_B\mu_B R_{0B})}$, therefore $DetM > 0$. This implies that Routh-Hurwiz criterion holds. Thus the endemic equilibrium EE of system (4.1) is locally asymptotically stable. □

4.4.5 Global Stability Analysis of the Endemic Equilibrium (EE)

Theorem 4.4.5. *For $R_{0B} > 1$ EE is globally asymptotically stable for system (4.1) in Ω*

Proof. The Jacobian matrix of (4.1) at EE is as follows

$$J(EE) = \begin{pmatrix} \frac{-\pi I^\star}{1+\alpha_B I} - \mu_B & -\frac{\pi S^\star}{(1+\alpha_B I)^2} & 0 \\ \frac{\pi I^\star}{1+\alpha_B I} & \frac{\pi S^\star}{(1+\alpha_B I)^2} - (1-\phi)\sigma - \mu_B & 0 \\ 0 & (1-\phi)\sigma & -(\delta+\mu_B) \end{pmatrix} \quad (4.28)$$

$$J^{(2)} = \begin{pmatrix} \frac{-\pi I^\star}{1+\alpha_B I^\star} + \frac{\pi S^\star}{(1+\alpha_B I^\star)^2} - (1-\phi)\sigma - 2\mu_B & 0 & 0 \\ (1-\phi)\sigma & \frac{-\pi I^\star}{(1+\alpha_B I^\star)} - \delta - 2\mu_B & \frac{-\pi S^\star}{(1+\alpha_B I^\star)^2} \\ 0 & \frac{\pi I^\star}{1+\alpha_B I^\star} & \frac{\pi S^\star}{(1+\alpha_B I^\star)^2} - (1-\phi)\sigma - \delta - 2\mu_B \end{pmatrix} \quad (4.29$$

We define an auxiliary matrix function P on Ω as $P := diag(\frac{1}{S^\star}, \frac{1}{I^\star}, \frac{1}{A^\star})$ and $P^{-1} = (S^\star, I^\star, A^\star)$ where P is smooth and nonsingular, $P_f = diag(\frac{-\dot{S^\star}}{(S^\star)^2}, \frac{-\dot{I^\star}}{(I^\star)^2}, \frac{-\dot{A^\star}}{(A^\star)^2})$ and $P_f P^{-1} = diag(\frac{-\dot{S^\star}}{S^\star}, \frac{-\dot{I^\star}}{I^\star}, \frac{-\dot{A^\star}}{A^\star})$.

Therefore the matrix $B = P_f P^{-1} + P J^{(2)} P^{-1}$ can be written in block form as follows

$$B = \begin{pmatrix} B_{11} & B_{12} \\ B_{21} & B_{22} \end{pmatrix} \quad (4.30)$$

with $B_{11} = C - \frac{\dot{S^\star}}{S^\star}$, $B_{12} = (0,0)$, $B_{21} = (\frac{S^\star}{I^\star}D, 0)^T$, $B_{22} = \begin{pmatrix} E - \dot{I^\star} & \frac{A^\star}{I^\star}F \\ \frac{I^\star}{A^\star}G & H - \frac{\dot{A^\star}}{A^\star} \end{pmatrix}$, where

$C = \frac{\pi S^\star}{(1+\alpha_B I^\star)^2} - \frac{\pi I^\star}{1+\alpha_B I^\star} - 2\mu_B - (1-\phi)\sigma$

$D = (1-\phi)\sigma$

$E = \frac{-\pi I^\star}{(1+\alpha_B I^\star)} - 2\mu_B - \delta$

$F = \frac{-\pi S^\star}{(1+\alpha_B I^\star)^2}$

$G = \frac{\pi I^\star}{1+\alpha_B I}$

$H = \frac{\pi S^\star}{(1+\alpha_B I^\star)^2} - (1-\phi)\sigma - 2\mu_B - \delta$

We choose a vector norm $|\ .\ |$ in $R^3 \cong R \begin{pmatrix} 3 \\ 2 \end{pmatrix}$ as

$$\| (u,v,w) \| = max\{| u |, | v | + | w |\} \quad (4.31)$$

then the Lozinskii measure [9], $\mu(B)$ with respect to $|\ .\ |$ can be estimated as follows

$$\mu(B) \leq \sup\{g_1, g_2\} \quad (4.32)$$

where

$$g_1 = B_{11} + | B_{12} | \quad (4.33)$$

$$g_2 = \mu(B_{22}) + | B_{21} | \quad (4.34)$$

We now obtain $B_{11} = c - \frac{\dot{S^\star}}{S^\star} = \frac{\pi S^\star}{(1+\alpha_B I^\star)^2} - \frac{\pi I^\star}{1+\alpha_B I^\star} - 2\mu_B - (1-\phi)\sigma - \frac{\dot{S^\star}}{S^\star}$ and $\mid B_{12} \mid = 0$,

$g_1 = \frac{\pi S^\star}{(1+\alpha_B I^\star)^2} - \frac{\pi I^\star}{1+\alpha_B I^\star} - 2\mu_B - (1-\phi)\sigma - \frac{\dot{S^\star}}{S^\star}$

and from system (4.1) $\frac{\dot{S^\star}}{S^\star} = \frac{\Lambda}{S^\star} - \frac{\pi I^\star S^\star}{(1+\alpha_B I^\star)S^\star} - \mu_B$.

Thus $g_1 = \frac{\pi S^\star}{(1+\alpha_B I^\star)^2} - \frac{\pi I^\star}{1+\alpha_B I^\star} - \frac{\Lambda}{S^\star} + \frac{\pi I^\star S^\star}{(1+\alpha_B I^\star)S^\star} - (1-\phi)\sigma - \mu_B$.

which reduces to

$$g_1 = \frac{\pi S^\star}{(1+\alpha_B I^\star)^2} - \frac{\Lambda}{S^\star} - (1-\phi)\sigma - \mu_B \tag{4.35}$$

Next we calculate $\mu_1(B_{22})$ by taking the non-diagonal elements of each column of B_{22} in absolute value, and then adding to the corresponding columns of the diagonal elements we get

$$B_{22} = \begin{pmatrix} \frac{I^\star}{A^\star}(\frac{\pi I^\star}{1+\alpha_B I^\star}) - \frac{\pi I^\star}{1+\alpha_B I^\star} - 2\mu_B - \delta - \dot{I^\star} & \frac{A^\star}{I^\star}(\frac{-\pi S^\star}{(1+\alpha_B I^\star)^2}) \\ \frac{I^\star}{A^\star}(\frac{\pi I^\star}{1+\alpha_B I^\star}) & \frac{\pi S^\star}{(1+\alpha_B I^\star)^2} - \frac{A^\star}{I^\star}(\frac{\pi S^\star}{(1+\alpha_B I^\star)^2}) - (1-\phi)\sigma - 2\mu_B - \delta - \frac{\dot{A^\star}}{A^\star} \end{pmatrix} \tag{4.36}$$

Taking the maximum of two diagonal elements of B_{22}; we have

$\mu_1(B_{22}) = max\{\frac{I^\star}{A^\star}(\frac{\pi I^\star}{1+\alpha_B I^\star}) - \frac{\pi I^\star}{1+\alpha_B I^\star} - 2\mu_B - \delta - \dot{I^\star}, \frac{\pi S^\star}{(1+\alpha_B I^\star)^2} - \frac{A^\star}{I^\star}(\frac{\pi S^\star}{(1+\alpha_B I^\star)^2}) - (1-\phi)\sigma - 2\mu_B - \delta - \frac{\dot{A^\star}}{A^\star}\}$

$$= \frac{\pi S^\star}{(1+\alpha_B I^\star)^2} - \frac{A^\star}{I^\star}(\frac{\pi S^\star}{(1+\alpha_B I^\star)^2}) - (1-\phi)\sigma - 2\mu - \delta - \frac{\dot{A^\star}}{A^\star} \tag{4.37}$$

therefore we have

$$g_2 = \mu_1(B_{22}) + \mid B_{21} \mid = \frac{\pi S^\star}{(1+\alpha_B I^\star)^2} - \frac{A^\star}{I^\star}(\frac{\pi S^\star}{(1+\alpha_B I^\star)^2}) - (1-\phi)\sigma - 2\mu_B - \delta - \frac{\dot{A^\star}}{A^\star} + \frac{S^\star}{I^\star} \tag{4.38}$$

Next we obtain

$$\mu(B) \leq \sup\{g_1, g_2\} \leq \{\frac{\pi S^\star}{(1+\alpha_B I^\star)^2} - \frac{\Lambda}{S^\star} - (1-\phi)\sigma - \mu_B, \tag{4.39}$$
$$\frac{\pi S^\star}{(1+\alpha_B I^\star)^2} - \frac{A^\star}{I^\star}(\frac{\pi S^\star}{(1+\alpha_B I^\star)^2}) - (1-\phi)\sigma - \frac{(1-\phi)\sigma I^\star}{A^\star} - \mu_B + \frac{S^\star}{I^\star}\}$$

From system (4.1) $\frac{\dot{I^\star}}{I^\star} = \frac{\pi S^\star}{1+\alpha_B I^\star} - (1-\phi)\sigma - \mu_B$ and

$\frac{\dot{A^\star}}{A^\star} = \frac{(1-\phi)\sigma I^\star}{A^\star} - (\delta + \mu_B)$ Then we have

$$\mu(B) \leq \sup\{g_1, g_2\} \leq \{\frac{\dot{I^\star}}{I^\star} - \frac{\Lambda}{S^\star}, \frac{\dot{I^\star}}{I^\star} - \frac{\dot{A^\star}}{A^\star} - (\delta + \mu_B)\} \leq \frac{\dot{I^\star}}{I^\star} - \frac{\dot{A^\star}}{A^\star} - (\delta + \mu_B) \tag{4.40}$$

Integrating both sides of inequality (4.40) simultaneously we obtain

$$\frac{1}{t}\int_0^t \mu(B)ds \leq \frac{1}{t}\int_0^t (\frac{\dot{I}^\star}{I^\star} - \frac{\dot{A}^\star}{A^\star} - (\delta + \mu_B)ds < 0 \tag{4.41}$$

$$\frac{1}{t}\int_0^t \mu(B)ds \leq \limsup_{t\to\infty} \sup \frac{1}{t} \ln \frac{I^\star}{A^\star} - (\mu + \delta) < 0 \tag{4.42}$$

□

From equation (3.40), inequality (4.42) imply that $\bar{q} \leq -(\mu + \delta) < 0$. Hence, we have shown that the endemic equilibrium EE of system (4.1) is globally asymptotically stable in the region Ω. Epidemiologically this means that, the spread of HIV and AIDS persists in the population.

4.5 Numerical Simulations for the Between Host HIV transmission Model

In order to verify our analytical results, system (4.1) is simulated numerically for various sets of parameter values given in Table (4.1). In addition the simulation is meant to analyse the dynamics of the disease progression with time and investigate the impact of various parameters on the transmission dynamics of HIV/AIDS.

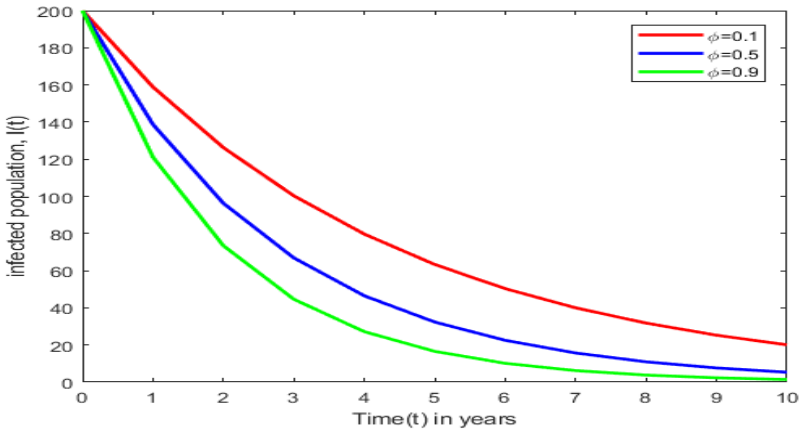

Figure 4.1: effect of ϕ on the population of the Infectives (I) in the first 10 years

Table 4.1: Variables and Parameters used in system (4.1)

Parameters/variable	units	Description	source
dependent variables			
$S(t)$	1000 per year	Susceptible population	estimated
$I(t)$	200 per year	Asymptomatically infected individuals	estimated
$A(t)$	100 per year	Symptomatically infected individuals	estimated
parameters and constants			
Λ	2258 per year	Recruitment rate into the population via birth and immigration	[35]
π	0.000157	Transmission or Infection rate	[35]
μ_B	0.2 per year	Natural death rate of the population	[35]
σ	0.34 per year	Rate of transmission from infected status to AIDS status	[35]
δ	0.2 per year	death rate of AIDS individuals	[35]
α_B	0.2	The saturation factor that measures the inhibitory effect	[35]
ϕ	varies:$0 < \phi < 1$	Treatment efficacy	[35]

Figure (4.1) represents the behaviour of the infected population over a period of ten years under different treatment efficacies. The infected population is seen to experience a continuous decline in population in the first ten years. This decline can be attributed to the progression of the infected individuals into the AIDS class. On the other hand the use of high treatment efficacy plays a major role in accelerating this decline as opposed to low treatment efficacy (ϕ). It can be noted that, for some values of (ϕ), e.g 0.1, 0.5 and 0.9 the corresponding values of R_{0B} are $R_{0B} = 0.00034$, $R_{0B} = 0.000214$ and $R_{0B} = 0.000157$ thus $R_{0B} \ll 1$. This clearly shows that DFE is both locally and globally asymptotically

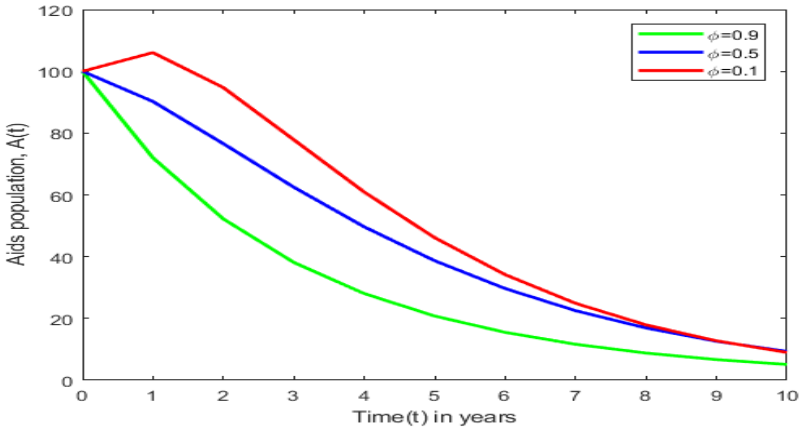

Figure 4.2: effect of ϕ on the population of AIDS (A) in the first 10 years

stable which is in line with (Theorem (4.4.2)). A similar scenario is observed, in figure (4.2), which represents the behaviour of AIDS population within the same period of time. **For values of** $\Lambda = 0.55year^{-1}$, $\pi = 0.003$, $\mu_B = 0.0196year^{-1}$, $\sigma = 0.15year^{-1}$, $\delta = 0.0909year^{-1}$ we obtain the following graphs:

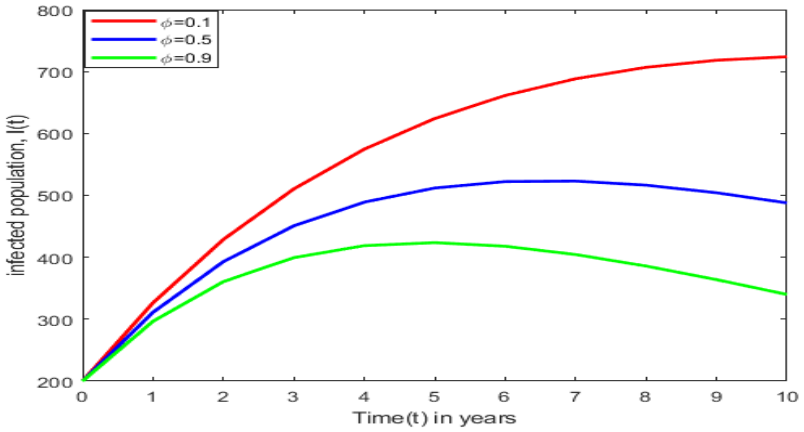

Figure 4.3: effect of ϕ on the population of the Infectives (I) in the first 10 years

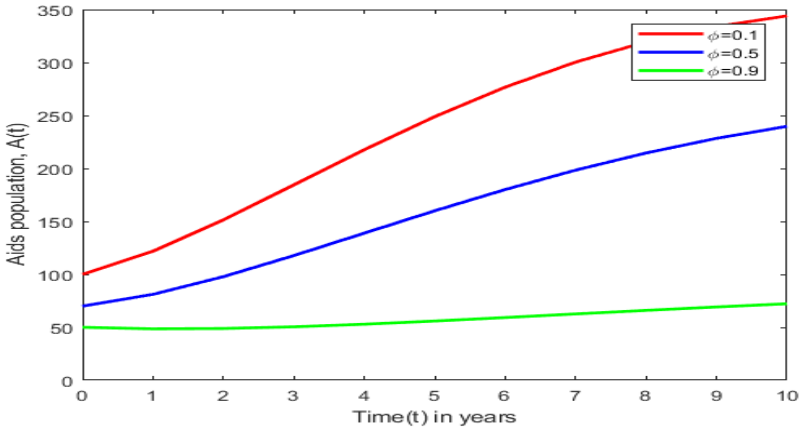

Figure 4.4: effect of ϕ on the population of the Aids individuals (A) in the first 10 years

It can be observed from Figures (4.3) and (4.4), that low treatment efficacy of $\phi = 0.1$ corresponds to $R_{0B} = 2.4$. This means that the endemic equilibrium is globally asymptotically stable (Theorem (4.4.5)) implying disease persistence in the population. On the other hand high treatment efficacy of $\phi = 0.5$ and $\phi = 0.9$ yields $R_{0B} = 0.88$ and $R_{0B} = 0.54$ respectively. This means that the endemic equilibrium is unstable, and that the infected population is gradually reduced. Similarly from figure (4.4) it can be deduced that the transfer rate of individuals to the AIDS class declines steadily due to the high treatment efficacy. Also due to high treatment efficacy the increase in the number of AIDS population is relatively low compared to the case when treatment efficacy is low.

4.6 Discussion and Conclusion

We have modeled a between-host HIV/AIDS infection, by taking into account a saturated incidence rate and treatment efficacy. Through meticulous mathematical analysis, we have theoretically proved that both local and global dynamics of the proposed model are fully determined by the basic reproduction number R_{0B}. More precisely the disease free equilibrium is both locally and globally asymptotically stable if $R_{0B} < 1$. Biologically this implies that HIV/AIDS is theoretically extinct hence the prevalence rate among the population is low and that the fight against HIV/AIDS through antiretroviral treatment is efficient. The endemic equilibrium has been proved to be globally asymptotically stable whenever $R_{0B} > 1$ by the geometric approach method, as used by Li and Muldowney [18], which implies that HIV/AIDS persists in the population. Numerical simulations conducted confirm our theoretical results and further show that early treatment with high treatment efficacy is important in combating the spread of HIV/AIDS.

CHAPTER FIVE

COUPLED IMMUNOEPIDEMIOLOGICAL MODEL FOR HIV AND AIDS TRANSMISSION

5.1 Introduction

Since its discovery over thirty years ago, mathematical modelling of HIV and AIDS disease transmission has mainly concentrated on modelling the two transmission levels separately, namely the immunological process and the epidemiological process. This is due to the tractability of modelling the immunological process independent of the between host process [14]. Yet coupled models have the capacity to unravel pertinent questions such as the effect of within host on between host models. Attempts to use immunoepidemiological models in modelling disease dynamics of other diseases have been successful, for example recent study by [41] used a multiscale modelling framework to investigate transmission dynamics of cholera while [4] developed an immunoepidemiological framework on malaria. However the application of this modelling framework on HIV and AIDS has received little attention. In this chapter we endeavour to bridge the two scales of HIV transmission and generate an immunoepidemiological model. This is motivated by the fact that there exists an interdependence of parameters between the two scales of infection such as virulence and transmission rate.

5.2 Model Description and Formulation

In this section, we construct a coupled HIV and AIDS model linking both the within-host and between-host transmission subsystems. The coupled model will consist of two processes, one for the epidemiological processes at the population level and the other for the viral dynamics within an individual host. System (4.1) developed in chapter four

of this study forms the between host component of the coupled system, while model (3.1) formulated in chapter three of this study is used as the within host component in formulating the coupled model. Both systems (4.1) and (3.1) have been discussed extensively in literature.

5.2.1 Coupling the subsystems

In order to link the two processes, we examine the relationship between the two subsystems (4.1) and (3.1), by employing the method used by [14]. From the SIA subsystem (4.1), it can be established that the host viral load has significant effect on HIV transmission rate in the population, hence we suppose that the rate of transmission of HIV is indeed proportional to virulence levels of the transmitting host, this can be represented by the functional relationship of the form

$$\begin{aligned} \pi &= \pi(V) \\ \pi(0) = 0, \pi'(V) &= \frac{d\pi}{dV} \end{aligned} \tag{5.1}$$

We further explore how the viral and cellular system depends on HIV prevalence in the host population, I. Let $N(t) = S(t) + I(t) + A(t) \to \frac{\Lambda}{\mu_B}$ as $t \to \infty$, be the total host population and denoting $\frac{\Lambda}{\mu_B}$ by $\hat{N}$ in the remainder of this chapter, we consider n systems, where every(each) system represents the viral dynamics of one host. We can obtain an average system that can be used to describe the average cell densities and viral load from the n systems. Therefore for every single host $j(j = 1, 2, ..., N)$, denote the viral load of an infective as V_j while the number of uninfected and infected cells can be denoted as T_j and $T_j^\star$ respectively. Define

$$\begin{aligned} V_{av} &= \frac{1}{\hat{N}} \sum_{j=1}^{\hat{N}} V_j \\ T_{av}^\star &= \frac{1}{\hat{N}} \sum_{j=1}^{\hat{N}} T_j^\star \\ T_{av} &= \frac{1}{\hat{N}} \sum_{j=1}^{\hat{N}} T_j \end{aligned} \tag{5.2}$$

Where T_{av}, $T^{\star}_{av}$ and V_{av} are average number of uninfected cells, infected T cells and viral load respectively, For $0 < I < \hat{N}$, the following assumptions hold

- that only individuals with indices $j = 1, 2, ..., I$ are infected i.e $V_j > 0$ for $j = 1, 2, ..., I$
- $V_j = 0$ for $j = I + 1, ..., \hat{N}$.

Thus for each individual, the within host HIV infection dynamics is described as

$$\begin{aligned}
\frac{dT_j}{dt} &= rT_j(1 - \frac{T_j}{T_{jmax}}) - (1-\rho)\beta V_j T_j - (1-\vartheta)\alpha_W T_j T^{\star}_j - \mu_W T_j \\
\frac{dT^{\star}_j}{dt} &= (1-\rho)\beta V_j T_j + (1-\vartheta)\alpha_W T_j T^{\star}_j - \kappa T^{\star}_j \\
\frac{dV_j}{dt} &= \omega\kappa T^{\star}_j - cV_j, j = 1, 2, ..., \hat{N}
\end{aligned} \tag{5.3}$$

To derive an equation for the average T_{av}, we sum up the whole population and using (5.2) and T_j equation in (5.3) we obtain

$$\begin{aligned}
\frac{dT_{av}}{dt} &= \frac{1}{\hat{N}}\sum_{j=1}^{\hat{N}} \frac{dT_j}{dt} \\
&= rT_j(1 - \frac{T_j}{T_{jmax}}) - (1-\rho)\beta\frac{1}{\hat{N}}\sum_{j=1}^{\hat{N}} V_j T_j - (1-\vartheta)\alpha_W \frac{1}{\hat{N}}\sum_{j=1}^{\hat{N}} T_j T^{\star}_j - \mu_W T_{av} \\
&= rT_j(1 - \frac{T_j}{T_{jmax}}) - (1-\rho)\beta\frac{1}{\hat{N}}\sum_{j=1}^{I} V_j T_j - (1-\vartheta)\alpha_W \frac{1}{\hat{N}}\sum_{j=1}^{I} T_j T^{\star}_j - \mu_c T_{av}
\end{aligned} \tag{5.4}$$

where the term $\sum_{j=1}^{I} V_j T_j$ and $\sum_{j=1}^{I} T^{\star}_j T_j$ represent the total incidence. To maintain the mass action law for the averages, the total contact rate and the average contact rate is assumed to have a relationship of the form:

$$\sum_{j=1}^{I} V_j T_j = \Theta(I) T_{av} V_{av} \tag{5.5}$$

and

$$\sum_{j=1}^{I} T^{\star}_j T_j = \Theta(I) T^{\star}_{av} T_{av} \tag{5.6}$$

Where the function Θ is dependent on how HIV transmission processes at the population level affect the within host HIV infection dynamics, hence a simple linear relation

that preserves the mass action law for the contact rate incorporated in equation (5.3) is proposed as follows:

$$\Theta(I) = \theta I \tag{5.7}$$

where θ is a constant of proportionality. Therefore the terms $\sum_{j=1}^{I} V_j T_j$ and $\sum_{j=1}^{I} T_j^{\star} T_j$ in equation (5.4) can be replaced by

$$\theta I V_{av} T_{av} \tag{5.8}$$

and

$$\theta I T_{av}^{\star} T_{av} \tag{5.9}$$

respectively, that is,

$$\sum_{j=1}^{I} V_j T_j = \theta I V_{av} T_{av} \tag{5.10}$$

and

$$\sum_{j=1}^{I} T_j^{\star} T_j = \theta I T_{av}^{\star} T_{av} \tag{5.11}$$

Expanding the RHS of equation (5.10) and (5.11) we obtain

$$\theta I T_{av} V_{av} = \frac{\theta I}{\hat{N}^2}(\sum_{i=1}^{\hat{N}} V_i T_i + \sum_{i \neq j}^{\hat{N}} V_i T_j) \quad = \quad \frac{\theta I}{\hat{N}^2}(f(V_i, T_i) + \sum_{i \neq j}^{I} V_i T_j) \tag{5.12}$$

where $(f(V_i, T_i) = \sum_{i=1}^{I} V_i T_i$

similarly

$$\theta I T_{av} T_{av}^{\star} = \frac{\theta I}{\hat{N}^2}(\sum_{i=1}^{\hat{N}} T_i^{\star} T_i + \sum_{i \neq j}^{\hat{N}} T_i^{\star} T_j) \quad = \quad \frac{\theta I}{\hat{N}^2}(f(T_i^{\star}, T_i) + \sum_{i \neq j}^{I} T_i^{\star} T_j) \tag{5.13}$$

where $(f(T_i^{\star}, T_i) = \sum_{i=1}^{I} T_i^{\star} T_i$

Let $\hat{\beta} = \theta$ and $\hat{\alpha}_W = \theta$

then

$$\frac{\hat{\beta}}{\hat{N}} \sum_{j=1}^{I} V_j T_j = \frac{\theta}{\hat{N}} f(V_i, T_i) \geq \frac{\theta}{\hat{N}} \frac{1}{\hat{N}} (f(V_i, T_i)) \tag{5.14}$$

and

$$\frac{\hat{\beta}}{\hat{N}}\sum_{j=1}^{I} T_j^{\star}T_j = \frac{\theta}{\hat{N}}f(T_i^{\star},T_i) \geq \frac{\theta}{\hat{N}}\frac{1}{\hat{N}}(f(T_i^{\star},T_i)) \tag{5.15}$$

assuming that both $\frac{\theta I}{\hat{N}^2}\sum_{i\neq j}^{I} V_iT_j$ and $\frac{\theta I}{\hat{N}^2}\sum_{i\neq j}^{I} T_i^{\star}T_j$ are small enough, then from equation (5.4) we obtain an equation for $\frac{dT_{av}}{dt}$ as follows

$$\frac{dT_{av}}{dt} = rT_{av}(1-\frac{T_{av}}{T_{max}}) - (1-\rho)\beta IV_{av}T_{av} - (1-\vartheta)\alpha_W IT_{av}T_{av}^{\star} - \mu_C T_{av} \tag{5.16}$$

similarly from $T_j^{\star}$ and V_j equations in (5.3) we get

$$\frac{dT_{av}^{\star}}{dt} = (1-\rho)\beta IV_{av}T_{av} + (1-\vartheta)\alpha_W IT_{av}T_{av}^{\star} - \kappa T_{av}^{\star} \tag{5.17}$$

,

$$\frac{dV_{av}}{dt} = \omega\kappa T_{av}^{\star} - cV_{av} \tag{5.18}$$

assembling equations (5.16), (5.17) and (5.18) we obtain a system for the averages for the within-host dynamics given as,

$$\begin{aligned}
\frac{dT_{av}}{dt} &= rT_{av}(1-\frac{T_{av}}{T_{max}}) - (1-\rho)\beta IV_{av}T_{av} - (1-\vartheta)\alpha_W IT_{av}T_{av}^{\star} - \mu_W T_{av} \\
\frac{dT_{av}^{\star}}{dt} &= (1-\rho)\beta V_{av}T_{av} + (1-\vartheta)\alpha_W T_{av}T_{av}^{\star} - \kappa T_{av}^{\star} \\
\frac{dV_{av}}{dt} &= \omega\kappa T_{av}^{\star} - cV_{av}
\end{aligned} \tag{5.19}$$

From subsystems (4.1) and (5.19) for the between- and within-host dynamics respectively, and dropping subscripts av for the averages (i.e, $T = T_{av}$, $T^{\star} = T_{av}^{\star}$, $V = V_{av}$) we obtain the coupled model (5.20) linking the immunological and epidemiological transmission processes for HIV. The summary of the model can be described schematically as shown below.

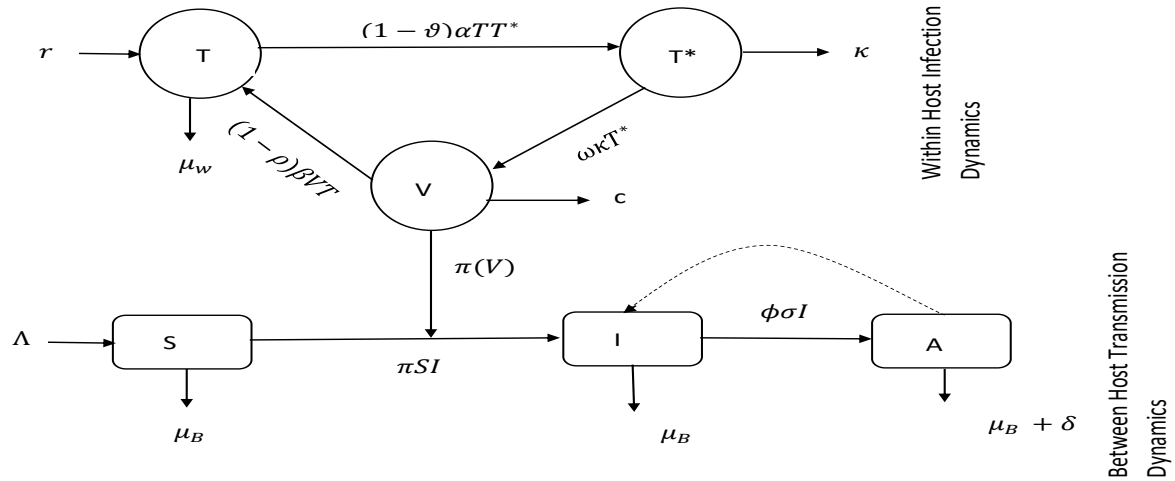

Figure 5.1: Flow chart of the coupled immunoepidemiological model for HIV/AIDS

Mathematically, this can be described by the following system of equations;

$$\begin{aligned}
\frac{dS}{dt} &= \Lambda - \frac{\pi VSI}{1+\alpha_B I} - \mu_B S \\
\frac{dI}{dt} &= \frac{\pi VSI}{1+\alpha_B I} - (1-\phi)\sigma I - \mu_B I \\
\frac{dA}{dt} &= (1-\phi)\sigma I - \delta A - \mu_B A \\
\frac{dT}{dt} &= rT(1-\frac{T}{T_{max}}) - (1-\rho)\beta IVT - (1-\vartheta)\alpha_W ITT^\star - \mu_W T \\
\frac{dT^\star}{dt} &= (1-\rho)\beta IVT + (1-\vartheta)\alpha_W ITT^\star - \kappa T^\star \\
\frac{dV}{dt} &= \omega\kappa T^\star - cV
\end{aligned} \tag{5.20}$$

Since the rate of transmission of HIV in the human population is considered as a function of the number of free viruses, then the viral load (V) at the between-host compartments can be considered as a parameter value and can therefore be denoted as θ_1. Similarly the infectives (I) at the within host can also be taken as a parameter and denoted as θ_2. Hence model (5.20) becomes

$$\frac{dS}{dt} = \Lambda - \frac{\pi\theta_1 SI}{1+\alpha_B I} - \mu_B S$$

$$
\begin{aligned}
\frac{dI}{dt} &= \frac{\pi\theta_1 SI}{1+\alpha_B I} - (1-\phi)\sigma I - \mu_B I \\
\frac{dA}{dt} &= (1-\phi)\sigma I - \delta A - \mu_B A \\
\frac{dT}{dt} &= rT(1-\frac{T}{T_{max}}) - (1-\rho)\beta\theta_2 VT - (1-\vartheta)\alpha_W\theta_2 TT^\star - \mu_W T \\
\frac{dT^\star}{dt} &= (1-\rho)\beta\theta_2 VT + (1-\vartheta)\alpha_W\theta_2 TT^\star - \kappa T^\star \\
\frac{dV}{dt} &= \omega\kappa T^\star - cV
\end{aligned} \tag{5.21}
$$

5.3 Analysis of the coupled Immunoepidemiological model

5.3.1 Basic Reproductive Ratio

The local stability of the model (5.21) is governed by the basic reproduction number $R_0 = Max\{R_{0B}, R_{0W}\}$, where R_{0B} and R_{0W} are the basic reproduction numbers for between-host and within-host subsystems respectively. Model (5.21) has four infected compartments, namely I, A, $T^\star$ and V. Using the next generation matrix method as applied by [37], the new infection terms and the remaining transfer terms for those four compartments are given below, in partitioned form.

$$
\mathcal{F} = \begin{pmatrix} \frac{\pi\theta_1 SI}{1+\alpha_B I} \\ 0 \\ (1-\rho)\beta\theta_2 VT + (1-\vartheta)\alpha_W\theta_2 TT^\star \\ 0 \end{pmatrix} \tag{5.22}
$$

and

$$
\mathcal{V} = \begin{pmatrix} (1-\phi)\sigma I + \mu_B I \\ \delta A - \mu_B A - (1-\phi)\sigma I \\ \kappa T^\star \\ cV - \omega\kappa T^\star \end{pmatrix} \tag{5.23}
$$

The Jacobian of f and ν evaluated at the Infection Free Equilibrium $E_0 = (\frac{\Lambda}{\mu_B}, 0, 0, T_{max}(1-\frac{\mu}{r}), 0, 0)$ yields ;

$$F = \begin{pmatrix} \frac{\pi\theta_1\Lambda}{\mu_B} & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & (1-\rho)\alpha_W\theta_2 T_{max}(1-\frac{\mu_W}{r}) & (1-\rho)\beta\theta_2 T_{max}(1-\frac{\mu_W}{r}) \\ 0 & 0 & 0 & 0 \end{pmatrix} \tag{5.24}$$

$$V = \begin{pmatrix} (1-\phi)\sigma + \mu_B & 0 & 0 & 0 \\ -(1-\phi)\sigma & \delta + \mu_B & 0 & 0 \\ 0 & 0 & \kappa & 0 \\ 0 & 0 & -\omega\kappa & c \end{pmatrix} \tag{5.25}$$

and

$$V^{-1} = \begin{pmatrix} \frac{1}{(1-\phi)\sigma+\mu_B} & 0 & 0 & 0 \\ \frac{(1-\phi)\sigma}{((1-\phi)\sigma+\mu_B)(\delta+\mu_B)} & \frac{1}{\delta+\mu_B} & 0 & 0 \\ 0 & 0 & \frac{1}{\kappa} & 0 \\ 0 & 0 & \frac{\omega}{c} & \frac{1}{c} \end{pmatrix} \tag{5.26}$$

where F is nonnegative and V is nonsingular. Computing FV^{-1} we have

$$FV^{-1} = \begin{pmatrix} \frac{\pi\theta_1\Lambda}{\mu_B((1-\phi)\sigma+\mu_B)} & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & T_{max}(1-\frac{\mu_W}{r})[(1-\rho)\frac{\beta\theta_2\omega}{c} + (1-\vartheta)\frac{\alpha_W\theta_2}{\kappa}] & 0 \\ 0 & 0 & 0 & 0 \end{pmatrix} \tag{5.27}$$

The basic reproductive ratio is thus given by $R_{0C} = \rho(FV^{-1})$, where the term $\rho(FV^{-1})$ denotes the spectral radius of the matrix FV^{-1}. Hence

$$R_{0C} = Max\left(\frac{\pi\theta_1\Lambda}{\mu_B((1-\phi)\sigma+\mu_B)}, T_{max}(1-\frac{\mu_W}{r})\frac{\omega\beta\theta_2}{c}(1-\rho) + T_{max}(1-\frac{\mu_W}{r})(1-\vartheta)\frac{\alpha_W\theta_2}{\kappa}\right) \tag{5.28}$$

from equations (3.15) and (4.12), equation (5.28) can be expressed as

$$R_{0C} = Max\left\{R_{0B}, R_{0W}\right\} \tag{5.29}$$

R_{0B} is a measure of the average number of secondary HIV infections in human (host) population caused by a single infective host introduced into an entirely susceptible population. Similarly, R_{0W} is a measure of the average number of secondary viral and cellular infections within host caused by a single virion and infectious cells introduced into an entirely susceptible CD^+ T cell population.

5.3.2 Disease Free Equilibrium for the Coupled model

The system (5.21) always has a disease free equilibrium (DFE), $E_0 = (S, 0, 0, T, 0, 0,) = (\frac{\Lambda}{\mu_B}, 0, 0, T_{max}(1 - \frac{\mu_W}{r}), 0, 0)$. We examine the local stability of the DFE by analysing the eigenvalues of the Jacobian matrix of system (5.21) at the DFE. The Jacobian matrix of system (5.21) is as follows;

$$M = \begin{pmatrix} \frac{-\pi\theta_1 I}{1+\alpha_B I} - \mu_B & \frac{-\pi\theta_1 S}{(1+\alpha_B I)^2} & 0 & 0 & 0 & 0 \\ \frac{\pi\theta_1 I}{1+\alpha_B I} & \frac{\pi\theta_1 S}{(1+\alpha_B I)^2} - (1-\phi)\sigma - \mu_B & 0 & 0 & 0 & 0 \\ 0 & (1-\phi)\sigma & -\delta - \mu_B & 0 & 0 & 0 \\ 0 & 0 & 0 & r - \frac{2rT}{T_{max}} - b - \mu_W & -d & -e \\ 0 & 0 & 0 & b & d - \kappa & e \\ 0 & 0 & 0 & 0 & \omega\kappa & -c \end{pmatrix} \tag{5.30}$$

Where

$$\begin{aligned} b &= (1-\rho)\beta V\theta_2 + (1-\vartheta)\alpha\theta_2 T^\star \\ d &= (1-\vartheta)\alpha\theta_2 T \\ e &= (1-\rho)\beta\theta_2 T \end{aligned}$$

The Jacobian matrix M in equation (5.30) at $E_0 = (\frac{\Lambda}{\mu_B}, 0, 0, T_{max}(1 - \frac{\mu_W}{r}), 0, 0)$ is given

as

$$M = \begin{pmatrix} -\mu_B & -\frac{\pi\theta_1\Lambda}{\mu_B} & 0 & 0 & 0 & 0 \\ 0 & \frac{\pi\theta_1\Lambda}{\mu_B((1-\phi)\sigma+\mu_B)} - 1 & 0 & 0 & 0 & 0 \\ 0 & (1-\phi)\sigma & -\delta-\mu_B & 0 & 0 & 0 \\ 0 & 0 & 0 & r - \frac{2rT}{T_{max}} - \mu_W & a_1 & -a_2 \\ 0 & 0 & 0 & 0 & a_1 - \kappa & a_2 \\ 0 & 0 & 0 & 0 & \omega\kappa & -c \end{pmatrix} \tag{5.31}$$

Where $a_1 = T_{max}(1 - \frac{\mu_W}{r})(1-\vartheta)\alpha\theta_2$

$a_2 = T_{max}(1 - \frac{\mu_W}{r})(1-\rho)\beta\theta_2$

Since at the DFE $T_0 = T_{max}$, then the element $r - \frac{2rT}{T_{max}} - \mu_W$ reduces to $-r - \mu_W$. The eigenvalues of the matrix M (5.31) are

$$\lambda_1 = -\mu_B \tag{5.32}$$

$$\lambda_2 = \frac{\pi\theta_1\Lambda}{\mu_B((1-\phi)\sigma+\mu_B)} - 1 \tag{5.33}$$

$$\lambda_3 = -\delta - \mu_B \tag{5.34}$$

$$\lambda_4 = -r - \mu_W \tag{5.35}$$

while the remaining eigenvalues were determined from the reduced matrix A

$$A = \begin{pmatrix} T_{max}(1 - \frac{\mu_W}{r})(1-\vartheta)\alpha\theta_2 - \kappa & T_{max}(1 - \frac{\mu_W}{r})(1-\rho)\beta\theta_2 \\ \omega\kappa & -c \end{pmatrix} \tag{5.36}$$

Applying Routh-Hurwiz criteria , matrix A in equation (5.36) will guarantee negative real roots if and only if the $trA < 0$ and $detA > 0$ thus

$$trA = \theta_2 R_{0W} - 1 - \frac{c}{\kappa} - T_{max}(1 - \frac{\mu_W}{r})(1-\rho)\frac{\beta\omega\theta_2}{c} \tag{5.37}$$

and

$$detA = -\theta_2[T_{max}(1 - \frac{\mu_W}{r})(1-\rho)\frac{\beta\omega}{c} + T_{max}(1 - \frac{\mu_W}{r})(1-\vartheta)\frac{\alpha}{\kappa}] + 1 \tag{5.38}$$

Equation (5.38) reduces to

$$detA = 1 - \theta_2 R_{0W} \tag{5.39}$$

From (5.37) and (5.39) $trA < 0$ and $detA > 0$ if and only if $R_{0W} < 1$. Similarly equation (5.33) can be written as

$$\lambda_2 = R_{OB} - 1 \tag{5.40}$$

Thus the DFE is locally asymptotically stable whenever$R_{0W} < 1$ and $R_{OB} < 1$. The epidemiological significance of this is that; any introduction of an infected individual into the population would not lead to new transmission and the disease is wiped out.

5.3.3 Endemic Equilibrium for the Coupled model EE

A disease is endemic in a population if it persists in the population. The endemic equilibrium of system (5.21) can be studied using the Centre Manifold Theorem [8, 6].

Theorem 5.3.1. *Consider the following general system of ordinary differential equations with a parameter* $a^\star$

$\frac{dx}{dt} = f(x, a^\star), f : R^n \times R \to R^n$ *and* $f \in C^2(R^n \times R)$

Without loss of generality, it is assumed that zero is an equilibrium point for system (5.21) for all values of the parameter $a^\star$*, (that is* $f(0, a^\star) \equiv 0, \forall a^\star$*). Assume*

1 . $B = D_x f(0, 0) = (\frac{\partial f_i}{\partial x_i}(0, 0))$ *is the linearized matrix of system (5.21) around the equilibrium 0 with* $a^\star$ *evaluated at zero.*

2 . *Zero is a simple eigenvector of* B *and all other eigenvalues of* B *have negative real parts.*

3 . *Matrix* B *has a right eigenvector* w *and a left eigenvector* v *corresponding to the zero eigenvalue*

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

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

$$r^\star = \sum_{k,i=1}^{n} v_k w_i \frac{\partial^2 f_k}{\partial x_i \partial a^\star}(0,0)$$

The local dynamics of the system around the equilibrium point 0 is totally determined by the signs of $s^\star$ *and* $r^\star$ *Particularly*

(i) In the case where $s^\star > 0; r^\star > 0$ *we have that when* $\varphi < 0$, *with* $|\varphi| \ll 1$, *(0,0) is locally asymptotically stable and there exist a positive unstable equilibrium; when* $0 < a^\star \ll 1$, *(0,0) is unstable and there exists a negative and locally asymptotically stable equilibrium.*

(ii) In the case where $s^\star < 0; r^\star < 0$, *when* $a^\star < 0$ *with* $|a^\star| \ll 1$ *(0,0) is unstable; when* $0 < a^\star \ll 1$, *(0,0) is locally asymptotically stable, and there exists a positive unstable equilibrium.*

(iii) In the case where $s^\star > 0; r^\star < 0$, *when* $a^\star < 0$ *with* $|a^\star| \ll 1$, *(0,0) is unstable and there exists a negative and locally asymptotically stable equilibrium, when* $0 < a^\star \ll 1$, *(0,0) is stable and there exists a positive unstable equilibrium.*

(iv) In the case where $s^\star > 0; r^\star < 0$, $a^\star < 0$ *changes from negative to positive, (0,0) changes its stability from stable to unstable. Correspondingly, a negative unstable equilibrium becomes positive and locally asymptotically stable.*

To apply theorem (5.3.1) the following simplification and change of variables are made on the system (5.21). Let $S = x_1, I = x_2, A = x_3, T = x_4, T^\star = x_5, V = x_6$ so that $N_B = x_1 + x_2 + x_3$ and $N_W = x_4 + x_5 + x_6$. The system (5.21) can be written in the form

$$\frac{dx}{dt} = F(x)$$

where

$$X = (x_1, x_2, x_3 x_4, x_5, x_6)$$

$$F = (f_1, f_2, f_3, f_4, f_5, f_6)$$

such that

$$\begin{aligned}
\frac{dx_1}{dt} &= f_1 = \Lambda - \frac{\pi\theta_1 x_1 x_2}{1+\alpha x_2} - \mu_B x_1 \\
\frac{dx_2}{dt} &= f_2 = \frac{\pi\theta_1 x_1 x_2}{1+\alpha x_2} - (1-\phi)\sigma x_2 - \mu_B x_2 \\
\frac{dx_3}{dt} &= f_3 = (1-\phi)\sigma x_2 - \delta x_3 - \mu_B x_3 \\
\frac{dx_4}{dt} &= f_4 = r x_4(1-\frac{x_4}{T_{max}}) - (1-\rho)\beta\theta_2 x_6 x_4 - (1-\vartheta)\alpha\theta_2 x_4 x_5 - \mu_W x_4 \\
\frac{dx_5}{dt} &= f_5 = (1-\rho)\beta\theta_2 x_6 x_4 + (1-\vartheta)\alpha\theta_2 x_4 x_5 - \kappa x_5 \\
\frac{dx_6}{dt} &= f_6 = \omega\kappa x_5 - c x_6
\end{aligned} \tag{5.41}$$

It can be verified that the Jacobian of system (5.21) at the DFE, E_0 is given by

$$M = \begin{pmatrix}
-\mu_B & \frac{-\pi\theta_1\Lambda}{\mu_B} & 0 & 0 & 0 & 0 \\
0 & Q_1 - 1 & 0 & 0 & 0 & 0 \\
0 & (1-\phi)\sigma & -\delta-\mu_B & 0 & 0 & 0 \\
0 & 0 & 0 & -r-\mu_W & Q_2 & -Q_3 \\
0 & 0 & 0 & 0 & Q_2-\kappa & Q_3 \\
0 & 0 & 0 & 0 & \omega\kappa & -c
\end{pmatrix} \tag{5.42}$$

Where

$$Q_1 = \frac{\pi\theta_1\Lambda}{\mu_B((1-\phi)\sigma+\mu_B)} \tag{5.43}$$

$$Q_2 = T_{max}(1-\frac{\mu_W}{r})(1-\vartheta)\alpha\theta_2 \tag{5.44}$$

$$Q_3 = T_{max}(1-\frac{\mu_W}{r})(1-\rho)\beta\theta_2 \tag{5.45}$$

To analyze the dynamics of (5.21), we compute the eigenvectors of the Jacobian of (5.21) at the DFE. It can be shown that the Jacobian matrix (5.42) has a right eigenvector given by $W = (w_1, w_2, w_3, w_4, w_5, w_6)^T$ where $w_1 = 0$, $w_2 = 0$, $w_3 = 0$, $w_4 = \frac{w_5(Q_2 - Q_3\frac{\omega\kappa}{c})}{(r+\mu_W)}$, $w_5 = w_5 > 0$, $w_6 = \frac{w_5\omega\kappa}{c}$.

Similarly, the components of the left eigenvector of the jacobian matrix (5.42) denoted by

$U = (v_1, v_2, v_3, v_4, v_5, v_6)^T$ are given by $v_1 = 0$, $v_2 = 0$, $v_3 = 0$, $v_4 = 0$, $v_5 = v_5 > 0$ and $v_6 = \frac{Q_3 v_5}{c}$.

Let a and b be the coefficients defined in theorem (5.3.1) . We can calculate $s^\star$ as follows: for the transformed system (5.41), the associated nonzero partial differentials of f (evaluated at the DFE, (E_0) are given by;

$$\sum_{k,i,j}^{6} v_2 w_i w_j \frac{\partial^2 f_2}{\partial x_i \partial x_j}(0,0) = 2v_5 w_5^2 (Q_2 - Q_3)\frac{\omega\kappa}{c}[(1-\vartheta)\alpha\theta_2 + (1-\rho)\frac{\beta\theta\omega\kappa}{c}] > 0$$

Consider the case when $R_{0C} = 1$ (assuming that $R_{0W} > R_{0B}$) and choose $\theta_2 = \varphi$ as a bifurcation parameter. Solving for θ_2 from $R_{0C} = R_{0W} = 1$ gives

$$\theta_2 = \varphi = \frac{1}{T_{max}(1 - \frac{\mu_W}{r})[(1-\rho)\frac{\beta\omega}{c} + (1-\vartheta)\frac{\alpha}{\kappa}])} \tag{5.46}$$

Obtaining $r^\star$ we have

$$\begin{aligned} r^\star &= \sum_{k,i=1}^{n} v_k w_i \frac{\partial^2 f_k}{\partial x_i \partial \varphi}(0,0) \\ &= 2v_5 w_5 (1-\vartheta)\alpha T_{max}(1 - \frac{\mu_W}{r}) > 0 \end{aligned}$$

Since $s^\star > 0$ and $r^\star > 0$, Theorem (5.3.1) holds, thus system (5.21) has a unique endemic equilibrium which is locally asymptotically stable whenever $R_{0C} > 1$ and unstable when $R_{0C} < 1$.

5.4 Numerical Simulation of the Model

The aim of this section is to conduct numerical simulations to our proposed Immuno-epidemiological HIV and AIDS model (5.21), in order to verify our theoretical results and also explore emerging properties that are not covered in our theoretical analysis. This is made possible by using the base values of the model parameters given in Tables 3.2 and 4.1.

Figure 5.2 (a), illustrate how the within-host viral load impacts on the number of infected individuals in the population (between-host level). The graph depicts a logistic growth for the virus population, in which viral replication reveals an increase over time, attaining

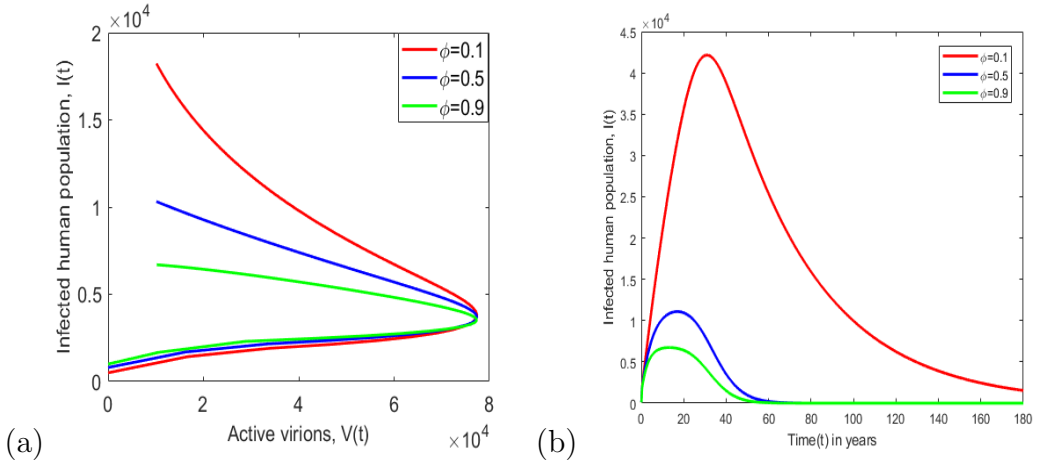

Figure 5.2: (a).The Graph of infected human population I(t) against Active virions V(t) (b).The Graph trajectory of infected human population I(t) within the first 30 years.

a maximum of approximately 78000 virions. Since this is a critical point (turning point) where the number of virions start to decline. This is attributed to immune response, the natural death of virions and/or exhaustion of uninfected $CD4^+$ T-cells, or the slow process of viral replication as a result of latency. On the other hand the number of infectives in the population increases gradually at a much slower rate despite an increase in viral load at the within-host level.

It can also be deduced that even with declining viral load, the number of infectives continue to rise. This is attributed to the fact that infectivity at the population is highly dependent on the contact rate between infected and susceptible individuals. One of the emerging phenomena from Figure 5.2 (a) is that even with low viral load transmission at the population level can persist as long as the contact rate is kept high.

Furthermore the graph shows that with high treatment efficacy the rate of increase in the number of infectives is decreased (kept at low level) while low efficacy of ART corresponds to an increase in the number of infectives. Hence the level of treatment efficacy is crucial in combating the spread of HIV and AIDS.

Figure 5.2 (b), illustrate the long term effect of various ART treatment efficacy levels on the number of infected human population. It can be observed that when efficacy level is low ($\phi = 0.1$), the number of infected individuals increases sharply to a peak of 40,000 infected individuals within the first one year, after which the numbers start to decline moderately to a minimum of 5000 for the next ten years. The decrease in the number of infected individuals can be attributed to factors independent of treatment efficacy such as:

- Measures put in place to combat the spread of HIV and AIDS such as public awareness campaigns.
- Most of the asymptomatically infected individuals transit to the symptomatically infected (AIDS) class.
- Positive behaviour change among the infected and susceptible individuals as a result of voluntary screening/testing and counselling.

On the other hand, when treatment efficacy is high, that is, 0.5 and 0.9, the graph trajectory of the infected human population $I(t)$, generally, depicts a very suppressed increase in the number of new infections, this is in contrast to the case when efficacy is at 0.1. We further observe that the effect of the two levels of antiretroviral treatment (RTI and PI) on viral replication is quite significant. This is due to the fact that the viral load at the within-host level almost immediately begins to decay exponentially with a negative value in less than one year. Also combined ART prevents successful infection of new cells, furthermore, the lifespan of free virus and infected cells is reduced. This has an overall effect on the transmissibility of HIV at the population level, hence the small number of infected individuals corresponding to high treatment efficacy.

5.5 Conclusion

In this chapter we have formulated and analysed a new model framework linking the two subsystems of within-and between-host HIV viral dynamics discussed in chapter three

and four respectively. The novelty in this chapter is in deriving the coupled model by expressing the transmission rate as a function of the viral load at the between host level, while expressing the infection rate at within host as a function of the infectives. This was based on the approach by [14]. The six component model obtained, despite incorporating various HIV viral dynamics such as treatment at both viral and cellular levels, remained mathematically and computationally tractable. Hence a detailed mathematical analysis was conducted, this involved determining the basic reproduction number for the coupled model. This was found to be a maximum of the two reproduction numbers for the between-and within-host subsystems, that is $R_{0C} = max\{R_{0W}, R_{0B}\}$. The analysis of the DFE was done using the Routh-Hurwiz criteria and was found to be asymptotically stable when $R_{0W} < 1$ and $R_{0B} < 1$. This has both immunological and epidemiological significance, in that the introduction of a few infected individuals into the population will not result into new HIV transmissions and thus the disease will be wiped out from the population. The centre manifold theorem was used to show that the coupled model has a unique endemic equilibrium. This was found to be locally asymptotically stable whenever $R_{0C} > 1$ and unstable when $R_{0C} < 1$. From the numerical simulations conducted it was deduced that an increase in viral load has a corresponding increase in the number of infectives at the population level. However a decline in the viral load at the within-host may not necessarily lead to a decline in the number of infectives at the population level. This is because transmissibility is highly dependent on the rate of contact between the infectives and the susceptibles. In addition numerical simulations revealed that the efficacy of ART treatment has remarkable effect on HIV transmission, with high efficacy leading to significant reduction of infectives within a short period of time. Specifically the high efficacy of both RTI and PI treatment contributes to low viral replication, since the RTI prevents successful infection of new cells while PI prevents infected cells from maturing into actively infectious virions. This is likely to result into low transmission of HIV at the population level. Hence the small number of infected individuals at the population when treatment efficacy is high.

CHAPTER SIX

CONCLUSIONS AND RECOMMENDATIONS

This research sought to develop and analyse a coupled immunoepidemiological model for HIV with viral and cellular transmission incorporating antiretroviral treatment. In order to achieve this, a within host HIV infection model incorporating cellular and viral infection with combined antiretroviral treatment was developed and analysed. The detailed mathematical analysis revealed that the eradication or persistence of HIV in the human blood is dependent on the threshold value of R_{OW}. While numerical simulation showed that high efficacy of combined treatment of RTI and PI levels help in stifling viral replication leading to low viral load and high $CD4^+$ T cell count. Thus objective (i) was achieved

The achievement of objective (ii) was realized by developing a between host model with saturated incidence rate and treatment efficacy. Theoretical analysis revealed that HIV and AIDS becomes extinct if the threshold value of $R_{0B} < 1$, which implies that there is low prevalence due to the treatment efficacy of ARV treatment. On the other hand, $R_{0B} > 1$ is indicative of HIV persistence in the population. By successfully coupling the two subsystems of within and between host models incorporating the two levels of treatment objective three was realized. In addition the use of numerical simulations to validate analytical results, ensured that objective four of the study was realized.

6.1 Recommendations

The study used the idea of coupling to investigate how viral load at the within-host level affect transmissibility at the population level, using ordinary differential equations. In particular, we incorporated RTI and PI treatment efficacy in the novel immunoepidemiological model.

Based on our analytical and numerical results obtained, the study recommends that treatment using high efficacy drugs of RTI and PI will go a long way in optimizing the fight against HIV and AIDS transmission in the population. In addition future design and development of ARV drugs should focus on improving efficacy of ARV drugs. This is in line with the global ARV optimization framework established with the purpose of ensuring transition to new drugs formulation with better efficacy, lower toxicity and high durability, among others [12, 39].

Further studies may be carried out to investigate the impact of other dynamics such as drug resistance on efficacy of ARV treatment using immuno-epidemiological models..

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