Mathematical Modelling of low HIV viral load within Ghanaian Population

by

Frank K. Owusu

submitted in accordance with the requirements
for the degree of

DOCTOR OF PHILOSOPHY

In the subject

APPLIED MATHEMATICS

In the

Department of Mathematical Sciences

at the

University of South Africa

Supervisor: Prof. Emile Franc Doungmo Goufo

(September 2020)

PREFACE

The spread of HIV has been very explosive, mercilessly and remains the most deadly disease which has ever hit the planet, since the last three decades. The complexities aligned with the spread of the virus have activated this dissertation for a workable mathematical model and a suitable treatment interruption.

Hence, the adopted model is momentous to the government, who is a major stakeholder for planning. Further, the study is essential to drug manufactures for implementing a workable drug and health workers for designing a suitable treatment option for HIV tainted individuals.

I am highly appreciative and beholden to Professor Emile Franc Doungmo Goufo for patiently facilitating the fruition of the study from 2015 to 2020.

ABSTRACT

Comparatively, HIV like most viruses is very minute, unadorned organism which cannot reproduce unaided. It remains the most deadly disease which has ever hit the planet since the last three decades. The spread of HIV has been very explosive and mercilessly on human population. It has tainted over 60 million people, with almost half of the human population suffering from AIDS related illnesses and death finally. Recent theoretical and computational breakthroughs in delay differential equations declare that, delay differential equations are proficient in yielding rich and plausible dynamics with reasonable parametric estimates.

This paper seeks to unveil the niche of delay differential equation in harmonizing low HIV viral haul and thereby articulating the adopted model, to delve into structured treatment interruptions. Therefore, an ordinary differential equation is schemed to consist of three components such as untainted CD4+ T-cells, tainted CD4+ T-cells (HIV) and CTL. A discrete time delay is ushered to the formulated model in order to account for vital components, such as intracellular delay and HIV latency which were missing in previous works, but have been advocated for future research. It was divested that when the reproductive number was less than unity, the disease free equilibrium of the model was asymptotically stable. Hence the adopted model with or without the delay component articulates less production of virions, as per the decline rate. Therefore CD4+ T-cells in the blood remains constant at δ_1/δ_3, hence declining the virions level in the blood. As per the adopted model, the best STI practice is intimated for compliance.

Key words: Cytotoxic Lymphocytes; Structured treatment interruption; Disease free Equilibrium: Human immunodeficiency virus; Basic reproductive number

DECLARATION 1 – PLAGIARISM

Student number: 57638888

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September 2020

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DECLARATION 2- PUBLICATIONS

Papers Published

- Modelling intracellular delay and therapy interruptions within Ghanaian HIV Population, Advances in Difference Equation. DOI-10.1186/513662-020-02856-X. PP 46 -84 (2020). https://doi.org/10.1186/s13662-020-02856-x

- Mathematical modelling of multiple target cells with delay, Alexandria Engineering Journal, Vol 2020. 130 (2020). PP. 111-127.

- Fractional SEIR Epidemic model for spatial and temporal spread of Tuberculosis in meta-population, Journal of Abstract and applied analysis, Vol 8, No 3, PP 406-418, 2016

Papers in Preparation

- Stability analysis of fractional order epidemics model with multiple equilibrium

- An efficient numerical technique for new fractional malaria model with nonsingular derivative operator

September 2020

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SIGNATURE Date
(Mr. Frank K. Owusu)

DEDICATION

This work is purely dedicated to my sons Kelvin Kwaku Owusu and Prince Nana Osei Owusu for their immeasurable sacrifice towards the fruition of the study.

ACKNOWLEDGMENT

Most importantly, I express my profound gratitude to the Almighty God, both for His grace and endowment of favor which has prompted the fruition of this study.

The writer is most grateful to Professor Emile Franc Doungmo Goufo for his inestimable assistance and whose persistence advice, valuable criticism and encouragement, engendered greater excitement for a more objective research.

Unique gratitude to my better half, Mrs. Joyce Owusu and sons Kelvin and Prince for their persistent love and sacrifice throughout the study. I am really beholden.

Many thanks to Rev Dominique and Mrs. Elizabeth Denyo (Minister, Church of Pentecost) for their assistance in the analysis of the developed model and prayer support.

Finally, to all my family and friends, without whom a drawn out period of this research is unimaginable. To my parents for affording the setup and support which embraced the fruition of this study. To my loved ones for their help and provision of distractions where necessary

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ACRONYMS

AIDS	Acquired immune deficiency syndrome
ART	Antiretroviral therapy
CDC	Center for disease control
CI	Chronic infection (model)
CTL	Cytotoxic lymphocytes
CRF	Circulating recombinant form
DDE	Delay differential equation
DIV	Defective interfering virus
DNA	Deoxyribonucleic acid
DRM	Drug resistant mutation
FIV	Feline immunodeficiency virus
GP	glycoprotein
HIV	Human immunodeficiency virus
HLA	Human Leukocyte antigen
HT	Helper T cell
ID	Intracellular delay (model)
IDU	Intravenous drug user
IR	Immune response (model)
LTNP	Long term non-progresses
MSM	Men who have sex with men
MTC	Multiple-target-cell (model)
NNRTI	Non-nucleoside reverse transcriptase inhibitor
NPE	National Prevalence Estimate
NRTI	Nucleoside reverse transcriptase inhibitor
ODE	Ordinary differential equation
OI	Opportunistic infection
PI	Protease inhibitor
RNA	Ribonucleic acid
RTI	Reverse transcriptase inhibitor

SIV	Simian immunodeficiency virus
STC	Single-target-cell (model)
STI	Structured treatment interruption
TB	Tuberculosis
UN	united Nations
WHO	World health organization

CHAPTER 1
INTRODUCTION

1.0 INTRODUCTION

The introduction of the thesis is activated by this chapter and therefore provides an insight to the background of the study, statement of the problem, Epidemiological trend of HIV in Ghana, mathematical model capable of modelling low HIV viral load, objectives aligned with the study, motivation of the study, significance of the study and finally the component of the structure of the thesis.

1.1 BACKGROUND

Current mathematical innovations and simulations in delay differential equation, reveals that delay differential equations are viable in producing rich and credible dynamics with acceptable parameter values. Delay differential equation works on an endless dimensional space which accommodates high-dimensional dynamics. The use of such mathematical dynamical models [1, 17] to describe a contagion such as the human immunodeficiency virus (HIV), became magnified when scientists discovered the menace and the threat HIV causes to mankind. AIDS intercepts when the contagion, remains untreated for a long period of time.

HIV has been projected to have killed over 25 million people [10], since its first recognition from the year 1981 to the year 2005. Significantly, HIV statistics from1999 to the year 2010 reveals a major drop of 19% in new HIV infections [20, 21]. However, new HIV contagions still remain unacceptably high. Currently about thirty three million (33 million) people are still residing with HIV/AIDS [10] and are not even aware of their status. Out of such huge infectious rate, 2.5 million of the infected are children. African continent alone is indebted with about 68% of the cumulative HIV infection in the world, representing 22.5 million of the people tainted by the virus [19].

Monitoring the spread of HIV across the world is very arduous and demanding due to the risk of being infected, hence key preventive measures are required to inhibit the propagation of the disease. Truly, controlling the disease HIV has been more arduous, due to the laxity of the methodology [4, 15] used in monitoring the infection and the spread of the disease. One of such approaches used to control HIV surveillance is basically by informing the public, about some of the new diagnoses of HIV and AIDS cases.

Ironically, the contagious rate of the pandemic is irrational and uncompromising, due to the huge number of people inclined with the alignment and the reality of a known vaccine to eliminate the disease assiduously. However the lives of HIV patients have been prolonged through the use of antiretroviral therapy (ART), which has assisted in slowing down the pace for the onset of AIDS or other related AIDS sickness. However, countries where people have access to ART have shown a realistic decline, on HIV death and a pitch in life expectancy [11]. Introduction of therapy has decreased the mortality rate [14] and hence by 20% in 2004.

Therefore since 1999, the advocacy for a viable treatment interruption has imparted roughly on about 14.4 million life-spans [10] on people tainted with HIV/AIDS.

Further, another means of limiting HIV transmission is marginalized, through total behavioral change such as absolute abstinence when not married, or faithfulness to one's partner in the case of married couples. [27]

Again, improved education and extensive access to condom use for individuals who cannot abstain completely from multiple partners, is essential in slumping down recent HIV attacks. [28]

However the unmatchable pinnacle of recent HIV infections has articulated an in-depth analysis relating to the use of the delay differential equation, to model low HIV viral state. The study further investigates the viral load of an infected individual and the need to ascertain when a particular therapy should be modified, continued or discontinued, due to drug-resistive modifications (DRMs) [52]. Drug resistive viruses, resides on a

particular drug type and regenerates its kind unnoticed, even when therapy is still ongoing [102, 104].

1.2 STATEMENT OF THE PROBLEM

Authentically, credible approaches to managing and mortifying the negative effects of any infectious disease, are aligned with a better comprehension of the nature and the mode of transmission of such disease. Tremendous and exciting researches are ongoing to unlock the treat caused by HIV/AIDS and also to stipulate a perpetual solution to the disease. These researches are underlined to underscore an in-depth comprehension of the disease at cellular level, by means of mathematical models. The incorporation of such mathematical models stimulates the advancement, or changes associated with a particular drug type and its administration [70]. HIV-1 has since been known to be the most hazardous virus, which after infection, focuses on the CD4+ T cells and ascertain access for its existence and continual replication. Per the infection of HIV-1 virus, the immune system is breached, resulting to lots of opportunistic diseases which are beyond the control and administration of the body's immune system.

The use of delay differential equation assists, by comparing the infected group of cells [6] with the uninfected cells, in relation to the time interval stipulated for such infection. Hence mathematical models, such as delay differential equations are key and vital in modelling the spread of HIV/AIDS, due to its associated time component. Most legitimate approaches have time delays embedded in them, but handfuls of researchers are able to model infectious diseases with time lags. However, the intricacies of time delays are associated with challenges ascribed to the layout of the model and the urgency to unlock and stabilize the unit, through dimensional analysis [125, 132].

In accordance to the above, most scientists [1, 2, 6, 7, 11] have therefore developed SIR models to include time lags. The time lags are designated for the arduous parameters in the model and their associated biological meanings. In relation to the above [13], a delayed model has been established to explain the standard mass

interaction and the universal soundness of the model. Again an SIR model which incorporates time delay was studied [12] for an infected state, to ascertain the significance of time lags in an SIR model. The resulting model was stabilized through Hopf bifurcation and hence supported the repercussions of the delay component. Further studies on SIR models [11] revealed the essence of stability and the heroics of density parameter in accounting for low HIV viral haul.

In congruence to the above problem and the need to find an amicable solution, this study designs an ordinary differential equation, composed of untainted $CD4^+$ T-cells, tainted $CD4^+$ T-cells and cytotoxic lymphocytes. The delay element is introduced in accordance to the formulated model, to enhance intracellular delay and HIV latency which were missing in previous works, but have been recommended for further research. The study further uses the stability of the developed DDE model to delve into structural treatment interruptions and intimates the best STI practice for compliance.

1.3 EPIDEMIOLOGICAL TREND OF HIV IN GHANA

Ghana's HIV prevalence rate has stabilised over the last five years, starting from the year 2014 through to the year 2020. A study conducted recently by Abigail et al (2019) intimated that about 334,714 people are currently tainted and residing with the virus, as well as 19,931 new mortality rate of infection. The study further intimates, that Greater Accra Region is recently on the pinnacle of infection with about 77,132 people tainted by the virus. Hence, per the number of tainted people, about 28,000 are currently adhering to ART, whilst 3,000 people have passed on. However, the country has recorded declines in the prevalence rate among key populations, such as the youth, pregnant women, children and the adult populace. Again, significant reductions have been realized in new contagions.

Again, according to Angela E.D (2015), an estimate of 235,982 people were living with the virus, together with 27,734 tainted children, representing 11.8 percent of the estimated figure.

Further, in 2016 [49], a national HIV Prevalence rate was conducted and revealed that about 13%, of the people are currently tainted with the disease, representing an estimate of 224,488. Out of the infected figures, 34,557 were adults and 18000 were children.

Again, additional review was conducted in 2017 [21] and intimated that 10,074 people passed away due to AIDS progression and other related disease [23]. Among those who died, 2,248 were children between the ages of 0-14 years whilst 7,826 were adults. However, life expectancy and HIV progression to AIDS could be delayed when ART is available for treatment options.

Notwithstanding, the national HIV Prevalence rate in 2018 also proclaimed that the percentage of pregnant women tainted by the virus and attending antenatal clinic were 1.9%, which portrays a decrease of 2.1% in 2017. The regional HIV prevalence from the northern region up to the southern region was 19.7%. Eastern region [23] has the lion's share of the menace, compared to the least infectious rate of 6.0% from the Northern and upper west part of the country.

Finally, Abigail et al (2020) also conducted a regional HIV prevalence study to reveal the spread and impact of the disease on regional basis. As per the study about 334,714 people are currently tainted and residing with the virus, with 19,931 new mortality rate of infection. They lamented further that, Greater Accra Region is recently on the pinnacle of the infection with about 77,132 people tainted by the virus. Hence, as per the number of tainted people, about 28,000 of them are currently adhering to the use of ART whilst 3,000 people have passed on. It was argued that the second most tainted HIV region was Ashanti region, with a peak infectious rate of 75,675. The percentage regional statistics in descending order stands as follows: Greater Accra Region 23.04%, Ashanti Region 22.6%, Eastern Region 20.8%, Western Region 17.6 % Brong Ahafo Region 17%, Upper East Region 10.2%, Volta Region 9.8%, Central Region 9.2%, Northern Region 6.9%, and Upper West Region 6.9%. The prevalence of HIV according to type, also stands as follows: HIV Type one 97.1%, HIV Type two 0.8% and combination of HIV Type one and two 2.1%.

1.4 NOTES ON MATHEMATICAL MODELLING OF HIV

Modelling of epidemic diseases using mathematical concepts has not only broadened our knowledge on HIV over the last decade, but has also provided answers and clues to areas of the pandemic that has not been explored. It has also helped in providing a genuine umbrella for drug induced viral suppression, evolved from a meaningful ART usage. Several researchers have invented stochastic and deterministic models [8, 10], which have imparted positively in curbing down the viral growth of the virus and tremendously improved drug therapy.

It's fair to acknowledge that (ODEs) have been significant in the cross examination of valuable cells, such as tainted and untainted cells. The study takes a look at ODE model which is later transformed to DDE model. Hence, the developed model is schemed of CD4+ T cells, tainted CD4+ T cells and Cytotoxic-T-lymphocytes (CTLs).

Further, the extremes associated with ODE models as eluded by previous researches, were accounted for and modified to include intracellular delay. The inclusion of the delay unit explains the interval essential for a cell to navigate before the propagation of virions.

Therefore per the achievement of the stipulated aim of the study, a non-continuous time delay(τ) is mooted to the formulated model, to mediate for vital components between the period of a contagion and the production of viral particle. Arguably, the incorporation of the time delay (τ) was first initiated by Herz et al. The necessity of this component was further highlighted by Nelson and Perelson. They intimated the essence of intracellular in viral production, when drug efficacy is fragile [124]. In addition, cytotoxic Lymphocytes have been extended to the parameters to account for immunological response. CTLs contribute immensely by attacking and killing infected cells in the blood. The activities of CTL are sparked by CD4+T cells through simulations, which results in the production of antibodies to combat the virus invasion in the blood. However CTL'S are known to have a protein called CD8, which are embedded on their surface. They are able to attach themselves to other molecules as a result of a receptor, which has the capacity of perceiving antigens produced by infected cells. CTL kills infected cells through recognition and perceiving process. The thymuses are sites of production of CTL cells.

The process of mathematical modelling orients on the complexity and evidence of clinical data obtained from patients infected with the Virus; hence due to the ambitions of the study, limited treatment transitions data was used to validate the model.

1.5 RESEARCH AIMS AND OBJECTIVES

This section deals with the questions which arose in the course of the research, as well as the objectives of the study.

1.5.1 RESEARCH QUESTIONS

The study uses the application of delay differential equation, to model low HIV viral load in a country like Ghana. In the course of applying the model, the following questions resulted thereof:

- What effects have strong CTL on low HIV viral load?
- What effects have the delay and non – delay component on viral production?
- What is the role of a delay model on low HIV viral load?
- What effects has Hopf bifurcation on the stability of the model?
- What are the impacts of the model on STI systems?
- What challenges are associated with ODE models and the need to transform them to DDE?

1.5.2 OBJECTIVES OF THE STUDY

In pursuit of the questions arriving from the study and the need to unlock such ideas, the following objectives have resulted thereof:

- To ascertain the effects of delay differential model on low HIV viral haul
- To verify the impact of delay and non-delay component on viral production in the blood
- To verify the conditions for the existence of Hopf bifurcation and the stability of the model

- To apply the adopted model to delve into structured treatment interruptions
- To identify the challenges associated with STI and suggest the way forward
- To address the limitations associated with ODE model
- To transform the ordinary differential model to delay differential model.
- To verify the effects of the reproduction number on the production of virions

1.6 MOTIVATION OF THE STUDY

The introduction of effective ART to HIV patients to eradicate the contagion, has contributed a lot to improving the life expectancy of people diagnosed with the disease. Studies have revealed [9] that, the administration of antiretroviral therapy (ART) in 1996 has approximately added 14.4 million years to people who have contracted the virus. However the unmatchable speed at which recent infections are diagnosed and the speed at which the disease is spreading has culminated an in-depth analysis to the spread of HIV/AID. Hence by this study, delay differential equation is adhered to model low HIV viral load and the adopted model, applied to therapy interruptions. The following have been the epitome, or the motivation for using delay differential equation for the study:

- To find out the impact of ordinary differential equation in modelling low HIV viral load
- To identify the deficiencies associated with the ordinary differential equation model and the need to introduce the delay component
- To find out the effect of a strong cytotoxic- lymphocytes (CTL) on a low HIV viral load
- To verify the influence of infected CD4+TCells, the uninfected CD4+TCells and CTL when the reproductive number is kept constant
- To verify the impact of delay and non-delay on viral production in the blood
- To uphold the existence of Hopf bifurcation and the stability of the model
- To apply the adopted model to delve into structured treatment interruptions

1.7 SIGNIFICANCE OF THE STUDY

Ideally, the study will have direct influence on the following stakeholders:

- A major and key stakeholder such as the government has been battling, to find a lasting remedy to HIV/AIDS which has direct bearing on the productivity of a country. The effect of HIV/AIDS is replicated in all the agencies within a country namely; health, education, services and so on. Therefore the outcome of this study will provide the needed knowledge on treatment options, required to improve life expectancy of the disease. Further the stability of the developed DDE model will be used to design a potential structured treatment interruption for future testing of the disease.

- The use of medication to curtail the virus is essential to HIV tainted individuals; however the virus develops resistance over time to a particular drug type. Therefore, this study has a significant contribution to manufacturers of drugs, by exposing them to knowledge on modifying, continuing or discontinuing a particular drug type due to drug-resistant mutations. Drug manufacturers through the recommendations of the study will now have the luxury of manufacturing drugs, which have the potency to resist mutations from virus. Drugs could then be produced with at least 100% efficacy.

- The results are also key to health personnel's and other health organizations, in designing a potential structured treatment interruption for future testing of HIV/AIDS and a more virulent treatment options to infected individuals

- The infected public could also benefit from a prolonged life expectancy of HIV/AIDS on the recommendations, relating to the design of a proper potential structured treatment interruption, as well as the administration of drugs which are 100% efficient

1.8 STRUCTURE OF THE THESIS

Provisionally, the thesis has been planned and divided into five chapters which are concealed in each other. The chapters are developed to provide the needed information

which is capable of formulating the ordinary differential model, as well as the transformation required for the ODE model to delay differential model. The attained DDE is used for modeling low HIV viral load as well as treatment options.

The chapters are developed in the following order:
Chapter 1 provides an insight into the introduction of the thesis and therefore deals with the background of the study, statement of the problem, Epidemiological trend of HIV in Ghana, the mathematical model capable of modelling low HIV Viral load, objectives of the study, motivation for the study, significance of the study and finally the component of the structure of the thesis.

Chapter 2 explains the general background pertaining to HIV/AIDS, including HIV transmission and how it can be controlled. Further, the chapter also builds up the biological background of the pandemic and how to develop deterministic ODE models and the need to transform it to intracellular delay differential equation

Chapter 3 addresses modelling in terms of in-vivo, in-vitro and in-silico analysis. Again, the chapter talks about the development of Pre-deterministic modelling, single target cell modelling and multiple target model. This is followed by doubling- time and half-life, as well as modelling multiple target cell model with chronic infection and intracellular delay

Chapter 4 is interlocked with the analysis of the model with delay, well posedness and existence of equilibrium points. Further consideration is given to the global stability of equilibrium and the endemic equilibrium. Application and proof of existence of Hopf Bifurcation are simulated by this chapter and hence the numerical simulations of the results are considered for discussion. The chapter finally assesses the repercussions of structured treatment options and the need to adopt a suitable option based on the model.

Chapter 5 deals with the general overview of the study and the summary of findings. The chapter is further interlocked with the future directions to researchers and the conclusion of the study.

CHAPTER 2
INCEPTION AND DEVELOPMENT OF HIV

2.0 INTRODUCTION

This chapter explains the general background pertaining to HIV/AIDS, including HIV transmission and how this can be controlled. Further, the chapter also builds up the biological background of this deadly disease and how to develop deterministic ODE model for further transformation to delay differential equation.

2.1 GENERAL BACKGROUND OF HIV/AIDS

HIV/AIDS can be referenced as early as the year 1920 when the initial infection was mooted through the blood samples of a man from Kinshasa, in the republic of Congo. Genetic analysis revealed that, the initial contact with the virus might have pranged in the late 1940s or 1950's. A similar analysis also revealed the existence of HIV-2 in humans which is less infectious than HIV-1[16, 63].

2.1.1 TRANSMISSION OF HIV-1

Earlier, scientist sourced that HIV-1 emanated from a peculiar blend of Chimpanzee in West Africa to humans. The assertion was that the Chimpanzee version of SIV was ushered to humans in the form of HIV-1, through blood affiliation, when those chimpanzees were hunted for meat (bush meat trading). Through the advancement of blood affiliation, the virus was propagated to Africa and the entire world at large. Scientist came with a generalized conclusion based on their findings that HIV-1 emanated from Chimpanzees. Secondly blood affiliation between chimps and humans articulated the transfer of the virus to humans. HIV and SIV share similar characteristics, therefore both diseases attack the immune systems of human beings, monkeys and apes respectively. HIV and SIV are both a lentivirus which attacks the immune system of human beings, apes and monkeys respectively.

2.1.2 TRANSMISSION OF HIV-2

It is remarkable to articulate that HIV-2 was transmitted to humans through SIV in sooty mangabey, associated in monkeys rather than chimpanzees. The initial contagion of HIV-2 to humans was activated by the same process, which initiated the contagion of HIV-1. Interestingly HIV-1 is more dangerous and highly contagious compared to HIV-2, however HIV-2 is commonly associated with people residing in countries such as West Africa, particularly in Mali, Nigeria and Sierra Leone.

Further, it is worth noting that the two different strains of SIV from monkeys and apes, as discussed above merged to reproduce a third virus called SIVcpz. This third discovered virus was also transferred to humans through direct blood affiliation, which emanated from the killing and eating of the Chimpanzee.

Genetically there exist four main types or groups of strains such as M, N, O and P, with slight differences in their composition. It's worth noting that the virus replicates in different strains in humans, hence making it arduous to combat the disease. The virus has the propensity to produce different types of strains of HIV-1 in an individual. The main types or groups of strains are further broken down into a number of sub-groups [36]. Arguably 90% of HIV-1 infection is attributed to the M strain of the virus, which has further division of strains such as A, B, C, D, F, G, H, J and K (http://en.wikipedia.org/wiki/File. :HIV-1 subtype prevalence 2002.). Realistically each strain of the virus is basically associated to a specific geographical area. It is hoped that the knowledge relating to the strains and the geographical areas, will enhance planning of successful treatment options. It is however relevant to reverence the necessity of a cross-subtype contagion, which enhances the advancement of a fresh breed of virus [15]. The production of new breed of viruses as a result of cross contagion between viral strains is referenced as CRFs (circulating recombinant forms). CRF's has pivoted the combat of the virus to an arduous level, due to its ability to propagate several viral strains which are resistive to treatment options. This explains why many treatment options have failed in the pass and hence the need to integrate two or more ARV's to combat the disease [37]. Therefore the success to any treatment option is linked with the knowledge about the viral haul, as well as the type of viral strain responsible for the

contagion. Ideally as per the above assertion, it’s essential to promote suitable and accessible HIV testing to all the people residing in a particular locality. This implies that for any successful treatment option and the combat of viral mutation, individuals should be encouraged to ascertain their viral haul and strain as well.

Finally as per the above discovery, it is suggested [30, 38] that HIV-1 evolved from primates. It is confided that the Sooty Mangabey monkey resident in sub- Saharan Africa, is responsible for the transmission of HIV-1. The inception of the virus is attributed to the trade-off between humans and monkeys, when such monkeys were killed and hunted for as food [30, 39]. On the other hand, Primates are host to SIV, yet they are able to impede the spread of the virus. This is due to its robust immunity which impedes the intercession of the virus as per humans which leads to AIDS [40]. The mechanism associated with the robustness of the immunity of primates and for that matter moneys, could be associated with the long term persistence of their immune system [30]. This special attributes of primates immune system cannot be said of humans, who advances to AIDS in the course of time and death finally.

2.2 BIOLOGICAL BACKGROUND OF HIV AIDS

Basically AIDS is an ailment portrayed by the dynamic weakening of a patient's resistive framework. This immunological weakness permits irresistible viruses, in the form of bacteria and parasites to attack the body and engender their kind rapidly. The occurrences of specific tumors are significant on HIV tainted patients, as a result of the weakened resistive framework. Therefore the contagion propagates death in the soonest of time.

The thump against the HIV plague has brought forth logical and exceptional methodologies relevant to combat the disease or suppress it amicably. The zeal to suppress the contagion has articulated a blend of clinical research, atomic science, immunology and mathematical sciences to combat the disease. Essentially, the virus has an exceptionally high transformation rate, which enables the virus to produce

several strains within the shortest possible time. This high change rate permits HIV to effectively develop protection from drugs and hence very arduous to stimulate an antidote for the disease. The tenacity of the virus in the human body is also attributed to its ability to adhere to latency for a period of time, before initiating an infection. In this way, the advancement of medications and antibodies depends not just on information on the arduous life pattern of the virus, but also understanding the complicated resistive system of the body. Ideally so, HIV suppressing requires more than the advancement of medications and antibodies, but a better understanding of the virus, in order to inhibit the production of different strains of viruses within an individual.

2.2.1 THE IMMUNE SYSTEM

Essentially, the human body has the ability to initiate both vague and explicit means of militating against the virus, hence understanding the different segments of the human resistive framework is vital to the thump against HIV. Vague defence system in the body functions rapidly and unpredictably to eliminate organisms in the body. Some of the vague defence systems in the body include the following: bodily fluid, gastric juice hairs, and cilia in the respiratory tract etc. This vague defence system sincerely prevents the entry of harmful organisms into the body.

The human body has been programmed to respond voluntarily to the occurrence of certain complex situations, such as initiation of fever and inflammation to seduce pathogens in the body. Noticeable among the vague defence system is the phagocytes, a specific kind of leukocyte (white platelet), which has the ability to circulate and destroy different viruses as well as residue and dust. In the event where the phagocytes are breached and penetrated, the leukocytes mount coordinated protections against the explicit intruders.

Conversely, an unsuccessful attack by the Lymphocytes triggers a further back up for the entire process. In the process of activating a successful response to the viral attack,

the B cell of lymphocytes develops into counter acting agent which terminates the intruder. Similarly, T cells also incorporate some amount of safety by legitimately eliminating tainted cells. The remaining T cells functions administratively by discharging signals worthy of invigorating the blood to function efficiently in the defence process. Unfortunately HIV specially contaminates one of the administrative functions of the T cells, specifically the T helper cells and subverts the body's resistive frame work prompting AIDS.

2.2.2 THE CENTRAL ROLE OF HELPER T CELL

It's worth noting that the organization and defensive mechanism of the body's resistive system are harmonized by the T helper cells. They discharge chemical information called (cytokines), which activates the vague resistive system of the body to proceed with reinforcement and support for the other cells. Basically Helper T cells coordinate the entire activities of the body's resistive system. Therefore they are termed as directors of the body's resistive system. Additionally they are also known as the "officers" of the body's resistive framework, because of their organizational role.

They are also responsible for organizing the other cells in the blood to fight and defend the body whenever a virus invades (figure 2.1). In the event of an invasion by a foreign particle, it is the sole responsibility of the T helper cells, to call upon other cells such as B cells, cytotoxic T cells, and other helper T cells to wrestle against such attacking pathogens (figure 2.1). Figure 2.1 depicts a specialized Macrophage cell which shows, the B cells, Helper T cells, plasma cells, macrophage, cytokines and the cytotoxic T cells.

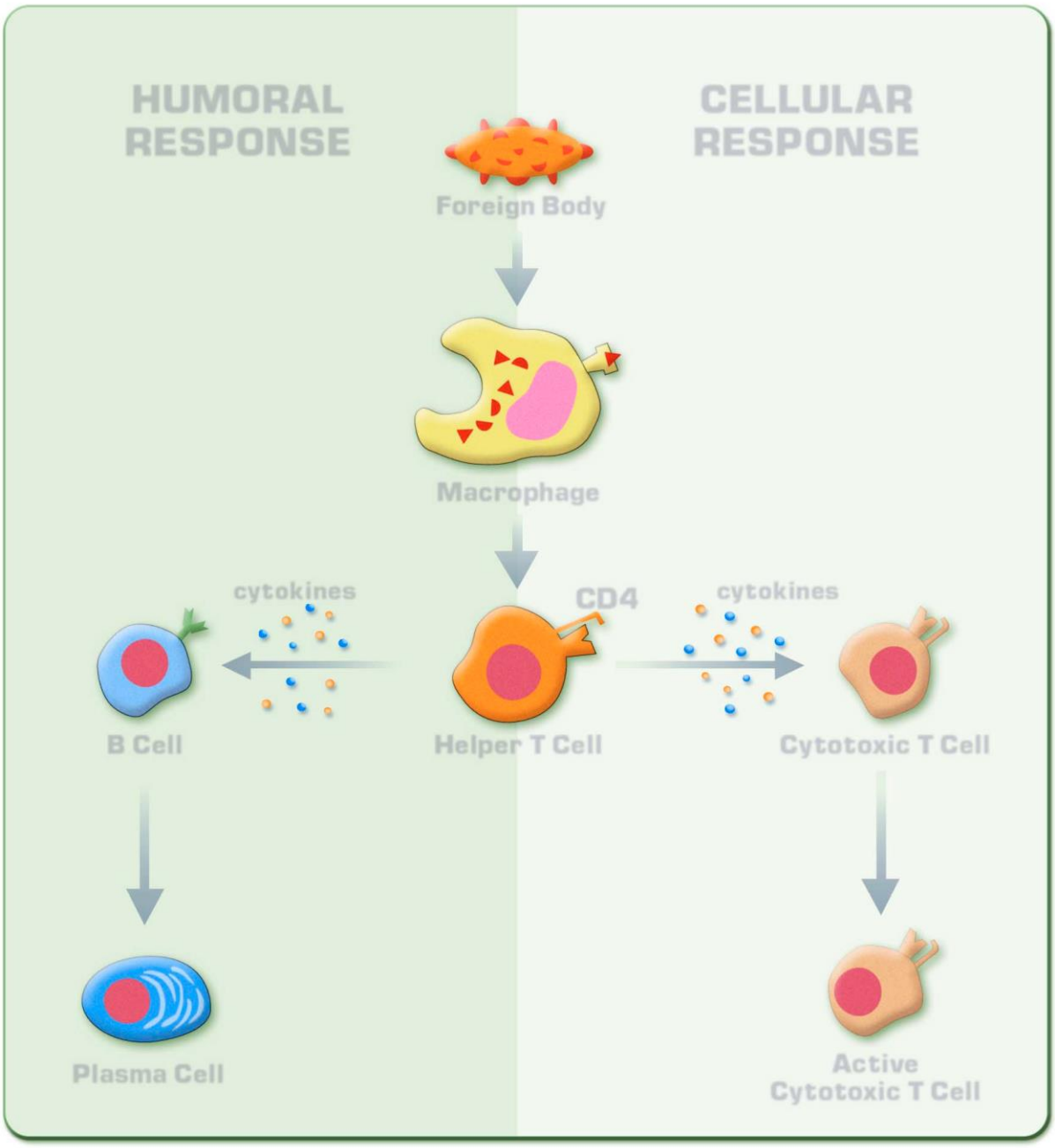

Fig 2.1 (Specialized Macrophage cell which ingest foreign antigens invading the host cell)

As per figure 2.1 above, when the cell's defence system is breached by the entrance of a virus, Macrophage cells articulate the information immediately to the T Helper cells to action it. Macrophage cell is a phagocytic cell, hence is able to encircle the unwanted bacteria, or virus, which has had entrance to the cell and destroys it completely.

Implanted inside the macrophage cell layer, is a particle created by the blood cells called human leukocyte antigen (HLA) complex. The HLA functions by assisting the Helper cells and antigen to be attached to it. However, Helper T cells which have receptors are able to link up with the antigen and get attached to the macrophage. When the cells are bounded together, the helper T cells multiply and advance to a clone of cells, equipped for perceiving a similar antigen. Again with reference to figure 2.1, the obtained T clone cells are known as the commanders of the cell, due to their specified roles. The T Clone cells function by producing chemical signals which instigate the cells to embattle any unwanted particle in the blood.

Additionally, T cells supports the body's defence system by invigorating cytotoxic T cells (TC), to eradicate cells that have been tainted by the HIV virus. Hence, there are antigens on the surface of the cell; which repairs the surface discarded by the tainted cells. The antigens are explicit to the culpable specialist, and hence link the receptors in the layers of the particular TC cell.

Moreover, TC cell attaches itself to the MHC atom from the outside of the tainted cell. Hence when TC cells are is limited by the antigen outside the HLA particle, the cytotoxic T cell releases a substance called "perforin," which wrecks the culpable cell (figure 2.2). The helper T cell likewise animates the creation of antibodies and also produces clues which invigorate the creation of B cells. The created B cells separate into plasma cells and the plasma cells are platforms responsible for the creation of antibodies. The antibodies are used to explicitly combat pathogens flowing in the blood or lymph. Antibodies work by hindering the receptors that permit pathogens to be connected to target cells, or by making holes on microscopic organisms. The sole duty of phagocytes is to encircle viruses and hence eliminated them. The phagocytes promptly encircle the invaded microbes in the blood. They are strengthened by the presence of opsonins, which are produced from jointed antibodies.

Further, it also advocated that antibodies [18] could activate a course of biochemical responses, which destroys the membrane of any invading cell. Therefore the

significance of the human resistive system depends on the helper T cells. A healthy T cells leads to the formation of a strong immune system and a tainted T cell, destroys the immune system completely. Surprisingly HIV targets the T cells and renders it useless, resulting to a low viral haul. Therefore, the advancement of HIV contagion disintegrates both arms of the T cells and AIDS intercedes.

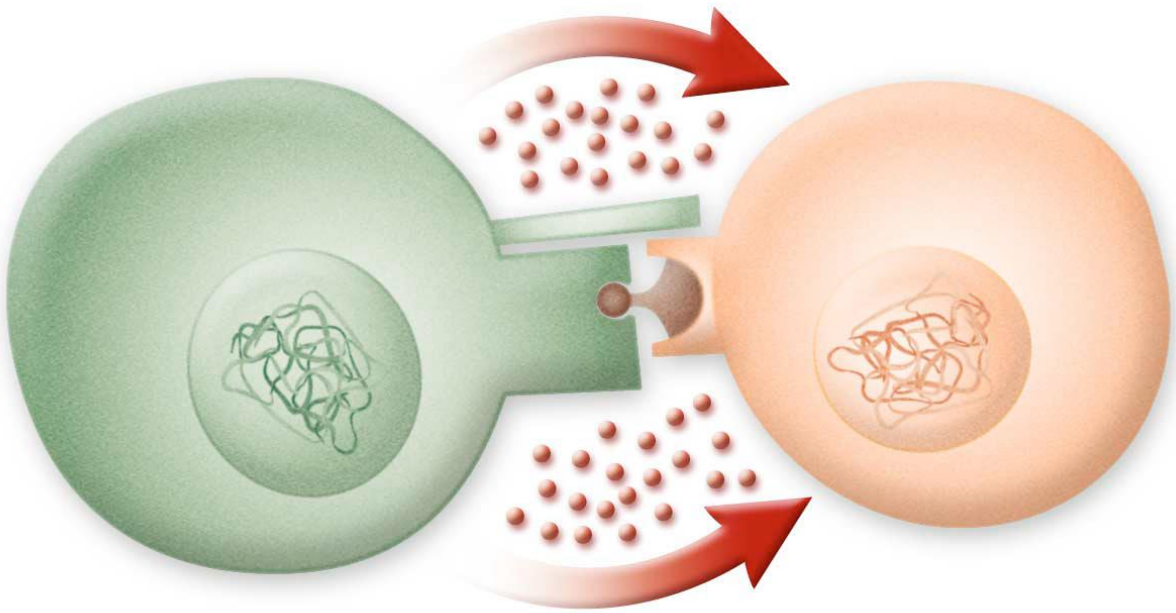

Fig 2.2 (Binding of antigens and Macrophage molecule which initiates secretion of lytic cells)

2.2.3 THE STRUCTURE AND LIFE CYCLE OF HIV

Comparatively, HIV like most viruses is very minute, unadorned organism which cannot reproduce unaided. It remains the most deadly disease which has ever hit the planet since the last three decades. The spread of HIV has been very explosive and

mercilessly on human population, tainting over 60 million people, with almost half of the human population suffering from AIDS related illnesses and death finally. Therefore a comprehension of the structure and life pattern of the contagion is critical in planning viable treatment systems. HIV is encompassed RNA infection which propagates from the host cell during replication. The replicate develops phospholipid envelope which has peg-like structures and allows the viral RNA to code itself. The pegs comprises of three or four glycoproteins (gp41 stem), which are embedded with three or four glycoproteins (gp120). Again within the envelope is the shot molded nucleocapsid which is manufactured from protein and encircled by two single strands of RNA. (Fig 2.3).

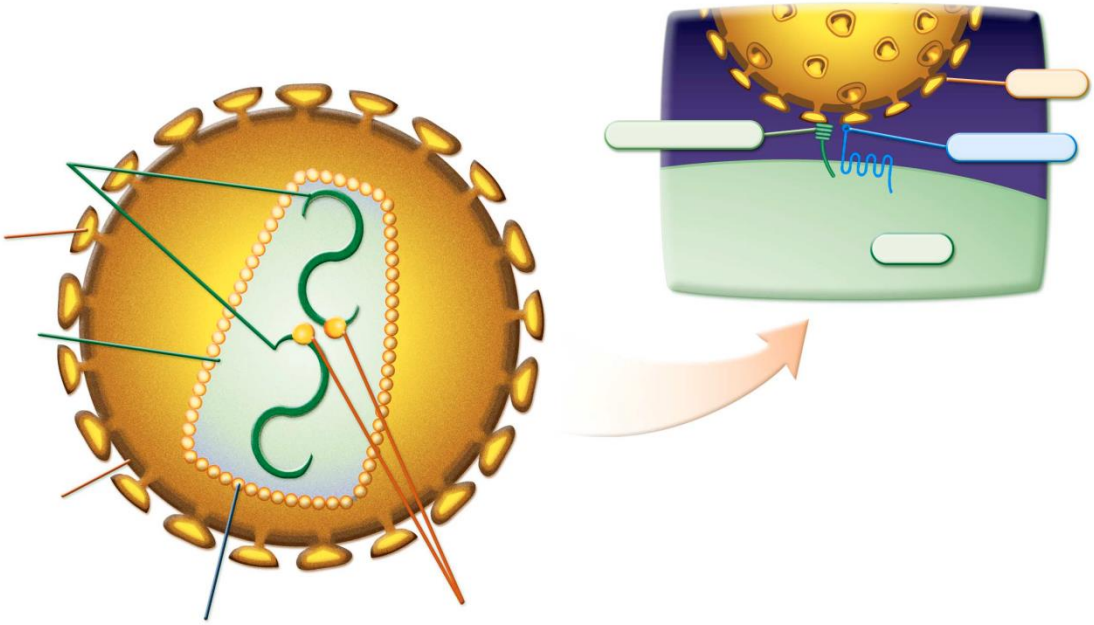

Figure 2.3 (Binding of HIV to the host cell using Gp20 of the virus to the CD4+T cells)

In spite of the fact that helper T cells appear to be the principal focus for HIV, different cells can get tainted too. Other cells which could get tainted include monocytes and macrophages which can hold huge quantities of infections within and without being destroyed. It is ascertained that some T cells harbors comparative repositories of

infections, which lie latent for a long period of time. The latent viruses are rekindled when the pool of virus has been eradicated by therapy. Since viruses are particles and only requires a host cell to become active, it takes support from one of the gp120 atoms in order to taint the CD4 particles on the host cell's surface.

However, for the virus to attach itself to the host cell, it requires two processes to get itself attached to the host cell. In the initial stages it adheres to CCR5 which is a chemokine receptor and provides support for the virus within the initial stages of the contagion. The virus finally gets the second support from chemokine receptor (CXCR4) during the later phase of the infection. Therefore during the asymptomatic stage of the infection, latent virus rekindles the infection on the macrophages and taints them amicably. This explains why a tainted individual appears to be healthy in the symptomatic stage of the infection. The signal for the contamination of the virus is not visible and hence integrates in numbers. This unseen process eventually destroys the human resistive system and integrates to AIDS in the course of time.

HIV has a novel life cycle and belongs to the group of retroviruses (fig. 2.4). When HIV ties to a host cell, the viral envelope wires with the cell layer, and the infection's RNA and chemicals enter the cytoplasm of the host cell. The virus activates its infection by making use of its reverse transcriptase which is a single stranded RNA. The single stranded RNA is used as a tool to duplicate the two folded DNA of the host cell. The chemical integrase in the RNA encourages the reconciliation of the viral DNA with the host cell’s chromosome. The virus’s DNA called Provirus is repeated alongside the chromosome of the host cell when the cell isolates. The coordination of provirus into the host DNA empowers the virus to replicate the host cell successfully. Therefore viral protein is created when the provirus is translated as per the successful replication of the virus. Viral proteins are then collected and this time, the virus utilizes the host cell's protein copy for the production of its kind. The virus's protease then articulates the manufacture of proteins by converting polypeptides to proteins and hence propagates the proteins into viral particles.

As per the above, the life cycle of the virus reaches its fruition stage; hence the virus inevitably buds out of the cell and starts a new contagion. Many viral particles continue to bud out of the tainted cell through its life span until the tainted cell is completely destroyed. Further, it should be noted that a tainted cell continues to be a host and a hide out for the virus once it has been budded by the RNA of the virus (figure 2.4). Figure 2.4 depicts how the virus binds with the host cell, fuses its self to the host cell's chromosome and propagates out of the host cell, to begin new infections.

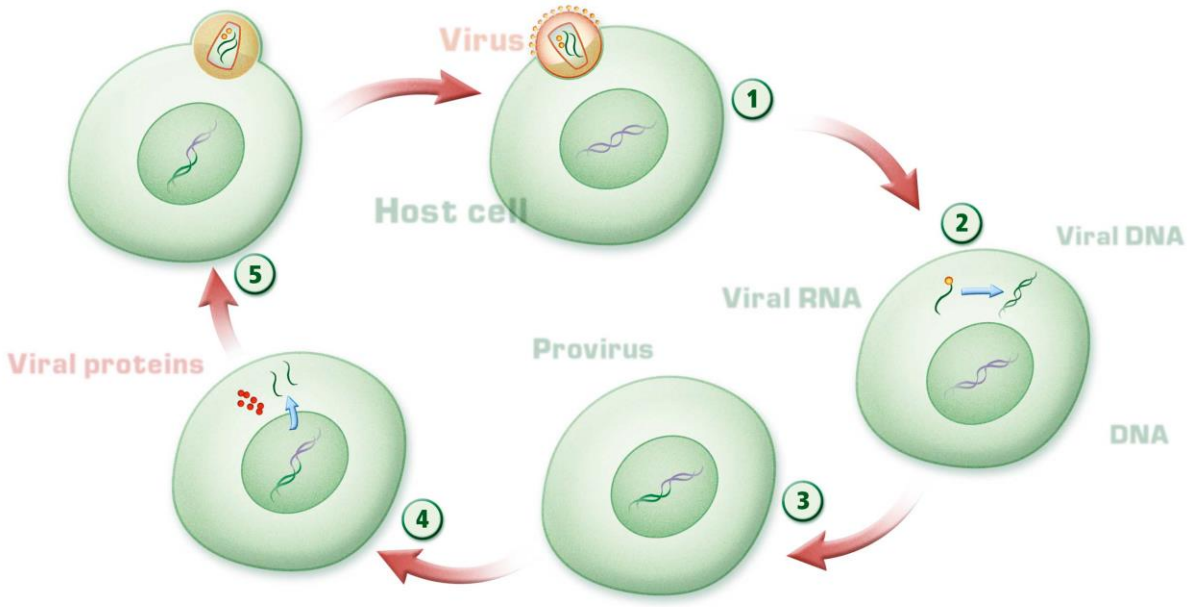

Figure 2.4 (Binding and budding of viral particle from a host cell)

As per figure 2.4, the following are the processes which take place in the binding and budding of a viral particle on a host cell:

Stage 1: The viral RNA and reverse transcriptase proceed to the cytoplasm of the host cell as per the budding of the virus and the host cell.

Stage 2: Reverse transcriptase mediates the process of integrating the viral RNA to the host cell's DNA

Stage 3: The budding process of the Viral DNA to the host cell yields a provirus

Stage 4: Transcription and translation process

Stage 5: Final stage which supports the budding out of the viral particle from the host cell

2.2.4 THE TRANSMISSION OF HIV

HIV is propagated primarily via several forms, but noticeable among the forms of transmission include sexual contact, blood and its product and maternal transmission during birth. Per the above mentioned, includes homosexuals who contribute significantly to the spread of the virus, as they disregard all precautionary measures related to their safety. In addition to homosexuals, lie drug users who are extensive contributors to the spread of the virus. It is of value to note that some of the drugs utilized by drug users cannot be assimilated directly, hence the need to inject the drug through a needle into the body.

Further, it is revealed [18, 19] that about 13% to 35% of tainted pregnant women are likely to pass on the disease to their infants. The transmission of the virus is articulated in the uterus and effected during birth. In addition, Breast milk from such tainted mothers also enhances the spread of the virus.

Finally, it is worth to note that the saliva of an HIV tainted individual contains little amount of the virus, however is not possible for kissing to instigate the spread of the virus. Again handshakes and mosquito bites do not contribute to the spread of the virus.

2.2.5 PROGRESSION OF HIV INFECTION

Realistically HIV has a long latency stage where the virus advances to AIDS. The period between the initial contamination and the inception of AIDS is between eight to ten years on the average. The time frame for HIV inception could be more or less depending on the immune system of the individual concerned. Consider the basketball player Magic Johnson who happens to be moderately sound, twelve years after he was reported of the virus. However not all tainted individuals or cases shows such a long time frame, whilst some tainted individuals spend less amount of years before the inception of AIDS.

Basically the inception of AIDS or the spread at which the ailment advances is influenced by numerous components, such as hereditary or underlying conditions of the individual. A critical study of the nature of HIV by the Center for Disease Control and Prevention (CDC) has recognized phases for HIV contamination. The phases are based on the symptoms one exhibit, when tainted by the virus in the initial stages. The categories are A, B, and C and are vital, since it is sometimes arduous to visualize some of the symptoms in a tainted individual. A look at individuals specified in category (A), reveals mononucleosis-like ailment such as cerebral pain, muscle hurt, sore throat, fever, swollen lymph nodes and headache. However a real and reliable confirmation to this deadly ailment is through blood test, since most of the people in this category are asymptomatic within the first three weeks of the contagion.

However, irrespective of each stage or classification of the symptoms, the inception of AIDS is projected by the development of a rash. Even though the occurrence of rash may help separate this disease from other different contaminations, it may not be applicable for all HIV tainted people.

2.3 DEVELOPMENT OF DETERMINISTIC ODE MODELS AND TRANSFORMATION

Modelling of epidemic diseases using mathematical concepts has not only broadened our knowledge on HIV over the last decade, but has also provided answers and clues to areas of the pandemic that has not been explored. It has also helped in crafting reliable treatment options, which has been helpful to HIV tainted individuals. Several researchers [27, 36] have invented stochastic and deterministic models, which have imparted positively to the control of the virus and slowing down the inception of AIDS. Again such models have broadened the knowledge based of the effects of the virus on therapy options [24, 25].

Ideally most of the deterministic models use Ordinary Differential Equations (ODE) to specify variations aligned with key cells of the model, such as target cells, tainted cells and virus level. The use of ODE models by previous researchers has been modified due to recommendations to include intracellular delay [135]. The inclusion of the delay component explains the duration specified for a cell to become tainted and produces virions. The inclusion of the delay component yields DDE, which has been activated for the study.

The rationale behind the study is to model low HIV viral haul of an infected state, using delay differential equation and hence use the resulting equation on therapy interruptions. Therefore, the developed model will be used to ascertain when a specified therapy [162] should be modified, continued or stopped and under what circumstances. Notwithstanding, the adopted model will further be adhered to structured treatment interruptions (STIs) and adoption for compliance.

The process of mathematical modelling is the art of articulating abstract situations [151,152, 153], such as HIV infection rate to real and marginable situation. Therefore in an attempt to marginalize the reality of the developed model, an STI data is used. The STI data generally occurs infrequently. Finally the validly and efficacy of the developed model is activated fully by applying it to treatment interruptions [34]

2.3.1 ORDINARY DIFFERENTIAL EQUATION (ODE)

In accordance with the development of a differential equation which is later transformed to a delay model, an ODE model is first formed from routine and restricted HIV data [42, 137]. The model is defined to include CD4+ T cells, tainted CD4+ T cells and Cytotoxic-T-lymphocytes cells (CTLs). Further, T, V and C are outlined respectively as the population compactness of CD4+ T cells, tainted CD4+ T cells and CTLs respectively at time (t).

First we express the population parameters T, V and C as a system of ordinary differential equation with respect to time as shown below:

$$\frac{dT}{dt} = \delta_1 - \delta_2 VT - \delta_3 T$$
$$\frac{dV}{dt} = \delta_4 VT - \delta_5 V - \delta_6 VC$$
$$\frac{dC}{dt} = \delta_7 V - \delta_8 C \qquad (2.1)$$

From equation (2..1), δ_1 represents the output rate of CD4+ T cells, (δ_2), represents the death rate of CD4+Tcells due to the contagion, (δ_3), represents the normal death rate of CD4+ T cells, (δ_4), represents the output rate of the virus, (δ_5), represents the death rate of a virus, (δ_7) represents the carbon copy of CTL, (δ_8) represents the natural death of CTLs, whilst $\delta_6 VC$ represents the reduction of the infective virus.

Now consider the introduction of new parameters and new variables to equation 2.1, where:

$a_1 = \delta_3, \quad a_2 = \delta_5, \; a_3 = \frac{\delta_1 \delta_4}{\delta_3 \delta_5}, \quad a_4 = \frac{\delta_3 \delta_6 \delta_7}{\delta_2 \delta_8}, \quad a_5 = \delta_8$ and

$$x = \frac{\delta_3}{\delta_1} T, \quad y = \frac{\delta_2}{\delta_3} V, \quad z = \frac{\delta_2 \delta_8}{\delta_3 \delta_7} \qquad (2.2)$$

The parameters $a_1 \; and \; a_4$, denotes the fundamental reproductive ratio and the death rate of the virus respectively. Therefore writing the equations in terms of x, y, and z where CD4+T-cell is symbolized as (x), tainted HIV cell symbolized as (y) and CTL, symbolized as (z). The equation can be written as follows:

$$\frac{dx}{dt} = a_1(1 - xy - x)$$

$$\frac{dy}{dt} = a_2(a_3xy - y) - a_4yz \qquad (2.3)$$
$$\frac{dz}{dt} = a_5(y - z)$$

We now define three non-linear functions as follows:

$$f(x,y,z) = a_1(1 - xy - x), \quad g(x,y,z) = a_2(a_3xy - y) - a_4yz, \quad h(x,y,z) = a_2(y - z) \qquad (2.4)$$

The three non-linear functions above are differentiated to produce equation (2.5) below:

$$\frac{dx}{dt} = f(x,y,z), \quad \frac{dy}{dt} = g(x,y,z), \quad \frac{dz}{dt} = h(x,y,z) \qquad (2.5)$$

We further define a point $(\overline{x}, \overline{y}, \bar{z})$ for equation (2.5) and initialize it as follows:

$$f(\overline{x}, \overline{y}, \overline{z}) = 0, \quad g(\overline{x}, \overline{y}, \bar{z}) = 0, \quad h(\overline{x}, \overline{y}, \bar{z}) = 0 \qquad (2.6)$$

Proposition 2.1

Now, if we expound the parameters a_2, a_3, a_4 from equation 2.3, as $a_2, a_3, a_4 > 0$ then, the following holds:

(i) if $a_3 \leq 1$, a non-negativity steady state exist for equation (2.3), where $(\bar{x}_o, \bar{y}_o, \bar{z}_o) = (1,0,0)$ (2.7)

(ii) if $a_3 > 1$, then the non-negativity steady state for equation (2.3) is the same as in equation (2.4). Hence the steady state is expounded as

$$(\overline{x}, \overline{y}, \overline{z}) = \left(\frac{1}{Z^*+1}, Z^*Z^*\right) \qquad (2.8)$$

Where $Z^* = -\frac{1}{2}\left(1 + \frac{a_2}{a_3}\right) + \frac{1}{2}\sqrt{\left(1 + \frac{a_2}{a_4}\right)^2 + 4\frac{a_{2\,(a_3-1)}}{a_4}}$ (2.9)

Further we expound a point near to the constant steady state and let $x = \overline{x} + X$,

$$y = \overline{y} + Y \qquad and \;\; z = \bar{Z} + Z$$

We expand the functions in terms of f, g and h and applies the Taylor Series technique about the point $(\overline{x}, \overline{y}, \bar{z})$. We then adheres to the linear terms only and we obtain

$$\begin{bmatrix} \frac{dX}{dt} \\ \frac{dY}{dt} \\ \frac{dZ}{dt} \end{bmatrix} = A \begin{bmatrix} X \\ Y \\ Z \end{bmatrix} \tag{2.10}$$

From equation 2.10, (A) represents the Jacobian matrix evaluated at $(\overline{x}, \overline{y}, \overline{z})$. Hence matrix (A) is defined as

$$A = \begin{bmatrix} -a_1(\bar{y}+1) & -a_1\bar{x} & 0 \\ a_2 a_3 \bar{y} & a_2(a_3\bar{x}-1) & -\ a_4\bar{y} \\ 0 & a_5 & -a_5 \end{bmatrix} \tag{2.11}$$

The stability of the developed model is further studied using eigenvalues from matrix (A) in equation (2.10). It was noted that the constant state of equation 2.10 is stationary, when no eigenvalue has positive real part. On the other hand if the entire eigenvalues have negative real part, then the determinant A$\neq 0$

Proposition 2.2

(I) Suppose $a_1,\ a_2, a_3\ > 0$, then the constant state of equation (2.10) and the linear system of equation (2.3) is asymptotically stable. On the other hand if $a_3\ < 1$, then equation 2.3 is asymptotically unstable.

(II) Further, if $a_1, a_2, a_4, a_5 > 0$ and $a_3\ > 1,$ then the constant state of equation (2.10) and the linear system of equation (2.6) is asymptotically stable.

Proof of Proposition 2.2

We expound the characteristic equation of the Jacobian matrix (A) in equation (2.10) as:

$$U_o(\lambda) = \lambda^3 + (b_1 + d_1)\lambda^3 + b_3 + d_3 = 0 \tag{2.12}$$

Where

$$b_1 = a_1(1+\bar{y}) + a_2 + a_5 + a_4\bar{z},$$
$$b_2 = a_1(1+\bar{y})(a_2 + a_5 + a_4\bar{z}) + a_5\big(a_2 + a_4(\bar{y}+\bar{z})\big),$$
$$b_3 = a_1a_5(1+\bar{y})(a_2 + a_4(\bar{y}+\bar{z})),$$
$$d_1 = -a_2a_3\bar{x},$$
$$d_2 = -a_2a_3(a_1+a_5)\bar{x},$$
$$d_3 = -a_1a_2a_3a_5\bar{x} \qquad (2.13)$$

Next we substitute the steady state equation of equation (2.11) into equation (2.12), and obtain the criterion equation given by:

$$(\lambda + a_1)\,(\lambda + a_1(1-a_3))(\lambda + a_5) = 0 \qquad (2.14)$$

Hence the eigenvalues of the Jacobian Matrix A, can now be written as $\lambda_1 = -a_1 < 0$, $\lambda_2 = -a_5 < 0$. and $\lambda_3 = -a_2(1-a_3)$. Again if $a_3 < 1$ and $\lambda_3 < 0$, then the constant state of equation (2.5) is asymptotically stable. Conversely, if $a_3 > 1$ and $\lambda_3 > 0$, then equation 2.8 is unstable.

Further, if from proposition 2.2, $a_3 > 1$, then the constant state of equation (2.6) exist at $z^* > 0$. It follows that by the Routh – Hurwitz criterion, all the roots of the characteristics equation in (2.12) have negative real part if and only if

$$b_1 + d_1 > 0, \quad b_3 + d_3 > 0, \quad (b_1 + d_1)(b_2 + d_2) - (b_3 + d_3) > 0 \qquad (2.15)$$

Hence, we verify equation (2.1), by substituting equation (2.8) into equation (2.12) and obtain the equations below:

$$b_1 + d_1 = a_2 + a_5 + a_1(1+z^*) - \frac{a_2a_3}{1+z^*} + a_4z^*,$$
$$b_3 + d_3 = a_1a_5(1+z^*)(a_2 + 2a_4z^*) - \frac{a_1a_2\,a_3a_5}{1+z^*},$$

where

$$\beta = -a_1 a_5(1+z^*)(a_2+2a_4z^*) + \frac{a_1a_2\,a_3a_5}{1+z^*} + \left[a_2 + a_5 + a_1(1+z^*) - \frac{a_2a_3}{1+z^*} + a_4z^*\right] \times$$
$$\left[a_5(a_2+2a_4z^*) - \frac{a_2\,a_3(a_1+a_5}{1+z^*} + a_1(a_2+a_5+a_4z^*)(1+z^*\right] \quad (2.16)$$

Further, from equation (2.5) we write a_2 and a_3 as:

$$a_2a_3 = a_4(z^*)^2 + a_4z^* + a_2z^* + a_2 \quad (2.17)$$

Substituting equation (2.13) into equation (2.12) and simplifying all the parameters, we obtain

$$b_1 + d_1 = a_1(1+z^*) + a_{5,} \qquad b_3 + d_3 + z^*a_1a_5(a_2 + a_4(1+2z^*))$$

Whilst

$$\beta = a_1{a_5}^2(1+z^*) + a_4{a_5}^2z^* + {a_1}^2(1+z^*)(a_2z^* + a_4(z^*)^2 + a_5(1+z^*)) \quad (2.18)$$

Hence, in accordance with proposition 2.2, we conclude that equation (2.12) satisfies the conditions of proposition 2.2 and therefore asymptotically stable.

Further, from the above deductions, patients with strong CTL will have a higher stable state and low viral haul. This indicates that patients with low CTL will demonstrate a higher rate of viral infection. Conditions in proposition 2.1 are satisfied by maintaining the physical parameters such as $\delta_1, \delta_{3,}\ \delta_4, \delta_5, a_3 > 1\ \ and\ a_3 < 1$. Hence, when $a_3 > 1$, intimates a successful infection by the virus. Therefore the uninfected steady state in equation (2.5) relinquishes its stability, whilst the tainted steady state in equation (2.7) becomes stable.

2.4 SUMMARY

The focus of the chapter has been on three main basic sections, such as the background pertaining to HIV/ AIDS, biological background of the deadly disease and how to develop deterministic ODE models for further transformation to intracellular delay differential equation. The history of HIV has been referenced as early as 1920,

when HIV-1 in humans, was discovered through the blood samples of a man from Kinshasa, in the democratic republic of Congo. Genetic analysis further revealed the existence of HIV-2 in humans, which is less infectious than HIV-1

The biological background has provided an insight on how the virus evades the human resistive system reliably. The query still remains on how, a particular virus is able to produce so many strains in a tainted individual.

Currently chapter three, been the next chapter is aligned with the modelling of in vivo, in vitro and in silico analysis. Further, the chapter is incorporated with, within host deterministic modelling of HIV continual and pointer to modelling of intracellular delay.

CHAPTER 3

SCIENTIFIC MODELLING OF HIV

3.0 INTRODUCTION

Refreshingly chapter two has been a pointer to the background pertaining to HIV/ AIDS, biological background of the deadly disease and how to develop deterministic ODE models for further transformation to delay differential equation. Currently chapter three is aligned with the modelling of in vivo, in vitro and in silico analysis. The chapter further deals with, within host deterministic modelling of HIV/AIDS continual and modelling of intracellular delay.

3.1.1 MODELLING IN TERMS OF IN VIVO ANALYSIS

This type of analysis involves a careful study of an organism in its natural environment, hence application of in-vivo analysis to HIV/AIDS in the case of human, requires clinical trials [43, 48, 101]. A controlled group is carefully pursued and monitored and may sometimes be fruitful or unfruitful due to treatment interruption. This is because, a particular STI regime could be stopped earlier, when the trials are unsuccessful [18, 19]. Several approaches have been devised in monitoring or studying this menace and male circumcision [26, 27, 28], has been momentous in minimizing the spread of HIV. The use of animals such as infected SIV macaque monkey as proxy, instead of humans has been insightful in providing useful information to scientist about HIV advancement. This is because HIV belongs to a family of virus which cannot propagate on their own [14, 48, 63], yet remains very virulent inside a host cell. A lot of viruses belong to the family of HIV and possess similar species characteristics. Scientists are therefore able to track a number of hosts in discovering HIV vaccine [29, 30]. Notwithstanding, clinical trials with humans are still considered as authentic, due to the slight difference between HIV and SIV. However, the chimeric mice have proven to be a good proxy for human, since it demonstrates similar cell characteristics and can be infected with HIV as well. Further, they are easy to produce in large quantities and have cells which resemble the complex human immune system, compared to using a costly infected chimpanzee as proxy [25].

It is however noted that the slow infection rate of HIV requires a longer amount of time in obtaining results. The earliest rate of obtaining HIV results is associated with feline immunodeficiency virus (FIV), an 'HIV-like sickness' which takes 6 to 8 years before the tainted individual dies. This contagion is similar to HIV progression, especially when the progression occurs in the soonest of time [26,154,155, 156, 157]. The in-vivo approach of modelling HIV is credited for the development and testing of new drugs.

3.1.2 MODELLING IN TERMS OF IN VITRO ANALYSIS

This method of modelling, in terms of in vitro analysis has been the pointer and success to the recognition of HIV. It requires scientist to obtain information, or data outside the defined environment of the organism under consideration. This modelling revolves around molecular biology but unfortunately, results obtained by this type of analysis are less accurate due to inexact cellular conditions for organisms. [28].

3.1.3 MODELLING IN TERMS OF IN SILICO

In the quest of discovering a vaccine for HIV by scientist [29, 30, 72], scientist have applied several approaches and modelling techniques, and the chief among such, is the in vivo and in vitro analysis. However, in-vivo and in-vitro analysis require mathematical simulations to integrate the pieces of information procured from such analysis or modelling. The use of computer simulations in such biological experiments is called in silico analysis. This scientific approach [39] intimates that mathematical models are platforms, for most computer simulations and hence fruitful through scientific interactions.

3.2. REVIEW OF PRE- DETERMINISTIC MODELLING

Modelling epidemic diseases using mathematical concepts has not only broadened our knowledge on HIV over the last decade [1, 2, 3, 4, 5, 6], but has also provided answers

and clues to areas of the pandemic that has not been explored. Several researchers have invented stochastic and deterministic models, which have imparted positively to the control of the virus and also tremendously on drug therapy [24, 25]. Over the years most scientist have resulted to the top down deterministic approach [42, 137], which has yielded successful results. Therefore application of mathematical concepts to epidemic disease has been progressive, from single-target-cell models to multi-target-cell models [40, 53, 54, 64, 65, 66].

Reibnegger et al. were among the early scientist who focused their discoveries on the immune system. According to Reibnegger et al. infected cells are progressively depleted in the passage of time leading to AIDS eventually. This is supported by Perelson et al. who initiated a categorized DDE model with various CD4+T cells. His compartment or population was embodied with Virgin cells, active cells and memory cells, which interacts with the HIV virus; hence the virus was produced by the active cells. Memory cells were only involved when they were triggered to beget a virus, a case similar to latent cells which are only activated when therapy is stopped [34, 116]. In congruence to the early discoveries made on the progression of HIV, Nowak et al, contributed to the discoveries by focusing on the dominant duplicative rate of the virus, as a platform for antigenic diversity and a minimum margin for the immune system to operate. He intimated that HIV invasion beyond the minimum margin, leads to the production of more viral strains. The production of viral strains is inhibited by the human resistive system and hence AIDS intercept [38, 39, 75, 76, 77, 78]. Therefore, Nowak's model is aligned with the high replication rate of the virus and the regulation of DRM associated with therapy regime.

Nevertheless precise computation of viral haul has changed the focus on high viral replication drastically and making it possible to access a person's viral haul in the passage of time [101, 113, 118].

3.3.1 THE SINGLE-TARGET-CELL MODEL (STC)

Refreshingly, the decay rate of a virus was precisely computed for the first time in the mid-1990, based on the progress made on current protease inhibitor (PI) drugs. The computation was made possible by administering (PI) drugs in relation to other drugs, which inhibited viral replication. However viral suppression by drugs could not provide a continual sustenance, hence Wei et al, in 1995 explained the consistent replication of the virus. He indicated that the replication of the virus was at maximum compared with previous information [50, 32]. Per Wei et al. the least computation estimate of viral production was 108 virions per day, based on 100% efficient drug usage [29, 100].The high production rate was attributed to imminent resistance to mono-therapy. However, after few weeks of administering the drugs [24, 25], some of the virus became mutants to the drugs and reduced its efficacy.

Hence, Perelson et al. contributed to the viral production rate by expounding equation 3.1 and hence developed a short term model. The model explains the rapid multiplication of the virus on short term basis [149, 162]. Hence the model operates on the assumption that pre-treatment viral levels are constant, when therapy is aligned to a stable system. Clinical latency was also acknowledged, whilst viral load disintegrates [34, 116,]. The developed STC model is composed of four key cells, aimed at describing the 'rate of change' of the viral load. The equation is expounded as:

$$\frac{dT_p(t)}{dt} = \lambda_p - \delta_p(t) - (1-\epsilon_{rt})k_p V_i(t) T_p(t)$$
$$\frac{dT_p^*(t)}{dt} = (1-\epsilon_{rt})k_p V_i(t) T_p(t) - \delta T_p^*$$
$$\frac{dV_i(t)}{dt} = \left(1-\epsilon_p\right) N_T \delta T_P^*(t) - cV_i(t)$$
$$\frac{dV_{ni}(t)}{dt} = \epsilon_p N_T \delta T_P^*(t) - cV_{ni}(t) \qquad (3.1)$$

The above equation is called the top-down deterministic model, with the following parameters: T_p = infected virus, λ_p = rate of production of uninfected virus. δ_p=rate at which the cells die, V_i= rate of change of infectious virus, δ= death rate of infectious virus, ϵrt = reverse transcription inhibitor, NT = virus production rate, C = rate at which

virus die, V_{ni} = non-infectious virus. Table 3.1 depicts some of the parameters and their definitions for the single target cell model.

VARIABLE	GROUPS	DEFINITION
$\boldsymbol{T_p}$	$\frac{cells}{ml}$	key target cells i.e.$CD4^{+}T$ cells)
$\boldsymbol{T_p^*}$	$\frac{cells}{ml}$	Key target acutely tainted cells
$\boldsymbol{V_i}$	$\frac{virions}{ml}$	Amount of tainted virus
$\boldsymbol{V_{ni}}$	$\frac{virions}{ml}$	Amount of Non-tainted virus

TABLE 3.1: Parameters and definitions for the single target cell model

3.3.2 THE MULTIPLE-TARGET-CELL MODEL (MTC)

The foundation for a more complex model has been echoed by the above STC model in section 3.3.1. However, the introduction of complex parameters have influenced the precision of the STC model and hence switching to models which incorporates key parameters relevant in dealing with treatment options [78, 79]. It is noted that such complexity could not be dealt with by the short-term ODE models, but the multiple target cell model. Multiple target-cell-models are oriented from increased number of target cells, such as primary and secondary target cells. It further permits several viral production rates by acknowledging chronic infection and increased details on the immune system. Multiple target cell models are further aligned with modelling of non-zero viral haul which is vital for long duration dynamics of treatment options [62, 165]. Two types of multiple target cell models are considered for discussion below; the

multiple target cell model for chronic infection (MTC-CI) and multiple-target-cell model for immune response (MTC-IR)

3.3.3 MULTIPLE-TARGET-CELL MODEL FOR CHRONIC INFECTION (MTC-CI)

It is worth to note that small residual of infected cells, ignites a re-stimulation of high viral replication. This is attributed to the particle nature of viruses outside a host cell and the tenacity to ignite an infection within a living cell [82, 165]. Hence the evolution of models with longer dynamics and capacity, such as the multiple targets cell model for chronic infection (MTC-CI). The MTC-CI model is appropriate to facilitate such complex behavior of the virus. [11, 39]. Find below the MTC-CI model for discussion;

$$\frac{dT_p}{dt} = \lambda_p - \delta_p T_P - (1-\epsilon)k_p V T_P$$
$$\frac{dT_s}{dt} = \lambda_s - \delta_s T_s - (1-f\epsilon)k_s V T_s$$
$$\frac{dT_p^*}{dt} = (1-\alpha)(1-\epsilon)k_p V T_P - \delta T_p^*$$
$$\frac{dT_s^*}{dt} = (1-\alpha)(1-f\epsilon)k_s V T_s - \delta T_s^*$$
$$\frac{dC_p^*}{dt} = \alpha(1-\epsilon)k_p V T_P - \mu C T_p^* \quad (3.2)$$
$$\frac{dC_s^*}{dt} = \alpha(1-f\epsilon)k_s V T_s - \mu C T_s^*$$
$$\frac{dV}{dt} = N_T\delta(T_p^* + T_s^*) + N_c\mu(C_P^* + c_s^*) - cV$$

Comparatively, equation (3.2) is heterogeneous to equation (3.1) and therefore acknowledges the incorporation of secondary target cells, (T_p and T_s) as parameters. Other parameters include the amount of virions produced over a period of time represented by (C_p and C_s). Additional variables and definitions for equation 3.2 are stipulated in Table 3.2 below.

VARIABLE	GROUPS	DEFINITION
T_P	$\frac{Cells}{ml}$	key target cells ($CD4^+cells$)
T_P^*	$\frac{Cells}{ml}$	Key target tainted cell
V	$\frac{virions}{ml}$	Amount of tainted virus
T_s	$\frac{Cells}{ml}$	Underlying target cells e.g. macrophages
T_S^*	$\frac{Cells}{ml}$	Underlying target acutely tainted cells
C_P^*	$\frac{Cells}{ml}$	Target chronically tainted cells
C_S^*	$\frac{Cells}{ml}$	Underlying target chronically tainted cells

TABLE 3.2: MTC-CI MODEL (Variables for the model and their definitions)

3.3.4 THE MULTIPLE-TARGET-CELL MODEL FOR IMMUNE RESPONSE (MTC-IR)

The (MTC-IR) model deals with prolonged HIV advancement and the embodiment of a more precise feature of the human resistive system, which supports further evaluation of viral reflex. MTC-IR models as described above are more detailed when embodied with the immune response component. Find below the model for discussion:

$$\frac{dT_P}{dt} = \lambda_p - \delta_p T_p - (1-\epsilon)k_p V T_P$$

$$\frac{dT_s}{dt} = \lambda_s - \delta_s T_s - (1-f\epsilon)k_s V T_s$$

$$\frac{dT_p^*}{dt} = (1-\epsilon)k_p V T_P - \delta T_p^* - m_p E T_p^*$$

$$\frac{dT_s^*}{dt} = (1-f\epsilon)k_s V T_s - \delta T_s^* - m_s E T_s^*$$

$$\frac{dV}{dt} = N_T \delta\left(T_p^* + T_s^*\right) - \left[(1-\epsilon)p_p k_p T_p + (1+f\epsilon)p_s k_s T_s\right]V - cV$$

$$\frac{dE}{dt} = \lambda_E + \frac{b_E(T_p^*+T_s^*}{(T_p^*+T_s^*)+k_b}E - \frac{d_E(T_p^*+T_s^*}{(T_p^*+T_s^*)+K_d}E - \delta_E E \qquad (3.3)$$

The equation above is a multifold model similar to the MTC-CI model discussed above. It is concentrated on two types of cells, namely CD4+T cells and macrophages cells which are fragile to HIV infection. However additional cells have been added to the model due to increase in the number of compartments involved. The operations of equation 3.3 are peculiar to the MTC-CI model but short of the chronic infection component represented by (C_p and C_s).

Notwithstanding, the above model compared to the MTC-CI model is further activated by the removal of the following parameters: tainted cells represented by ($m_p E T_p^* \; and \; m_s$) and effector cells (*E*), Additional variables for the model are defined in table 3.2 below.

Variable	Units	Description
T_p	$\frac{cells}{ml}$	key target cell ($CD4^+$Cells)
T_p^*	$\frac{cells}{ml}$	key target tainted cells
V	$\frac{virions}{ml}$	contagious virus concentration
T_s	$\frac{cells}{ml}$	Underlying target cells (eg macrophages)
T_s^*	$\frac{cells}{ml}$	Target productively tainted cells
E	$\frac{cells}{ml}$	Effector cells

Table 3.3: MTC-IR (variables and their descriptions)

3.3.5 DOUBLING-TIME AND HALF-LIFE

The duration relevant for a specified group of virus to increase in size when treatment options have been discontinued is called viral doubling-time. Find below the formula used for calculating the viral doubling-time

$$T_d = (t_2 - t_1)\frac{\ln(2)}{\ln(\frac{q_2}{q_1})} \quad (3.4)$$

Where T_d represents the viral doubling-time, t_1 and t_2 represents the growth duration, stipulated by (q_1, q_2). The growth rate is exponential and is not applicable to the whole model for a given infection. It is however significant in the maiden stages of the infection, where there is limited amount of infection. The parameter $\ln(2)$ is the

duration required for the system to double in size. Hence when a cell fails to double in size but rather reduce in size, the process is called half-life. Half-life occurs when a system dissociates with respect to time as a result of therapy removal. Find below the equation for a half-life:

$$T_{\frac{1}{2}} = (t_2 - t_1)\frac{\ln(2)}{\ln(\frac{q_1}{q_2})} \tag{3.5}$$

Equation (3.4) is similar to equation (3.5), the difference lays with the ratio $^{q_2}/_{q_1}$. The presence of $^{q_2}/_{q_1}$ accounts for the duration needed for a system to decrease in size. Doubling-time and half-life can be calculated easily by using clinical viral load data. Calculations made on viral doubling time and half-life is used in determining the effectiveness of intracellular delay in the model.

3.4 MODELLING MTC-CI WITH INTRACELLULAR DELAY (MTC-CI-ID)

In an attempt to model an MTC-CI, we initiate a classical model defined as follows:

$$\begin{aligned}
\dot{S} &= \Lambda - (\alpha(x) + \gamma_1 + \mu_1)S \\
I &= \alpha(x)\dot{S} - (\varepsilon + \xi + \lambda + \mu_1)I \\
\dot{I}_A &= \xi I - (\theta + \mu + X + \mu_1)I_A \\
\dot{I}_D &= \epsilon I - (\eta + \varphi + \mu_1)I_D \\
\dot{I}_R &= \eta I_D + \theta I_A - (\upsilon + \xi + \mu_1)I_R \\
\dot{I}_T &= \mu I_A + \upsilon I_R - (\sigma + \tau + \mu_1)I_T \\
\dot{R} &= \lambda I + \varphi I_D + X I_A + \xi I_R + \sigma I_T - (\phi + \mu_1)R \\
\dot{D} &= \tau I_T - \mu_1 D \\
\dot{V} &= \gamma_1 S + \phi R - \mu_1 V - \tau I_T
\end{aligned} \tag{3.6}$$

Further, equation 3.6 is simplified and the equations below resulted thereof:

$$
\begin{aligned}
\dot{s} &= \tilde{s}(t,S,I,I_A,I_D,I_{R,}I_T,R,D,V)\\
\dot{I} &= \tilde{I}(t,S,I,I_A,I_D,I_R,I_T,R,D,V)\\
\dot{I}_A &= \tilde{I}_A(t,S,I,I_A,I_D,I_R,I_T,R,D,V)\\
\dot{I}_D &= \tilde{I}_D(t,S,I,I_A,I_D,I_R,I_T,R,D,V)\\
\dot{I}_R &= \tilde{I}_R(t,S,I,I_A,I_D,I_R,I_T,R,D,V)\\
\dot{I}_T &= \tilde{I}_T(t,S,I,I_A,I_D,I_R,I_T,R,D,V)\\
\dot{R} &= \tilde{R}(t,S,I,I_A,I_D,I_R,I_T,R,D,V)\\
\dot{D} &= \tilde{D}(t,S,I,I_A,I_D,I_R,I_T,R,D,V)\\
\dot{V} &= \tilde{V}(t,S,I,I_A,I_D,I_R,I_T,R,D,V)
\end{aligned}
\tag{3.7}
$$

Equating 3.6 and 3.7, we obtain the following:

$$
\begin{aligned}
\tilde{s}\big(t,S,I,I_A,I_D,I_{R,}I_T,R,D,V\big) &= \Lambda-(\alpha(x)+\gamma_1+\mu_1)S\\
\tilde{I}(t,S,I,I_A,I_D,I_R,I_T,R,D,V) &= \alpha(x)\dot{S}-(\varepsilon+\xi+\lambda+\mu_1)I\\
\tilde{I}_A(t,S,I,I_A,I_D,I_R,I_T,R,D,V) &= \xi I-(\theta+\mu+X+\mu_1)I_A\\
\tilde{I}_D(t,S,I,I_A,I_D,I_R,I_T,R,D,V) &= \epsilon I-(\eta+\varphi+\mu_1)I_D\\
\tilde{I}_R(t,S,I,I_A,I_D,I_R,I_T,R,D,V) &= \eta I_D+\theta I_A-(\upsilon+\xi+\mu_1)I_R\\
\tilde{I}_T(t,S,I,I_A,I_D,I_R,I_T,R,D,V) &= \mu I_A+\upsilon I_R-(\sigma+\tau+\mu_1)I_T\\
\tilde{R}(t,S,I,I_A,I_D,I_R,I_T,R,D,V) &= \lambda I+\varphi I_D+XI_A+\xi I_R+\sigma I_T-(\phi+\mu_1)R\\
\dot{\tilde{D}}(t,S,I,I_A,I_D,I_R,I_T,R,D,V) &= \tau I_T-\mu_1 D\\
\tilde{V}(t,S,I,I_A,I_D,I_R,I_T,R,D,V) &= \gamma_1 S+\phi R-\mu_1 V-\tau I_T
\end{aligned}
\tag{3.8}
$$

Next we apply the fractal- fractional integral with exponential kernel to equation 3.8 and obtain the following:

$$
s\big(t_{p+1}\big)=s\big(t_p\big)+\begin{bmatrix}\tilde{s}\big(t_p,S^p,I^P,I_A^P,I_D^P,I_R^P,I_T^P,R^PD^P,V^P\big)\\ -\tilde{S}\big(t_{p-1},S^{p-1},I^{p-1},I_A^{P-1},I_D^{P-1},I_R^{P-1},I_T^{P-1},R^{P-1},D^{P-1},V^{P-1}\big)\end{bmatrix}
$$

$$
+\int_{t_p}^{t_{p+1}}\tilde{S}(\tau\,,S,I,I_A,I_D,I_R,I_T,R,D,V)d\tau
$$

$$I(t_{p+1}) = I(t_p) + \begin{bmatrix} \tilde{I}(t_p, S^p, I^P, I_A^P, I_D^P, I_R^P, I_T^P, R^P D^P, V^P) \\ -\tilde{I}(t_{p-1}, S^{p-1}, I^{p-1}, I_A^{P-1}, I_D^{P-1}, I_R^{P-1}, I_T^{P-1}, R^{P-1}, D^{P-1}, V^{P-1}) \end{bmatrix}$$

$$+ \int_{t_p}^{t_{p+1}} \tilde{I}(\tau, S, I, I_A, I_D, I_R, I_T, R, D, V) d\tau$$

$$I_A(t_{p+1}) = I_A(t_p) + \begin{bmatrix} \tilde{I}_A(t_p, S^p, I^P, I_A^P, I_D^P, I_R^P, I_T^P, R^P D^P, V^P) \\ -\tilde{I}_A(t_{p-1}, S^{p-1}, I^{p-1}, I_A^{P-1}, I_D^{P-1}, I_R^{P-1}, I_T^{P-1}, R^{P-1}, D^{P-1}, V^{P-1}) \end{bmatrix}$$

$$+ \int_{t_p}^{t_{p+1}} \tilde{I}_A(\tau, S, I, I_A, I_D, I_R, I_T, R, D, V) d\tau$$

$$I_D(t_{p+1}) = I_D(t_p) + \begin{bmatrix} \tilde{I}_D(t_p, S^p, I^P, I_A^P, I_D^P, I_R^P, I_T^P, R^P D^P, V^P) \\ -\tilde{I}_D(t_{p-1}, S^{p-1}, I^{p-1}, I_A^{P-1}, I_D^{P-1}, I_R^{P-1}, I_T^{P-1}, R^{P-1}, D^{P-1}, V^{P-1}) \end{bmatrix} \quad (3.9)$$

$$+ \int_{t_p}^{t_{p+1}} \tilde{I}_D(\tau, S, I, I_A, I_D, I_R, I_T, R, D, V) d\tau$$

$$I_R(t_{p+1}) = I_R(t_p) + \begin{bmatrix} \tilde{I}_R(t_p, S^p, I^P, I_A^P, I_D^P, I_R^P, I_T^P, R^P D^P, V^P) \\ -\tilde{I}_R(t_{p-1}, S^{p-1}, I^{p-1}, I_A^{P-1}, I_D^{P-1}, I_R^{P-1}, I_T^{P-1}, R^{P-1}, D^{P-1}, V^{P-1}) \end{bmatrix}$$

$$+ \int_{t_p}^{t_{p+1}} \tilde{I}_R(\tau, S, I, I_A, I_D, I_R, I_T, R, D, V) d\tau$$

$$I_T(t_{p+1}) = I_T(t_p) + \begin{bmatrix} \tilde{I}_T(t_p, S^p, I^P, I_A^P, I_D^P, I_R^P, I_T^P, R^P D^P, V^P) \\ -\tilde{I}_T(t_{p-1}, S^{p-1}, I^{p-1}, I_A^{P-1}, I_D^{P-1}, I_R^{P-1}, I_T^{P-1}, R^{P-1}, D^{P-1}, V^{P-1}) \end{bmatrix}$$

$$+ \int_{t_p}^{t_{p+1}} \tilde{I}_T(\tau, S, I, I_A, I_D, I_R, I_T, R, D, V) d\tau$$

$$R(t_{p+1}) = R(t_p) + \begin{bmatrix} \tilde{R}(t_p, S^p, I^P, I_A^P, I_D^P, I_R^P, I_T^P, R^P D^P, V^P) \\ -\tilde{R}(t_{p-1}, S^{p-1}, I^{p-1}, I_A^{P-1}, I_D^{P-1}, I_R^{P-1}, I_T^{P-1}, R^{P-1}, D^{P-1}, V^{P-1}) \end{bmatrix}$$

$$+\int_{t_p}^{t_{p+1}} \tilde{R}(\tau, S, I, I_A, I_D, I_R, I_T, R, D, V)d\tau$$

$$D(t_{p+1}) = D(t_p) + \begin{bmatrix} \tilde{D}(t_p, S^p, I^P, I_A^P, I_D^P, I_R^P, I_T^P, R^P D^P, V^P) \\ -\tilde{D}(t_{p-1}, S^{p-1}, I^{p-1}, I_A^{P-1}, I_D^{P-1}, I_R^{P-1}, I_T^{P-1}, R^{P-1}, D^{P-1}, V^{P-1}) \end{bmatrix}$$

$$+\int_{t_p}^{t_{p+1}} \tilde{D}(\tau, S, I, I_A, I_D, I_R, I_T, R, D, V)d\tau$$

$$V(t_{p+1}) = V(t_p) + \begin{bmatrix} \tilde{V}(t_p, S^p, I^P, I_A^P, I_D^P, I_R^P, I_T^P, R^P D^P, V^P) \\ -\tilde{V}(t_{p-1}, S^{p-1}, I^{p-1}, I_A^{P-1}, I_D^{P-1}, I_R^{P-1}, I_T^{P-1}, R^{P-1}, D^{P-1}, V^{P-1}) \end{bmatrix}$$

$$+\int_{t_p}^{t_{p+1}} \tilde{V}(\tau, S, I, I_A, I_D, I_R, I_T, R, D, V)d\tau$$

Now we introduce into equation 3.9 the following; primary target cell T_p, contagious virus V, Macrophage cells T_s and effector cells $\in$ and differentiate the system of equations with respect to time (t). When the parameters were simplified, the equations below resulted thereof;

$$\frac{dT_p}{dt} = \lambda_p - \delta_p T_P - (1-\epsilon)k_p V T_P$$
$$\frac{dT_s}{dt} = \lambda_s - \delta_s T_s - (1-f\epsilon)k_s V T_s$$
$$\frac{dT_p^*}{dt} = (1-\alpha)(1-\epsilon)k_p V T_P - \delta T_p^*$$
$$\frac{dT_s^*}{dt} = (1-\alpha)(1-f\epsilon)k_s V T_s - \delta T_s^* \qquad (3.10)$$
$$\frac{dC_p^*}{dt} = \alpha(1-\epsilon)k_p V T_P - \mu C T_p^*$$
$$\frac{dC_s^*}{dt} = \alpha(1-f\epsilon)k_s V T_s - \mu C T_s^*$$

$$\frac{dV}{dt} = N_T\delta(T_p^* + T_s^*) + N_c\mu(C_P^* + c_s^*) - cV$$

Next we consolidate into equation 3.10 the delay component, which yields the MTC-CI-ID model as shown below:

$$\frac{dT_p(t)}{dt} = \lambda_p - \delta_p T_P(t) - (1-\epsilon)k_p V(t)T_P(t)$$

$$\frac{dT_s(t)}{dt} = \lambda_s - \delta_s T_s(t) - (1-f\epsilon)k_s V T_s$$

$$\frac{dT_p^*(t)}{dt} = (1-\alpha)(1-\epsilon)k_p V(t-\tau)T_P(t-\tau)e^{-\delta\tau} - \delta T_p^*(t) \qquad (3.11)$$

$$\frac{dT_s^*}{dt} = (1-\alpha)(1-f\epsilon)k_s V(t-\tau)T_s(t-\tau)e^{-\delta\tau} - \delta T_s^*(t)$$

$$\frac{dC_p^*(t)}{dt} = \alpha(1-\epsilon)k_p V(t-\tau)T_P(t-\tau)e^{\mu\tau} - \mu C T_p^*(t)$$

$$\frac{dC_s^*(t)}{dt} = \alpha(1-f\epsilon)k_s V(t-\tau)T_s(t-\tau) - \mu C T_s^*(t)$$

$$\frac{dV(t)}{dt} = N_T\delta(T_p^*(t) + T_s^*(t)) + N_c\mu\big(C_P^*(t) + c_s^*(t)\big) - cV(t)$$

From the above model, T_p represents the untainted CD4+ T cells, T_s the untainted secondary cell (macrophage), T_p^* and T_s^* respectively represents tainted CD4+T cells and macrophage, V denotes viral delay component, $e^{-\delta\tau}$ represents the rate at which target cells die and $e^{\mu\tau}$ represents the chronic infection rate.

CHAPTER 4

MODELLING OF INTRACELLUAR DELAY AND THERAPY INTERRUPTIONS

4.0 INTRODUCTION

Chapter three was engaging with the modelling of in vivo, in vitro and in silico analysis. It further dealt with within host deterministic modelling of HIV/AIDS continual and modelling of intracellular delay. Chapter four is interlocked with modelling of intracellular delay, well posedness and existence of equilibrium points. A further consideration is given to the global stability of equilibrium and the endemic equilibrium. Existence and proof for the existence of Hopf Bifurcation are simulated by this chapter and a confirmation of the results by numerical simulation. The chapter finally concludes on the analysis of structured treatment interruptions.

4.1 MODELLING INTRACELLULAR DELAY

Delay differential equations (DDEs) have been valuable for innumerable years in control theory and recently interrelated to biological and mathematical models. Most biological frames [36] have time delay embedded in them, yet few scientist collaborate them due to the intricacies they stimulate. The principal intricacies in studying DDEs lie in their solitary transcendental character.

Delay challenges invariably ushers to an immeasurable measure of prevalence. Hence, they are constantly unraveled using numerical methods, asymptotic solutions, approximations and graphical accessions. In this paper, we first formulate a system of DDE'S expounded as follows

$$\begin{cases} \frac{dx}{dt} = a_1(1 - xy - x) \\ \frac{dy}{dt} = a_2(a_3 x_1 y_1 - y) - a_4 yz \\ \frac{dz}{dt} = a_3(y - z) \end{cases} \tag{4.1}$$

The term $a_2 a_3 x_1 y_1$, represents the rate equation and reflects a boundless time lag between the infection of CD4+T-cell and the staging of new virions. Next we consider the well posedness and existence of equilibrium points.

4.2 WELL POSEDNESS AND EXISTENCE OF EQUILIBRIUM POINTS

We define equation (4.1) in terms of F, G and H as shown below;

$$\begin{aligned} \frac{dx}{dt} &= F(x, y, z, x_1, y_1, z_1) \\ \frac{dy}{dt} &= G(x, y, z, x_1, y_1, z_1) \\ \frac{dz}{dt} &= H(x, y, z, x_1, y_1, z_1) \end{aligned} \tag{4.2}$$

Equating 4.1 and 4.2, yields

$$\begin{aligned} F(x, y, z, x_1, y_1, z_1) &\coloneqq a_1(1 - xy - x) \\ G(x, y, z, x_1, y_1, z_1) &\coloneqq a_2(\, a_3, x_1, y_1 - y) - a_4 yz \\ H(x, y, z, x_1, y_1, z_1) &\coloneqq a_5(y - z) \end{aligned} \tag{4.3}$$

Further, we define a steady state for equation (4.2) in terms of $(\bar{x}, \bar{y}\,, \bar{z})$ and procure the equations below:

$$\begin{aligned} \mathrm{F}(\bar{x}, \bar{y}, \bar{z}\,, \bar{x}_1, \bar{y}_1, \bar{z}_1) &= 0 \\ \mathrm{G}(\bar{x}, \bar{y}, \bar{z}\,, \bar{x}_1, \bar{y}_1, \bar{z}_1) &= 0 \\ \mathrm{H}(\bar{x}, \bar{y}, \bar{z}\,, \bar{x}_1, \bar{y}_1, \bar{z}_1) &= 0 \end{aligned} \tag{4.4}$$

PROPOSITION 4.1

If $a_2 a_3$ and $z_1 \coloneqq T_\tau z$, then the steady state solution of equation (4.2) is in unison with the steady state solution of equation (4.4)

PROOF

Consider an immutable function S(t) and its derivative $\frac{ds}{dt}$, assuming that the derivative of the function $\frac{ds}{dt} = \frac{ds_1}{dt}$, then :

F$(\bar{x}, \bar{y}, \bar{z}, \bar{x}_1, \bar{y}_1, \bar{z}_1) = 0$, G$(\bar{x}, \bar{y}, \bar{z}, \bar{x}_1, \bar{y}_1, \bar{z}_1) = 0$ and H$(\bar{x}, \bar{y}, \bar{z}, \bar{x}_1, \bar{y}_1, \bar{z}_1) = 0$, hence equations (4.2) and (4.4) have the same unvarying states.

Further, by codifying a neighborhood close to the unvarying state solution, we let

$x = \bar{x} + X$, $y = \bar{y} + Y$, $z = \bar{z} + Z$, $x_1 = \bar{x} + X_1$, $y_1 = \bar{y} + Y_1$ and $z_1 = \bar{z} + Z_1$

Next, we exploit the Taylor series about the point $(\bar{x}, \bar{y}, \bar{z})$ and withholding only the linear terms yields

$$\frac{dX}{dT} = -a_1(\bar{y} + 1)X - a_1\bar{x}Y,$$

$$\frac{dY}{dt} = a_2a_3\bar{y}X_1 + [a_2(a_3\bar{x}Y_1 - Y) - a_4\bar{z}Y] - a_4\bar{y}Z \quad and \qquad (4.5)$$

$$\frac{dZ}{dt} = a_5Y - a_5Z$$

Further, we linearized equation 4.5 as:

$$\begin{bmatrix} \frac{dX}{dt} \\ \frac{dY}{dt} \\ \frac{dZ}{dt} \end{bmatrix} = \begin{bmatrix} -a_1(\bar{y} + 1) & -a_1\bar{x} & 0 \\ a_2a_3\bar{y}e^{-\lambda t} & a_2\left(a_3\bar{x}e^{-\lambda t} - 1\right) - a_4\bar{z} & -a_4\bar{y} \\ 0 & a_5 & -a_5 \end{bmatrix} \begin{bmatrix} X \\ Y \\ Z \end{bmatrix} \qquad (4.6)$$

Next we let $B = \begin{bmatrix} -a_1(\bar{y} + 1) & -a_1\bar{x} & 0 \\ a_2a_3\bar{y}e^{-\lambda t} & a_2\left(a_3\bar{x}e^{-\lambda t} - 1\right) - a_4\bar{z} & -a_4\bar{y} \\ 0 & a_5 & -a_5 \end{bmatrix}$

Where B is the coefficient matrix of the linearized system and λ is the eigenvalue of matrix B. Hence the unvarying state of the delay system can be explored in terms of the eigenvalues of matrix B.

4.3 GLOBAL STABILITY OF EQUILIBRIUM E_O

In this section, we proceed by analyzing the universal stability of the disease-free equilibrium of the model. Hence we let (x_o, y_o, z_o) be an unvarying state solution of the following equations:

$\frac{dx}{dt} = F(x, y, z, x_1, y_1, z_1)$, $\frac{dy}{dt} = G(x, y, z, x_1, y_1, z_1)$ and $\frac{dz}{dt} = H(x, y, z, x_1, y_1, z_1)$, then

(x_o, y_o, z_o) is stable if $\epsilon > 0$ and $\delta > 0$ for (x, y, z) when

$$[x(t_o) - x_o]^2 + [y(t_o) - y_o]^2 + [z(t_o) - z_o]^2 < \delta^2 \qquad (4.7)$$

Given that $t_o \in [t_1 - \tau, t_1]$, $then$ $[x(t) - x_o]^2 + [y(t) - y_o]^2 + [z(t) - z_o]^2 < \epsilon^2$ for all $t > t_1$.

On the other hand if (x_o, y_o, z_o) is stable and δ is chosen so that equation (4.7) is elucidated as $[x(t), y(t), z(t) \rightarrow (x_o, y_o, z_o)]$. Then as $t \rightarrow \infty$, (x_o, y_o, z_o) is globally asymptotically stable.

PROPOSITION 4.2

Suppose $a_1, a_2, a_3, a_5 > 0$:

(i). then if $a_3 < 1$, then the unvarying state of equation (4.1) of the system (4.2) is universally asymptotically stable for $\tau \geq 0$. Hence E_O is stable

(ii). If $a_3 > 1$, then the unvarying state of equation (4.1) of the system (4.2) is globally unstable, hence E_O is unstable

PROOF

Suppose the characteristic equation of matrix B is written as

$U(\lambda) = \lambda^3 + b_1\lambda^2 + b_2\lambda + b_3 + (d_1\lambda^2 + d_2\lambda + d_3)e^{-\tau\lambda} = 0$ (4.8)

Now if $\tau = 0$, then there is no delay in equation 4.8, hence proposition 4.2 reduces to proposition 4.1

Conversely, when $\tau > 0$, and we surrogate the unvarying state of equations (4.1) and (4.3) and solve, we generate the characteristic equation

$(\lambda + a_1)\left(\lambda + a_2 - a_2a_3e^{-\lambda\tau}\right)(\lambda + a_5) = 0$

Next, by considering the unvarying state of equation 4.1, we ascertain that matrix B has three eigenvalues: $\lambda_1 = -a_1 < 0,\ \lambda_2 = -a_5 < 0$ and λ_3 in the form

$\lambda_3 + a_2\left(a_3e^{-\tau\lambda_3} - 1\right) = 0$

Therefore, to find the location of λ_3, we propose a function of the form

$u(t) \coloneqq t + a_2 - a_2a_3e^{-\lambda\tau}$, where $t \in R$

By differentiating, we obtain $u'(t) = 1 + a_2a_3\tau e^{-\lambda\tau}$, which is always positive, hence the limit of the original equation is written as $\lim_{t\to\infty} u(t) = -\infty$ and

$\lim_{t\to\infty} u(t) = \infty$. Therefore u(t) has a distinctive zero revealed as $u(0) = a_2(1 - a_3)$.

Hence we conclude that if $a_3 < 1,\ u(0) > 0$ and $\lambda_3 < 0$. Then the unvarying state of equation (4.6) is globally asymptotically stable for $\tau > 0$.

Conversely if $a_3 > 1$, then we conclude that the unvarying state of equation (4.1) is globally asymptotically unstable for $a_3 < 0$, $\lambda_3 > 0$ and $\tau > 0$

4.4 THE ENDEMIC EQUILIBRIUM

The endemic equilibrium E^* is obtained by filtering the real and imaginary parts from the equation below

$[b_3 + b_2\alpha + b_1\alpha^2 + \alpha^3 - b_1\omega^2 - 3\alpha\omega^2 + i(b_2\omega + 2b_1\alpha\omega + 3\alpha^2\omega - \omega^3) + e^{-\tau\alpha}[(0d_2\omega + 2d_1\alpha\omega)sin\omega\tau + (d_3 + d_2\alpha + d_1\alpha^2 - d_1\omega^2)cos\omega\tau + ie^{-\tau\alpha}$
$[(d_1\omega^2 - d_3 - d_2\alpha - d_1\alpha^2)sin\omega\tau + (d_2\omega + 2d_1\omega)cos\omega\tau] = 0$ (4.9)

which yields

$d_2\omega sin\omega\tau + (d_3 - d_1\omega^2)cos\omega\tau = b_1\omega^2 - b_3$ (4.10)

$d_2\omega cos\omega\tau - (d_3 - d_1\omega^2)sin\omega\tau = \omega^3 - b_2\omega$ (4.11)

Summing the squares of equations (4.10) and (4.11)

$u(\omega) \coloneqq \omega^6 + (b_1^2 - 2b_2 - d_1^2)\,\omega^4 + (b_2^2 - 2b_1b_3 + 2d_1d_3 - d_2^2)\omega^2 + b_3^2 - d_3^2 = 0$ (4.12)

We further exploit equation (4.12) by surrogating the parameters below

$m \coloneqq \omega^2,\ \ p \coloneqq b_1^2 - 2b_2 - d_1^2,\ \ q \coloneqq b_2^2 - 2b_1b_3 + 2d_1d_3 - d_2^2,\ and\ \ r \coloneqq b_3^2 - d_3^2$

Hence, the new equation reads

$k(m) = \ m^3 + pm^2 + qm + r = 0$ (4.13)

LEMMA 4.1

Suppose $\tau > 0$ then equation (4.13) has no positive real root, hence all the roots have negative real parts.

PROOF

Since equation (4.13) has no positive root, then ω is not the root of equation (4.12). Therefore for any real number ω, the value of $i\omega$ is also not the root of equation (4.12), hence $\lambda(\tau_c = i\omega(\tau_c)$ is not the root of equation (4.12). This implies that only one positive real root exist for equation (4.13). Hence differentiating equation 4.13 yields

$k'(m) = 3m^2 + 2pm + q$ (4.14)

Therefore the roots of equation 4.13 are:

$$m_o = \frac{-p + \sqrt{p^2 - 3q}}{3} \quad and \quad \frac{-p - \sqrt{p^2 - 3q}}{3}$$

LEMMA 4.2

(i). if $r < 0$ then it follows that $p^2 - 3q > 0$ has a positive root, provided $p < 0$

(ii) On the other hand if $r > 0$ then $p^2 - 3q < 0$, has no positive real roots.

PROOF

(i). Suppose condition (i) holds and $r < 0$, then k(0) $= r < 0$, hence $\lim_{m\to\infty} k(m) = \infty$. Exploiting the intermediate value theorem, equation (4.14) yields t_o as a positive root and therefore $k(t_o) = 0$.

Conversely, if condition (ii) holds for which $r > 0$ and $p^2 - 3q < 0$, then m_o is real, for which $m_o > 0$. Since $k(0) = r > 0 \; and \; k(m_o) < 0$, then by the intermediate value theorem, k has zero between the origin and m_o

(ii). conversely, if $q > \frac{1}{3}p^2$ then the zeros of $m_o \; and \; m_1 \; of \; K'(m)$ are not real. Henceforth $K'(m) = 0$ has no real root.

Consequently, $q > \frac{1}{3}p^2 \geq 0$, has no real roots, given that K is an increasing function where $K(0) = r \geq 0$. We conclude that the model has a unique endemic equilibrium which is asymptotically stable if and only if $R_o > 1$, otherwise unstable. This unique endemic equilibrium occurs at $\tau \geq 0$

4.5. EXISTENCE OF HOPF BIFURCATION

We introduce the Hopf bifurcation and therefore appraise the 3- dimensional system of differential equations as follows

$$\frac{dx}{dt} = F(x, y, z, \tau)$$

$$\frac{dy}{dt} = G(x, y, z, \tau) \qquad (4.15)$$

$$\frac{dy}{dt} = H(x, y, z, \tau)$$

The following conditions holds if :

(i). $F(\bar{x}, \bar{y}, \bar{z}, \tau) = G(\bar{x}, \bar{y}, \bar{z}, \tau) = H(\bar{x}, \bar{y}, \bar{z}, \tau) = 0$, then $\tau_c \; and \; (\bar{x}, \bar{y}, \bar{z},)$ remains as a steady state solution for equation (4.13)

(ii). F, G and H are analytic in terms of (x, t, z), then they are within the neighborhood of $(\bar{x}, \bar{y}, \bar{z}, \tau_c)$

(iii). the Jacobian matrix of equation (4.6) at $(\bar{x}, \bar{y}, \bar{z}, \tau)$ has a pair of complex conjugate eigenvalues, $\lambda \; and \; \bar{\lambda}$, then

$$\lambda(t) = \alpha(\tau) + i\omega(\tau) , \quad \omega(\tau_c) = \omega_c > 0, \; \alpha(\tau_c) = 0 \quad and \; \frac{d\alpha(\tau)}{dr} I_\tau = \tau_C \neq 0 \qquad (4.16)$$

(iv). the remaining eigenvalues of the Jacobian matrix at $(\bar{x}, \bar{y}, \bar{z}, \tau_c)$ have strictly negative real part. Then the system (4.9) has a family of periodic solution: $\in_H > 0$ and analytic function $\tau^H(\epsilon) = \sum_2 \infty T_i^H \in^i, \; where \; 0 < \in < \in_H$. Hence, $T^H(\in) of \; p_\in(t)$ is analytic and of the form

$$T^H(\in) = \frac{2\pi}{\omega_c}(1 + \sum_2^\infty T_i^H \in^i)(0 < \in < \in_H) \qquad (4.17)$$

Next, we exploit the parameters of the analytic function to ensure the occurrence of Hopf bifurcation. Hence we denote the positive roots of equation (4.1) by $m_j, j, where \; j \in [0,1,2]$, depending on the number of positive roots in the equation. Therefore equation (4.9) has six positive roots such as $\omega_j, \; \lambda = i\omega$ and $\pm\sqrt{m_j} \; where \; j =$ 0,1,2,. Consequently, substituting $\omega_j$into equation (4.10) and (4.11) and solving for τ produces

$$\tau_j^{(n)} = \frac{1}{\omega_j}\arcsin\left[\frac{d_1\omega_j^5+(b_1d_2-d_3-d_1b_2)\omega_j^3+(d_3b_2-b_3d_2)\omega_j}{d_2^2\omega_j^2+(d_3-d_1\omega_j^2)^2}\right] + \frac{2\pi(n-1}{\omega_j} \quad (4.18)$$

Where $j = 0, 1,2\ and\ n = 1,2, \ldots$

Again, when we consider $\tau_c > 0$ to be a smaller value, where $\alpha(\tau_c) = 0$, then

$$\tau_c T_{jc}^{(nc)} = \min\{\tau_j^{(\tau)} > 0, 0 \leq j \leq 2, n \geq 1\} \quad (4.19)$$

Where $\omega_c = \omega_{jc}$

THEOREM 4.1

Consider the time lag τ and the critical time lag $\tau_c\ and\ \omega_c$ as defined in equation (4.13) and suppose $3\omega_c^6 + 2p\omega_c^4 + q\omega_c^2 \neq 0$ then the system of delay differential equation in terms of equation (4.2), portrays the Hopf bifurcation at the steady state in equation (4.1).

PROOF

We show that $\frac{d\alpha(\tau)}{d\tau} I_\tau = \tau_C \neq 0$ (4.20)

The existence of Equation (4.14) personifies the occurrence of Hopf bifurcation. Hence equating the real and imaginary parts of equations (4.10) and (4.11) to zero, we obtain the following

$$e^{-\tau\alpha}[(d_2 + 2d_1\alpha)\omega sin\omega\tau + [(d_3 + d_2\alpha + d_1(\alpha^2 - \omega^2)]\cos\omega\tau] =$$

$$(b_1 + 3\alpha)\omega^2 - b_3 - b_2\alpha - b_1\alpha^2 - \alpha^3] \quad (4.21)$$

and

$$(e^{-\tau\alpha}[(d_1\omega^2 + d_3 - d_2\alpha - d_1\alpha^2)sin\omega\tau + (d_2\omega + 2d_1\alpha\omega)cos\omega] = \omega^3 - b_2\omega - 2b_1\alpha\omega - 3\alpha^2\omega \quad (4.22)$$

Further, we differentiate equations (4.21) and (4.22) with respect to τ and evaluate at $\tau = \tau_c$ where $\alpha\tau_c = 0\ and\ \omega(\tau_c) = \omega_c$ and obtains the following

$$E_1 \frac{d\omega}{d\tau}\Big|\tau = \tau_c - E_2 \frac{d\alpha}{d\tau}\Big|\tau = \tau_c = E_3 cos\omega_c\tau_c + E_4 sin\omega_c\tau_c \quad (4.23)$$

$$E_2 \frac{d\omega}{d\tau}\Big|\tau = \tau_c - E_1 \frac{d\alpha}{d\tau}\Big|\tau = \tau_c = E_3 sin\omega_c\tau_c + E_4 cos\omega_c\tau_c \quad (4.24)$$

Where $E_1 \coloneqq 2b_1\omega_c + (2d_1\omega_c - \tau_c d_2\omega_c)cos\omega_c\tau_c + (\tau_c d_3 - d_2 - \tau_c d_1\omega_c^2)sin\omega_c\tau_c$

$E_2 \coloneqq b_2 - 3\omega_c^2 + (d_2 + \tau_c d_1\omega_c^2 - \tau_c d_3)cos\omega_c\tau_c + (2d_1\omega_c - \tau_c d_2\omega_c)sin\omega_c\omega_c$

$E_3 \coloneqq d_2\omega_c^2 \quad and\ E_4 \coloneqq d_1\omega_c^3 - d_3\omega_c$

Now by solving equations (4.23) and (4.24) together we have

$$\frac{d\alpha}{d\tau}\Big|\tau = \tau_c = \frac{(E_1E_4 - E_2E_4)sin\omega_c\tau_c - (E_1E_4 + E_2E_3)cos\tau_c}{E_1^2 + E_2^2} \quad (4.25)$$

Next we substitute equations (4.10) and (4.11) into equations (4.23) and (4.24) and yields

$$cos\omega_c\tau_c = \frac{(b_1\omega_c^2 - b_3)(d_3 - d_1\omega_c^2 + d_2\omega_c(\omega_c^3 - b_2\omega_c)}{d_2^2 + (d_3 - d_1\omega_c^2)^2} \quad (4.26)$$

$$sin\omega_c\tau_c = \frac{d_2\omega_c(b_1\omega_c^2 - b_3) - (d_3 - d_1\omega_c^2)(\omega_c^3 - b_2\omega_c)}{d_2^2\omega_c^2 + (d_3 - d_1\omega_c^2)^2} \quad (4.27)$$

Finally, we incorporate equations (4.26) and (4.27) into equation (4.25) and obtains

$$\frac{d\alpha}{d\tau}\Big|\tau = \tau_c = \frac{3w_c^6 + 2p\omega_c^4 + q\omega_c^2}{E_1^2 + E_2^2} \neq 0 \quad (4.28)$$

Consequently we conclude based on equations (4.26), (4.27) and (4.28), the existence of Hopf bifurcation when, τ passes through the critical value τ_c

4.6 PROOF FOR THE EXISTENCE OF HOPF BIFURICATION

In this section we prove for the existence of Hopf Bifurcation by assuming that $a_1, a_2, a_5 > 0$ and $a_3 > 1, for$ τ_c and ω_c as defined in equation (4.14). Therefore by lemma 4.2 (i) if $p \geq 0, q \geq 0$, then we conclude that the system of delay differential equations proposed in equation (4.2) for the whole delay process has Hopf bifurcation. Consequently, the Hopf bifurcation occurs at $p \geq 0, q \geq 0$, when $3w_c^6 + 2p\omega_c^4 + q\omega_c^2 \neq 0$. This is further supported by lemma 4.1 and theorem 4.1. The forward bifurcation analysis is portrayed by figure 4.1, where $\tau = q\omega_c$, $\omega_c = 0.024$, $P = 1000$, $q = 2200$, $E_1 = 0.029$ and $E_2 = 0.06$. The conditions for the existence of Hopf bifurcation have been extrapolated by the above analysis. Hence, figure 4.1 portrays the conditions for the model to have a forward bifurcation under a single endemic equilibrium.

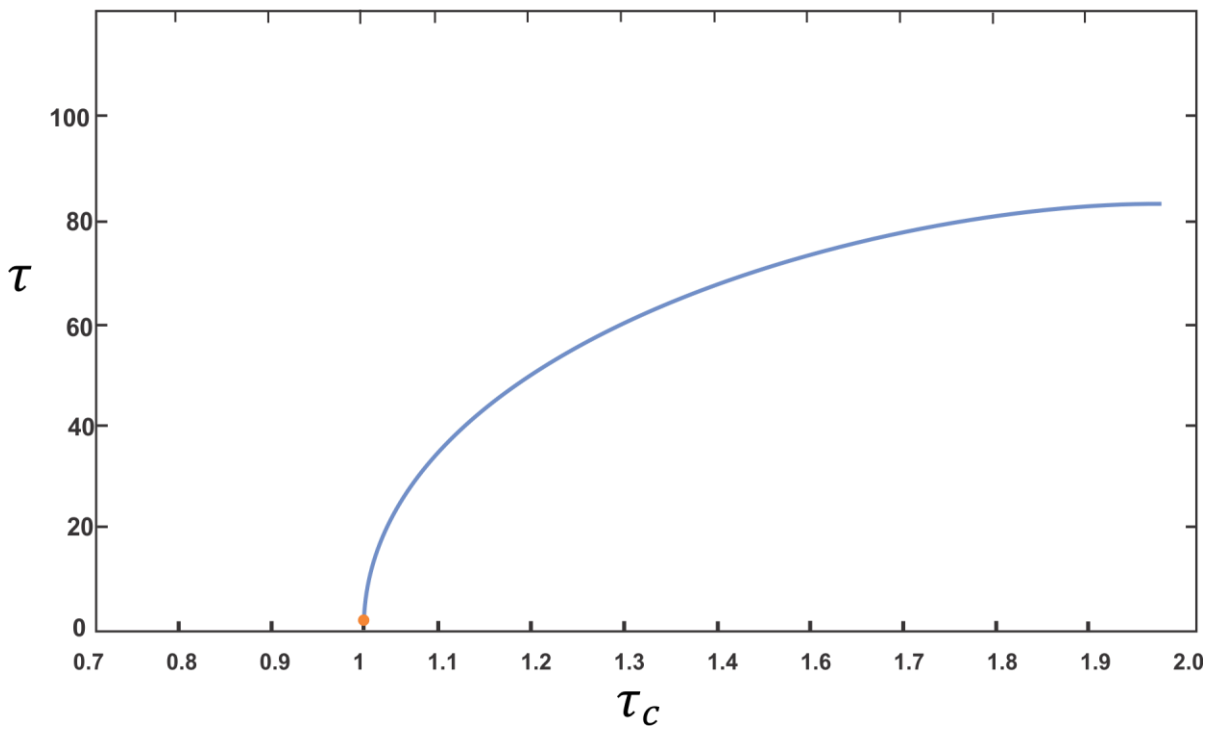

Figure 4.1: Demonstration of the forward bifurcation process of the model with τ against τ_c: where $\tau_c = q\omega_c$, $\omega_c = 0.024$, $P = 1000$, $q = 2200$, $E_1 = 0.029$ and $E_2 = 0.06$.

4.7 NUMERICAL SIMULATION

The numerical simulations are engaging around the convergence of orbits of the global stability and the presence of Hopf bifurcation for the system (4.28). The results are enjoined to flaunt the effects of intracellular delay on the affirmative behavior of the three variables: CD4+T-cell, symbolized (x), cells tainted with HIV, symbolized (y) and CTL, symbolized (z).

The numerical simulations are wielded on the variables to corroborate the theoretical anticipations deliberated in chapters 2, 3 and 4. The values of the parameters such a_1, a_2, a_3, a_4, a_5, were used as seen from the above propositions and equations in chapter four to corroborate a pragmatic biological simulation of the results. The numerical results of the system of equations as per chapters 2, 3 and 4 were solved numerically as per the sixth order Runge –Kutta method with parametric values from $a_1, a_2, a_3, a_4 \; and \; a_5$.

Firstly, the model was analyzed without the delay component embedded (only ODE), under the following conditions: justification of the qualitative conduct of the three variables such as CD4+T-cell(x), HIV(y), and CTL(z) and controlling the fundamental reproductive rate of the virus. This was made possible through numerical simulations to vouch the theoretical conjecture stipulated in chapters 2, 3 and 4. When intracellular delay was overlooked and the fundamental reproductive number was under control, equation 2.2 was solved numerically as per the 6th order Runge-Kutta strategy with $a_1 = 0.224\,,\ a_2 = 0.941,\ a_3 = 0.369,\ a_4 = 4.651,\ a_5 = 1.311.$

Figure 4.2 (appendix A.1), portrays the numerical simulation of the quantum of CD4+T-cells, HIV virus and CTL in the blood discretely. CD4+T-cell were consistent over time, whilst the quantum of CTL and the virus in the blood approaches zero. Figure 4.2d (appendix A.1) centers on the compactness of HIV and CTL in the blood, as they approaches the vanishing stretch to confirm the connection amidst the virus and the immune response

Hence, the numerical outcome represented in Figure 4.2 (appendix A.1) correlates with the theoretical conjectures anticipated in Proposition 4.2(i) and equation 2.2. Therefore when $a_3 < 1$, a steady state was attained at (1, 0, 0). This implies that the essential conceptive pace of the infection was under control level hence, the decline rate of viral

production is higher than the production rate. Consequently, the virus could not spread and it's eliminated from the blood, when CD4+T-cell become consistent at δ_1/δ_3

On the contrary, when the model was analyzed with the embedment of the delay component (DDE), under the following conditions: justification of the qualitative conduct of the three variables such as CD4+T-cell(x), HIV(y), and CTL (z) and controlling the fundamental reproductive rate of the virus, equation 4.1 was solved numerically using the 6th order Runge-Kutta technique were $a_1 = 0.224$, $a_2 = 0.941$, $a_3 = 0.369$, $a_4 = 4.651$, $a_5 = 1.311$, $\tau = 0.191$. Figure 4.3 (appendix A.2), portrays the quantum of CD4+T-cells, HIV virus and CTL in the blood discretely. The quantum of CD4+T-cell gets consistent over time, whilst CTL and the virus in the blood approaches zero. Figure 4.3(d), (appendix A.2) centers around the conduct of the compactness of HIV and CTL as they approach the vanishing point, to confirm the connection amidst the virus and the immune response. Therefore, the numerical outcome represented in Figure 4.3(a, b, c) (appendix A.2), correlates with the theoretical conjecture anticipated in Proposition 4.2(i) and equation 4.1. Therefore when $a_3 < 1$, a steady state was attained at (1, 0, 0). This implies that the essential conceptive pace of the infection was under control level hence, the decline rate of viral production is higher than the production rate. Consequently, the virus could not spread and its eliminated from the blood, when CD4+T-cell become consistent at δ_1/δ_3.

The model with delay was more advantageous over the non-delay model, because it was more stable at the trajectory. It supports viral peak postponement and virological suppression better than the non-delay (figure 4.2 and 4.3).

Another dimension to the analysis was the removal of the delay component under the following conditions: justification of the qualitative conduct of the three variables such as CD4+T-cell(x), HIV(y), and CTL (z) and this time, not controlling the fundamental reproductive rate of the virus. When intracellular delay was overlooked and the fundamental reproductive number was on grip, equation 2.2 was solved numerically as

per the 6th order Runge-Kutta strategy with now $a_1 = 0.1038$, $a_2 = 3.22$, $a_3 = 2.64$, $a_4 = 7.41$, $a_5 = 4.17$.

Figure 4.4c, (appendix A.3), portrays the quantum of CTL in the blood which congregates at a universal point. Figure 4.4(d) (appendix A.3) centers around the conduct of the compactness of HIV and CTL, as they approach the vanishing stretch to confirm the connection amidst the virus and the immune response.

Therefore, the numerical outcome represented in Figure 4.4(a, b, c) (appendix A.3) correlates with the theoretical conjectures anticipated in Proposition 4.2(ii) and equation 2.2. Hence, a steady state was attained at (0.83, 0.46, 0.46), when $a_3 > 1$. This intimates that the essential conceptive pace of the infection is not under control hence, the decline rate of viral production is lower than the production rate. Infection rate emerges and more virions are produced in the blood.

Contrary to the above, the model was further analyzed with the delay component (DDE), under the following conditions: justification of the qualitative conduct of the three variables such as CD4+T-cell(x), HIV(y), and CTL (z). The fundamental reproductive rate of the virus was uncontrolled and equation 4.1 was solved numerically using the 6th order Runge-Kutta technique with $a_1 = 0.1038$, $a_2 = 3.22$, $a_3 = 2.64$, $a_4 = 7.41$, $a_5 = 4.17$, $\tau = 0.19$. Figure 4.5(a, b) (appendix A.4), portrays the quantum of CTL in the blood which congregate at a universal point. Figure 4.5(d) (appendix A.4) centers around the conduct of the compactness of HIV and CTL in the blood. The levels of CTL and HIV in the blood approach the vanishing stretch, to confirm the connection amidst the virus and the immune response.

Therefore, the numerical outcome represented in Figure 4.5(appendix A.4) correlates with the conditions of proposition 4.2 (i) and equation 4.1. Hence, when $a_3 > 1 \; and \; \tau < \tau_c$, a constant steady state of (0.83, 0.46, 0.46) was attained. This intimates that the essential conceptive pace of the infection was not under control hence, declining the rate of viral production. Infection rate emerges and more virions are produced in the blood. The elongation of the infection leads to the inception of AID. Figure 4.5

4.8 STRUCTURED TREATMENT INTERRUPTION

The quest for legit structured treatment interruptions has necessitated the essence of intracellular delay in STI models. Currently, the adopted STI used by many HIV individuals does not incorporate days-off for drug assimilation by the body. Arguably therapy interruptions should align across days and weeks, in order to allow for drug assimilation. Find below some of the STI systems embedded to validate the model.

4.8.1 TWO-WEEKS-ON TWO-WEEKS-OFF STRATEGY (14/14)

The scenario above relates to 14 days on treatment and 14 days off regime therapy, designed for HIV patients. However, adherence to the regime yields an auto viral control compared to the primitive STI system [24, 25, 128], which aligns with lengthy periods of therapy. In reference to Fig. 4.8, this strategy yields a momentous average viral load of 586virions/ml and 3371virions/ml at peak level. On the contrary, a continuous therapy without any interruption increases the viral haul to 633virions/ml on the average. This implies that the shorter the period for a particular therapy, the lower the peak viral haul. Therefore the lower the peak viral haul, the less the augmentation of viral strains, responsible for drug resistance mutations (figure 4.8).

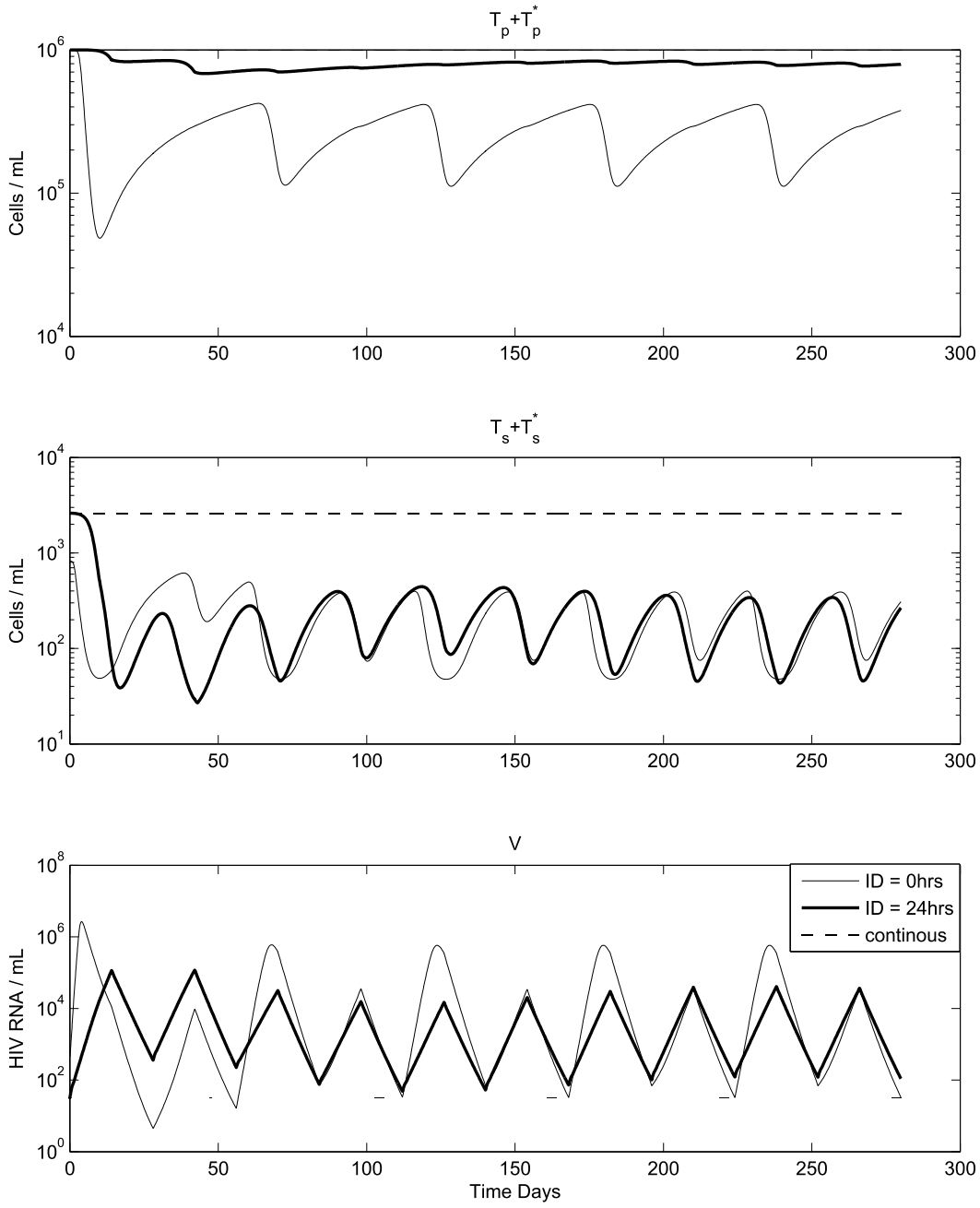

Figure 4.8: Graphs of STI which shows 14 days on and 14days off:

Figure 4.8 (a), shows a therapy of 14 days on treatment and 14 days off therapy. It reveals an average viral haul of 8446virions/ml with zero delay and 586virions/ml for a

24hr delay. In addition to the average viral haul, the peak viral hauls were 5837virions/ml and 3371virions/ml respectively.

Again, figure 4.8 (b), reveals that a ceaseless therapy permits a 50% cost saving, because it limits the replication of target cells and allow them to uphold feasible levels. Hence, a ceaseless therapy has the tendency of migrating high viral haul of 5837virions/ml, which is an epitome for the development of drug resistant mutations (DRMs). Therefore, with reference to the ongoing discussion, a short cycle therapy is recommended on the basis of controlling viral rebound.

4.8.2 FIVE-DAYS-ON TWO-DAYS-OFF STRATEGY (5/2)

The five days on and two days off STI strategy allows treatment from Monday to Friday, with Saturday and Sunday as weekends off treatment. This strategy, also inferred as weekend off strategy is vital in subduing long term viral replication [43, 61, 101]. It enhances a decrease in drug residual level, since its squatty intermission period allows for the assimilation of DRM. Hence in curbing down monotherapy situations, the usage of particular drugs should be disengaged for suitable metabolism rate.

In addition, the five days on and two days off regime, supports a decline of the maximum viral haul. It is worth to note that escalations in viral haul have been a headache for most scientists. Therefore knowledge about the peak viral haul is crucial and personifies a larger viral pool which begets mutations. Based on the 5/2 strategy a cost saving of 29% is marginalized, as compared to the continual therapy. In addition, the 5/2 strategy produces low viral haul due to limited viral rebound. Furthermore, the strategy is useful to places where therapy is not consistent and hence reliable to stop therapy for two days, than to abort the whole process due to limited drug availability. In accordance with the above discussions, the 5/2 strategy appears to be reasonably successful in producing positive results [138, 158, 163], as depicted by figure 4.9.

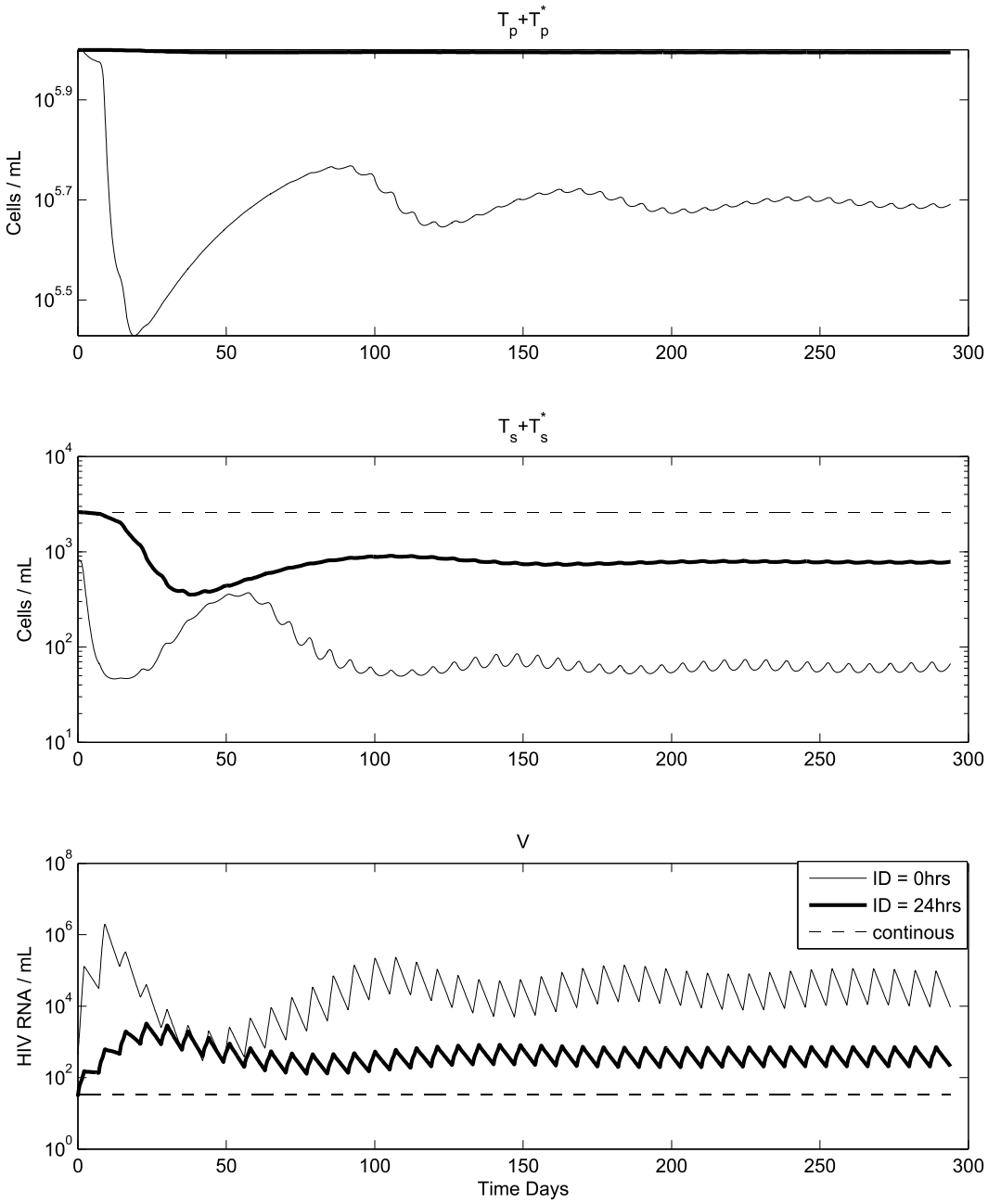

Figure 4.9: Demonstration of 5 days on and 2 days off therapy

From figure 4.9, the 5 days on and two days off therapy induces a mean viral haul of 331virions/ml with zero delay and 412virions/ml within 24hours.

4.8.3 IMPACT OF VARYING THE ON AND OFF PERIOD

The idea of varying treatment on and off has conceited imperative due to less access to ARV, cost concerns and ceaseless treatment. However off-treatment should not be prolonged due to high viral rebound and viral mutation to drugs.

This section contrasts the 5/2 system, the 20/8 system and the 26/2 system and suggest the way forward. The ceaseless treatment period was used as reference and therapy was tempered as per the three systems above (Figure 4.10). It was observed that tempering with therapy for a short period of time was essential due to the following reasons: accessibility to ARV, cost concerns and discontinuity of therapy due to ARV shortage. Therefore the shorter the time frames for off treatment, the better the results and the lesser the viral rebound [107, 109, 128].

In accordance with the ongoing analysis, it was ascertained that the 26/2 system (table 4.1) stimulates a reliable outcome, however the system is not decisive due to its little cost sparing of about 7%. On the other side, the 20/8 system appears to have a lower viral haul than the 5/2 system. The respective average and peak viral hauls for the 20/8 system were 352virions/ml and 751virions/ml respectively. The 5/2 system also articulated 437virions/ml and 756virions/ml respectively. In view of the above outcome a trade- off is simulated to enhance the choice and adoption of a suitable treatment interruption (figure 4.10). Therefore the next section enhances the selection of the overall regime for compliance.

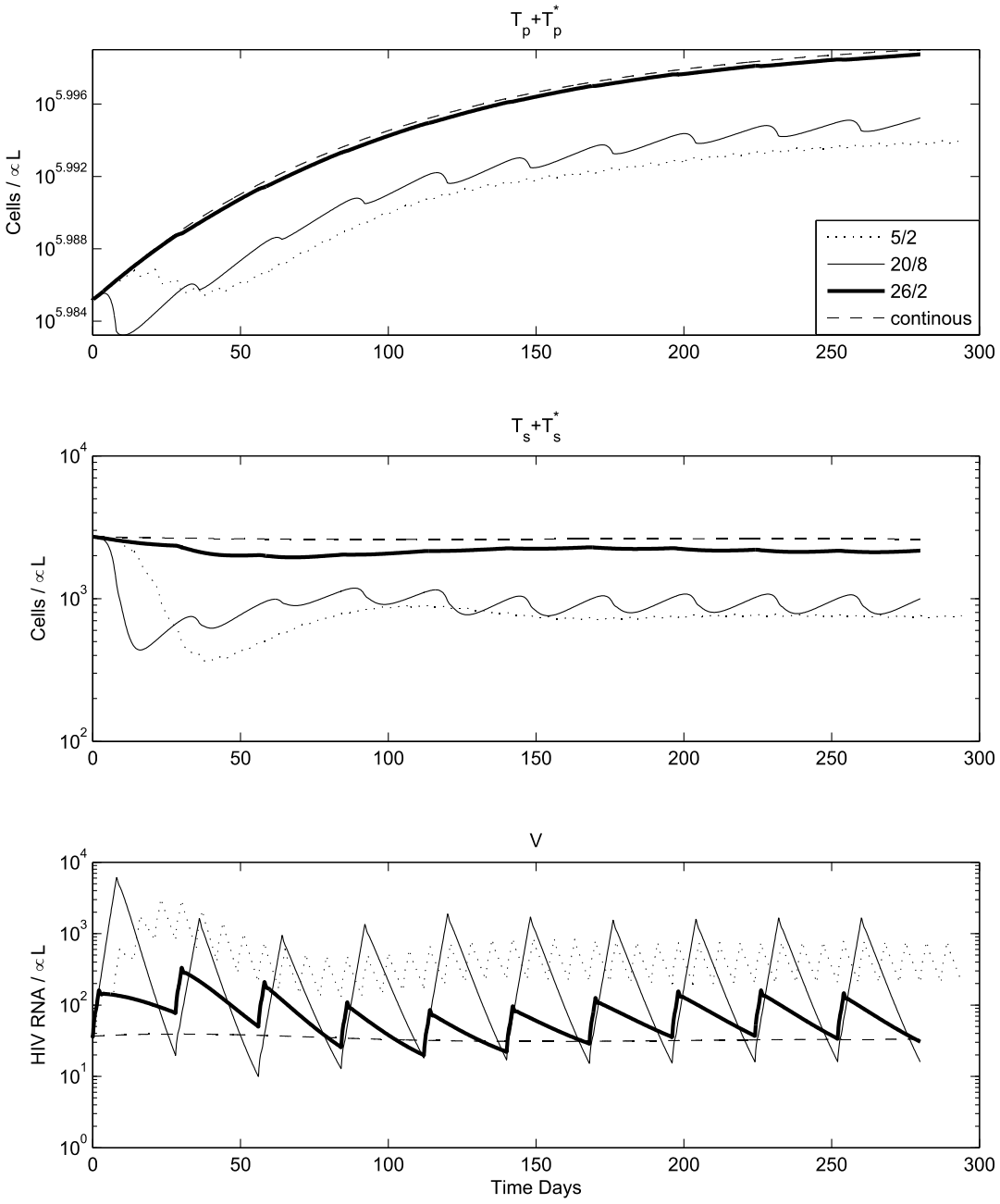

Figure 4.10: Correlation of the 5/2, 20/8 and 26/2 STI Regime

The average viral haul as per the 5/2, 20/8 and 26/2 discretely were 437virions/ml, 352virions/ml and 70virions/ml respectively. On the other hand the peak viral hauls stands at 756virions/ml, 751virions/ml and 138virions/ml respectively.

4.8.4 OVERALL STI REGIME COMPARISON

The above examination has conceited essential in adjusting treatment on and off, thereby diminishing the pinnacle viral haul. The 18/3 and 24/4 systems enhances a minimum viral haul of 120 and 118virions/ml respectively and a peak viral haul of 285 and 338virions/ml respectively (Table. 4.1). In accordance with the above analysis, the 18/3 system permits a 14% decrease in the total cost of treatment whilst subduing the control of HIV replication. Further the 18/3 and 24/4 systems articulates an additional time for ARV to be cleared from the body, compared to the 12/2 system and other systems discussed above. Moreover, it is worth to articulate that the accumulation of treatment period brings about viral escalation. Hence the 24/4 system and the 18/3 system, adheres to both week by week and month to month cycle, whist keeping the viral haul at low levels. Additionally, the systems keep up key cell levels, important to permit the human resistive system to ward off shrewd diseases.

Therefore, based on the above analysis the 18/3 and 24/4 systems have been recommended for compliance and adoption due to low viral haul production (figure 4.11). The 18/3 system produces an average and peak virions of 120 and 285virions/ml respectively, whilst the 24/4 system produces 118 and 338virions/ml respectively (Table 4.1).

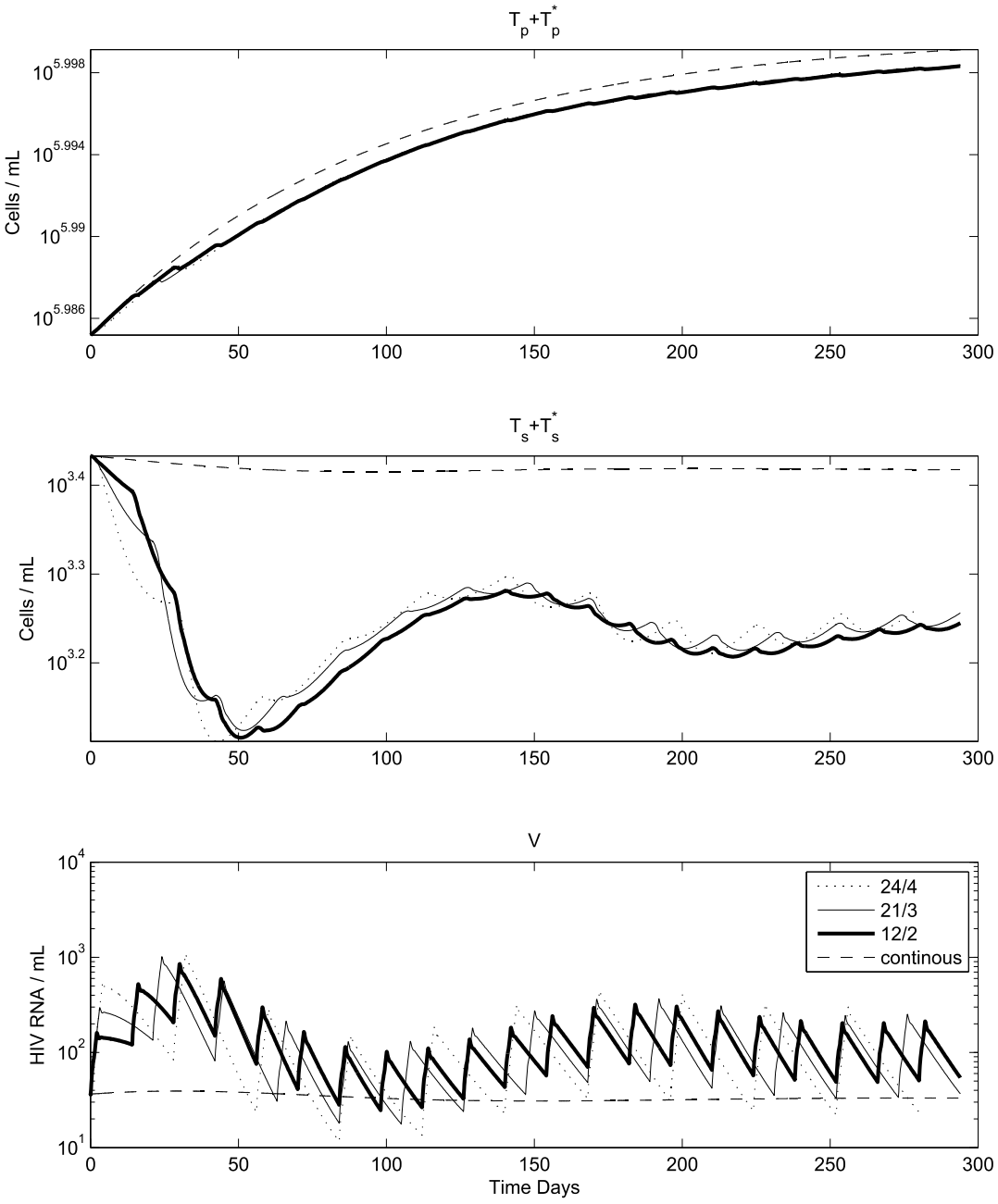

Figure 4.11: Comparison of the STI systems; (24/4, 21/3, 12/2)

From the graph above, the 24 days on treatment and 4 days off treatment was found to be more reliable due to its low cost effectiveness. The 18/3 system is also supported.

Procedure (on/off days)	Mean Viral haul Virions/ml	highest Viral haul Virions/ml	% Cost Saving
5/2	437	756	29
12/2	126	320	14
11/3	209	623	21
19/2	86	171	10
18/3	120	285	14
17/4	168	465	19
16/5	235	751	24
26/2	70	138	7
25/3	92	218	11
24/4	118	338	14
23/5	151	507	18
22/6	201	743	21
21/7	558	1086	25
30/5	114	408	14
36/6	121	495	14
42/7	117	610	14

Table 4.1: Demonstration of treatment strategies, viral load level and corresponding cost

The table shows the average viral haul, peak viral haul and cost savings, relevant for choosing a suitable treatment regime.

4.8.5 SUMMARY OF STRUCTURED TREATMENT INTERRUPTIONS

This area has specifically dealt with the various treatment systems and the system which supports the adopted model for compliance. The systems have featured on the significance of time on- and –off therapy and how to meliorate life expectancy under HIV [11]. However, the 18 days on treatment and 3 days off treatment was recommended as a suitable tradeoff between viral concealment and cost sparing. It allows the cells of the body 3 days' rest, to incorporate the assimilated drugs. Therefore the 18/3 system is likewise suggested for utilization, for circumstances where accessibility for treatment isn't predictable.

Further, the 24/4 system of treatment is proposed as well, due to its adherence to month to month cycle and cost sparing for constrained zones.

CHAPTER 5

CONCLUSION AND FUTURE DIRECTIONS

5.0 INTRODUCTION

This chapter is interconnected with the general overview of the study and the summary of findings. The chapter is further interlocked with future directions to researchers and the conclusion of the study.

5.1 GENERAL OVERVIEW

In HIV tainted people, the disease displays an extended unidentifiable stage, realistically around 10 years before the beginning of AIDS. During this brooding space which is the clinical inactivity time frame, the person seems, by all account to be credible and may contribute fundamentally to the propagation of the virus within a locality. Some clinical attributes, for example, CD4 cell count and RNA viral haul (viraemia), are some of the indicators which articulate clues about the buildup of the disease [159]. Likewise, the clinical idleness time supports the ailment to escalate unobtrusively.

Arguably, the conception of medication was triggered by the pathogenesis of the virus, which embodies the strapping of the virus to gp120 protein on the CD4 cell, the passage of the viral RNA into the objective cell, the opposite exchange of viral RNA to viral DNA and the mixing of the viral DNA with the host cell. In an attempt to inhibit the replication of the virus, scientist has developed drugs such as AZT and Ritonavir, among others to combat or inhibit the spread of the virus. The drugs are meant to inhibit the reverse transcriptase and the protease transcriptase of the virus. The reverse and the protease inhibitors diminishes the creation of the virus and hence deferred the onset of AIDS [16, 150, 157]

A remedy for HIV is yet to be found, however progress is being made in acquiring powerful vaccines for destroying the infection from the human body. For instance, as of

late a bone marrow transplant of an HIV tainted individual suffering from leukemia, was auspicious with no traits of the virus in his framework (the blood and the reservoirs were not tainted with the virus). Based on this successful bone marrow transplant, one could retort that the redress to HIV/AIDS is within reach. However this redress is not dependable, due to its extravagant nature and requires a lot of investment form the tainted individual. Again, it requires the passage of time for the tainted individual to advance in immunity, since a quantum of time is needed for the new stem cells to advance and duplicate (http://www.welt.de/english-news/article2715739/HIV-patient-curedby-marrow transplant.html).

Further, it worth to articulate that, with the boundless nature of the pandemic and a redress not in sight, it is worthwhile to rely on remedial and therapeutic mediation [29, 30, 133, 134]

Notwithstanding, in the past and even recently several researches are ongoing to explore the repercussions of therapy on HIV tainted people. [121,152,153,154]. Hence, researchers have resulted to remediation [100, 165], which has the capacity to defer the onset of AIDS through defective interfering virus (DIVs). DIVs meddle with the replication of the virus [152, 153]. Hence, it is a cancellation mutant which is unequipped for duplication without a host cell (CD4 cell), but reproduces when the host cell is contaminated with HIV.

Noting that DIV relies on HIV to increase, a scientific model [39, 40] was developed to imbibe HIV, DIV and uninfected CD4+Tcells. A compartmental approach was used to confine DIV and HIV in a solitary cubicle. This was followed by an arrangement for normal differential conditions, including eight factors and a few parameters relating to DIV and HIV. Further, a more significant degree of DIV was created to consist of contaminated CD4+Tcells, which was used as a hindrance to the replication of the virus [39, 40]

Notwithstanding, the aftermath of several investigations on HIV replication were examined [29, 30, 49, 50, 51] and the remarks was that, the virus has a tremendous

potentials in demonstrating a high impedance against HIV drugs. Further, it was discovered that [112] the virus has a high drug opposition and a remarkable mix of change in individuals, when a stochastic model was proposed to test the impact of protease inhibitors. Again through numerical approach [63, 100] the dynamic image of HIV pathogenesis was utilized, to ascertain how Ritonavir could repress strongly against the virus. In relation to finding a drug which could suppress HIV [100, 101], elements of cell contamination and viral creation after the administration of ritonavir were considered. Hence ordinary differential equation was used to infer a 100% inhibition by the drug. Therefore by utilizing the numerical model and non-direct least squares fitting of the viral burden of five people, the projection of the viral clearance rate, cell duration and viral procreation time were ascertained [137].

In addition, a discovery on the evolution of HIV, based on a universal-space model was accustomed. Hence HIV tainted people, experiencing a blend of treatment, with a mix of antiviral medications (AZT and Ritonavir), were used to restrain the reverse transcriptase or the protease transcriptase [83]. The model flourished on the creation of irresistible free and noncontagious free HIV. This was achievable through the creation of methodology which assesses and anticipates the quantity of untainted CD4+Tcells, irresistible free HIV, non-irresistible free HIV and HIV tainted CD4+Tcells.

Per the achievement of Tan and Xiang, not only did they broaden Perelson et al's model into a stochastic model, but additionally applied the model stochastically to HIV tainted individuals [143, 144]. They developed a discrete time model which was depicted by an arrangement of stochastic contrast conditions, inferred on the organic details of HIV replication.

Nonetheless it's worth articulating that the HIV virus has the propensity to unfold at a faster rate, about 1 million times faster than the human DNA. This hallmark of the virus is advantageous in evolving over antiviral treatments and sometimes replicating unnoticed.

This high replicative ability of the virus renders drugs ineffective, hence the luxury of this study in using delay differential equation to model low HIV viral haul. The model is

further extended to explore the effects of structured treatment interruptions and adoption of the best STI regime for compliance.

5.2 SUMMARY OF FINDINGS

The aim of the paper is to unveil the niche of delay differential equation in harmonizing low level HIV viral haul and thereby articulating the adopted model to delve into structured treatment interruptions.

Hence, the sturdiness of the model with delay (equation 4.1) and without delay (equation 2.2) was assessed. Numerical simulations were used to consolidate the results.

The demands for the stability of Hopf bifurcation [12] was authenticated in itemizing the initial conditions of the model (figure 4.1). The existence of Hopf bifurcation [12, 137] has been proved and hence occurs when, τ passes through the critical value τ_c.

Firstly, the model was analyzed without the delay component embedded (only ODE), under the following conditions: justification of the qualitative conduct of the three variables such as CD4+T-cell(x), HIV(y), and CTL(z) and controlling the fundamental reproductive rate of the virus. This was made possible through numerical simulations to vouch the theoretical conjectures stipulated in chapters 2, 3 and 4. When intracellular delay was overlooked and the fundamental reproductive number was under control, equation 2.2 was solved numerically as per the 6th order Runge-Kutta strategy with $a_1 = 0.224\,,\ a_2 = 0.941,\ a_3 = 0.369,\ a_4 = 4.651,\ a_5 = 1.311.$

Figure 4.2 (appendix A.1), portrays the quantum of CD4+T-cells, HIV virus and CTL in the blood discretely. CD4+T-cell become consistent over time, whilst the quantum of CTL and the virus in the blood approaches zero. Figure 4.2d (appendix A.1) centers on the compactness of HIV and CTL in the blood, as they approaches the vanishing stretch to confirm the connection amidst the virus and the immune response

Hence, the numerical outcome represented in Figure 4.2 (appendix A.1) correlates with the theoretical conjectures anticipated in Proposition 4.2(i) and equation 2.2. Therefore when $a_3 < 1$, a steady state was attained at (1, 0, 0). This implies that the essential

conceptive pace of the infection was under control level hence, the decline rate of viral production is higher than the production rate. Consequently, the virus could not spread and it's eliminated from the blood, when CD4+T-cell become consistent at δ_1/δ_3

On the contrary, when the model was analyzed with the embedment of the delay component (DDE), under the following conditions: justification of the qualitative conduct of the three variables such as CD4+T-cell(x), HIV(y), and CTL (z) and controlling the fundamental reproductive rate of the virus, equation 4.1 was solved numerically using the 6th order Runge-Kutta technique were $a_1 = 0.224$, $a_2 = 0.941$, $a_3 = 0.369$, $a_4 = 4.651$, $a_5 = 1.311$, $\tau = 0.191$. Figure 4.3 (appendix A.2), portrays the time series plot of the quantum of CD4+T-cells, HIV virus and CTL in the blood discretely. The quantum of CD4+Tcell gets consistent over time, whilst CTL and the virus in the blood approaches zero. Figure 4.3(d), (appendix A.2) centers around the conduct of the compactness of HIV and CTL as they approach the vanishing point, to confirm the connection amidst the virus and the immune response. Therefore, the numerical outcome represented in Figure 4.3(a, b, c) (appendix A.2), correlates with the theoretical conjecture anticipated in Proposition 4.2(i) and equation 4.1. Therefore when $a_3 < 1$, a steady state was attained at (1, 0, 0). This implies that the essential conceptive pace of the infection was under control level, hence the decline rate of viral production is higher than the production rate. Consequently, the virus could not spread and its eliminated from the blood, when CD4+T-cell become consistent at δ_1/δ_3.

The model with delay was more advantageous over the non-delay model, because it was more stable at the trajectory. It supports viral peak postponement and virological suppression better than the non-delay (figure 4.2 and 4.3).

Another dimension to the analysis was the removal of the delay component under the following conditions: justification of the qualitative conduct of the three variables such as CD4+T-cell(x), HIV(y), and CTL (z) and this time, not controlling the fundamental reproductive rate of the virus. When intracellular delay was overlooked and the fundamental reproductive number was on grip, equation 2.2 was solved numerically as

per the 6th order Runge-Kutta strategy with now $a_1 = 0.1038$, $a_2 = 3.22$, $a_3 = 2.64$, $a_4 = 7.41$, $a_5 = 4.17$.

Figure 4.4c, (appendix A.3), portrays the quantum of CTL in the blood which congregates at a universal 'point. Figure 4.4(d) (appendix A.3) centers around the conduct of the compactness of HIV and CTL, as they approach the vanishing stretch to confirm the connection amidst the virus and the immune response.

Therefore, the numerical outcome represented in Figure 4.4(a, b, c) (appendix A.3) correlates with the theoretical conjectures anticipated in Proposition 4.2(ii) and equation 2.2. Hence, a steady state was attained at (0.83, 0.46, 0.46), when $a_3 > 1$. This intimates that the essential conceptive pace of the infection is not under control hence, the decline rate of viral production is lower than the production rate. Infection rate emerges and more virions are produced in the blood.

Contrary to the above, the model was further analyzed with the delay component (DDE), under the following conditions: justification of the qualitative conduct of the three variables such as CD4+T-cell(x), HIV(y), and CTL (z). The fundamental reproductive rate of the virus was uncontrolled and equation 4.1 was solved numerically using the 6th order Runge-Kutta technique with $a_1 = 0.1038$, $a_2 = 3.22$, $a_3 = 2.64$, $a_4 = 7.41$, $a_5 = 4.17$, $\tau = 0.19$. Figure 4.5(a, b) (appendix A.4), portrays the quantum of CTL in the blood which congregate at a universal point. Figure 4.5(d) (appendix A.4) centers around the conduct of the compactness of HIV and CTL in the blood. The level of CTL and HIV in the blood approaches the vanishing stretch, to confirm the connection amidst the virus and the immune response.

Therefore, the numerical outcome represented in Figure 4.5(appendix A.4) correlates with the conditions of proposition 4.2 (ii) and equation 4.1. Hence, when $a_3 > 1 \; and \; \tau < \tau_c$, a constant steady state of (0.83, 0.46, 0.46) was attained. This intimates that the essential conceptive pace of the infection was not under control, hence declining the rate of viral production. Infection rate emerges and more virions are produced in the blood. The elongation of the infection leads to the inception of AID (Figure 4.5)

In relation to the conditions imposed on the adopted model, a validation of the model is ascertained by relating it to potential treatment strategies for compliance. The adopted STI under consideration is significant due to limited ARV accessibility. It is also worth at asset restricted areas. Hence, such areas do not have consistent access to treatment and could lead to the escalation of the virus. A typical example is the restricted medication accessibility and sometimes shortage of TB vaccines.

In lieu of the various treatment strategies considered, the 24 days on treatment and 4 days off- treatment were found to be reliable. 24/4 system created a cost sparing of 14%, when contrasted with the continual therapy treatment. It is essential to note that the 4 days off therapy, allows the body some time to assimilate the medication without essentially influencing viral concealment. This is highly applicable in places or locations were ART is constrained. Refreshingly, it is smarter to stop treatment for a short period of time, instead of abandoning the whole process due to shortage of medication. This suspension lessens the possibility of curtailing drug resistance mutation, which may arise as a result of expanding viral haul, coupled with constant reduction of medication.

5.3 FUTURE DIRECTIONS

The DDE model created here depends on the ODE model, which was upgraded with the delay component to ascertain the viral haul of an individual. The embedment of intracellular delay depends on the time interval relevant for the body to produce virions.
However, the developed DDE model is authenticated through the recommended STI systems. The STI systems were developed based on strict ethical human data. Therefore, the verification of the recommended STI system is a gate way for future research and adoption [137].

Again several works have been done in this area which includes ODE modelling, optimal control and open-loop control [1137,165,], besides most of these models came

short of the addition of intracellular component, which appears to diminish viral haul, hence an exciting area for further research.

Notwithstanding, due to increased imposition on treatment interruptions the study recommends for the application of controlled techniques to enhance the adopted model.

Finally, the use of optimal control with distributed delay could also be exploited due to increase in target cells complexities [125, 132].

5.4 CONCLUSION

In reference to the aim of the study, the sturdiness of the model with delay (equation 4.1) and without delay (equation 2.2) was assessed. Numerical simulations were used to consolidate the results.

The demands for the stability of Hopf bifurcation were authenticated in itemizing the initial conditions of the model (figure 4.1). The existence of Hopf bifurcation [12,137] has been proved and hence occurs when, τ passes through the critical value τ_c.

The analysis of the results indicated that when the basic reproductive rate of the virus was under control and the delay component τ were embedded in the model to verify the qualitative behavior of the three variables, such CD4+Tcells (x), HIV cells (y) and CTL (z). It was concluded that when $a_3 < 1$, then by proposition 4.2(i): a steady state exists at (1,0, 0). Therefore the pace of infection of the virus is under control and the decline rate of viral production is higher than the production rate at δ_1/δ_3

Conversely when $a_3 > 1$, then as per proposition 4.2(ii) : a non-existence steady state occurs. Therefore the pace of the contagion is higher than the decline rate at δ_1/δ_3 and AIDS intercepts. [1, 16]

Adherence to the conditions imposed on proposition 4.2(i) when $a_3 < 1$, intimates that the reproductive ratio of the virus is under control. This signifies a stable CD4+ T cells, hence adherence to therapy could delay AIDS interception. Further, by the conditions of

proposition 4.2(i) we have revealed an abortive attempt by the virus, due to the consistent increase in CD4+ T cells (figure 4,4). Hence, CTL consequently eliminates the virus from the body. This is made possible when CD4+ T cells converges at δ_1/δ_3

Again sustenance of the imposed conditions on proposition 4.2(i), is central to virological suppression and increased life expectancy under HIV [122, 141, 152]. Therefore it is imperative to ascertain the time frame, for the adaptive immune response of the body to emerge in regulating viral replication. This is supported when $a_3 < 1$.

Further, from the above deductions, patients with strong CTL and CD4+T cells will have a higher stable state and low viral contagion. This indicates that patients with low CTL and CD4+T cells will demonstrate a higher rate of viral infection.

Consequently when the emanation of delay from latent cells is kept extremely low, then the immune reaction could be kept at a significant level. However the concepts of suppressing viral particle from emanating to larger quantities are relevant in the manufacture of drugs. The administration of drugs to HIV tainted individuals are made effective through the STI systems, which were discussed in detailed in chapter four.

Referencing the challenges associated with HIV tainted individuals seeking for treatment and the need to maximize the benefits accruing from treatment, requires a suitable STI system. This study articulates structured treatment interference as a potential method for accomplishing low treatment cost whilst, keeping up with fruitful treatment options, especially in asset restricted areas. Interestingly, past disappointment on the usage of the traditional treatment options, has necessitated the use of STI for better suppression of the infection level. [133,134]

It’s imperative to insinuate that the treatment interference models recommended by this study requires a short period off medication, meaning that treatment should just be expelled for some few days to allow for drug assimilation. The short interference period

demonstrates how unfruitful longer-term interference systems, have been over the years and hence the need for future alternatives.

Further, in compliance with the rigorous analysis imposed on treatment options, the study hereby recommends for a short period off medication. This certifies that treatment should be expelled for only few days to allow for drug assimilation [68]. Therefore In reference to the imposed interactions on STI systems, the study recommends for the 24 days on treatment and 4 days off treatment for compliance. 18 days on treatment and 3 days off treatment is also supported by the study. [8, 12]

Finally, it is further suggested that due to increase in treatment imposition, the recommended STI models (24 days on treatment and 4 days off treatment: 18 days on treatment and 3 days off treatment) could be made more potent and viable when controlled theory techniques are applied for future advancement.

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APPENDIX A.1

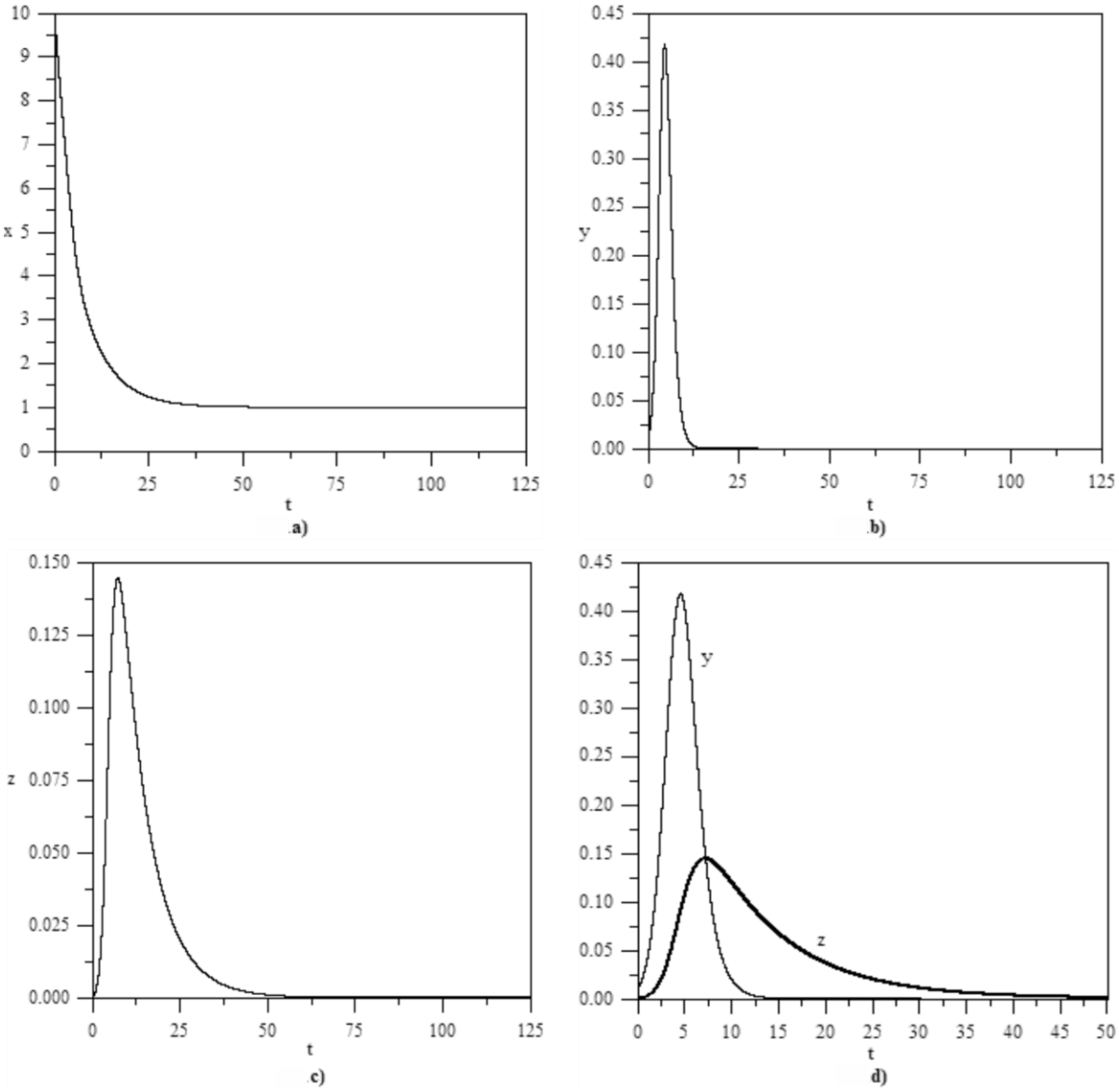

Figure 4.2 (a, b, c, d) shows the Numerical simulation of the model without the delay component.

Figure 4.2(a) shows how the quantum of CD4+T-cells approaches zero, while 4.2(b) and 4,2(c) shows the amount of HIV and CTL in the blood respectively Figure 4.2(d) shows how the virus component decreases over time as CTL approaches zero.

APPENDIX A.2

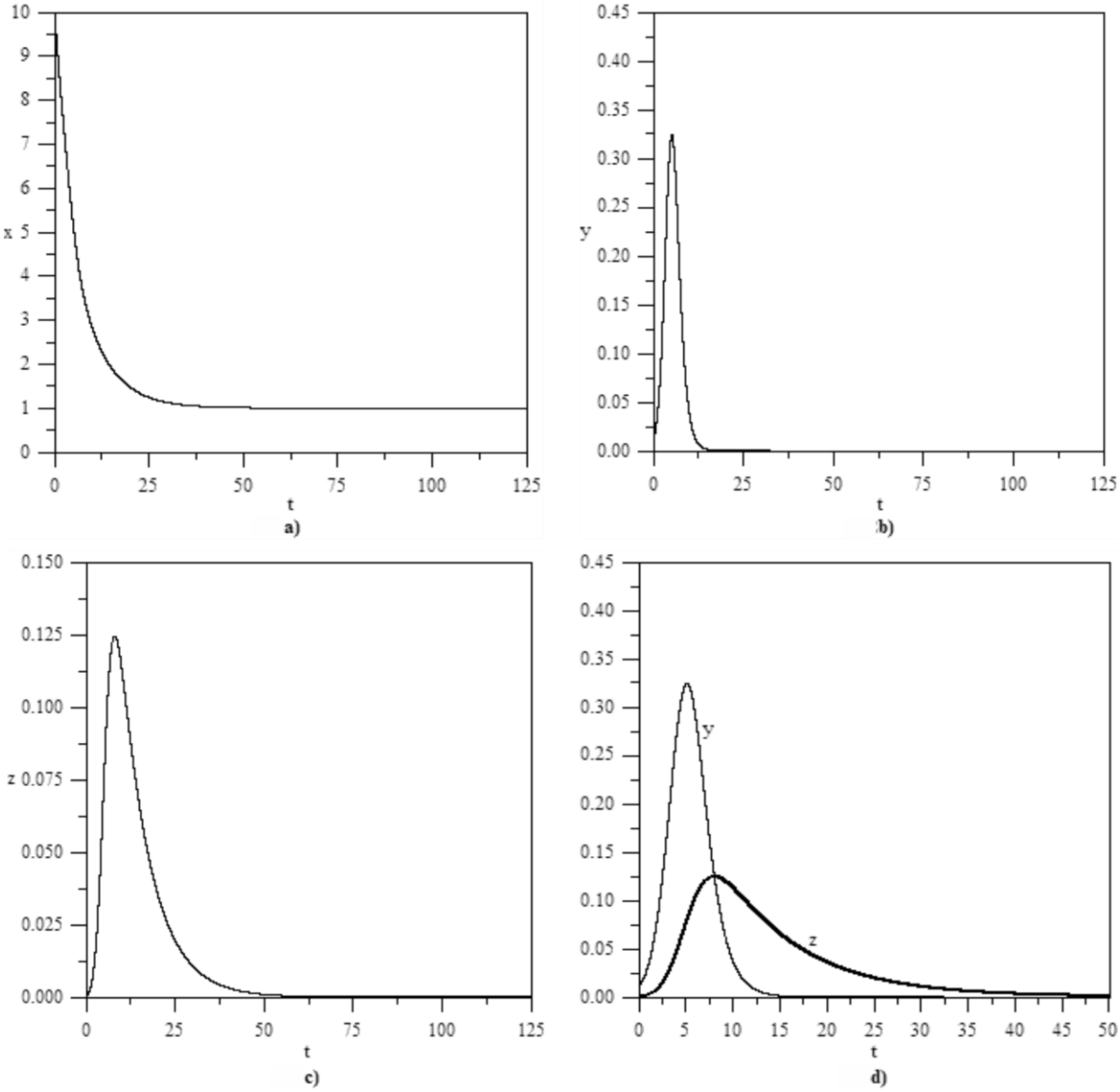

Figure 4.3(a, b, c, d) shows the Numerical simulation of the model with the delay component system.

Figure 4.3(a) shows how the quantum of CD4+T-cells approaches a constant value whilst 4.3(b) and 4.3(c) shows how the quantum of HIV decreases whilst CTL remains constant over time.

Figure 4.3(d) shows how the virus component decreases over time as CTL in the blood weakens and approaches zero

APPENDIX A.3

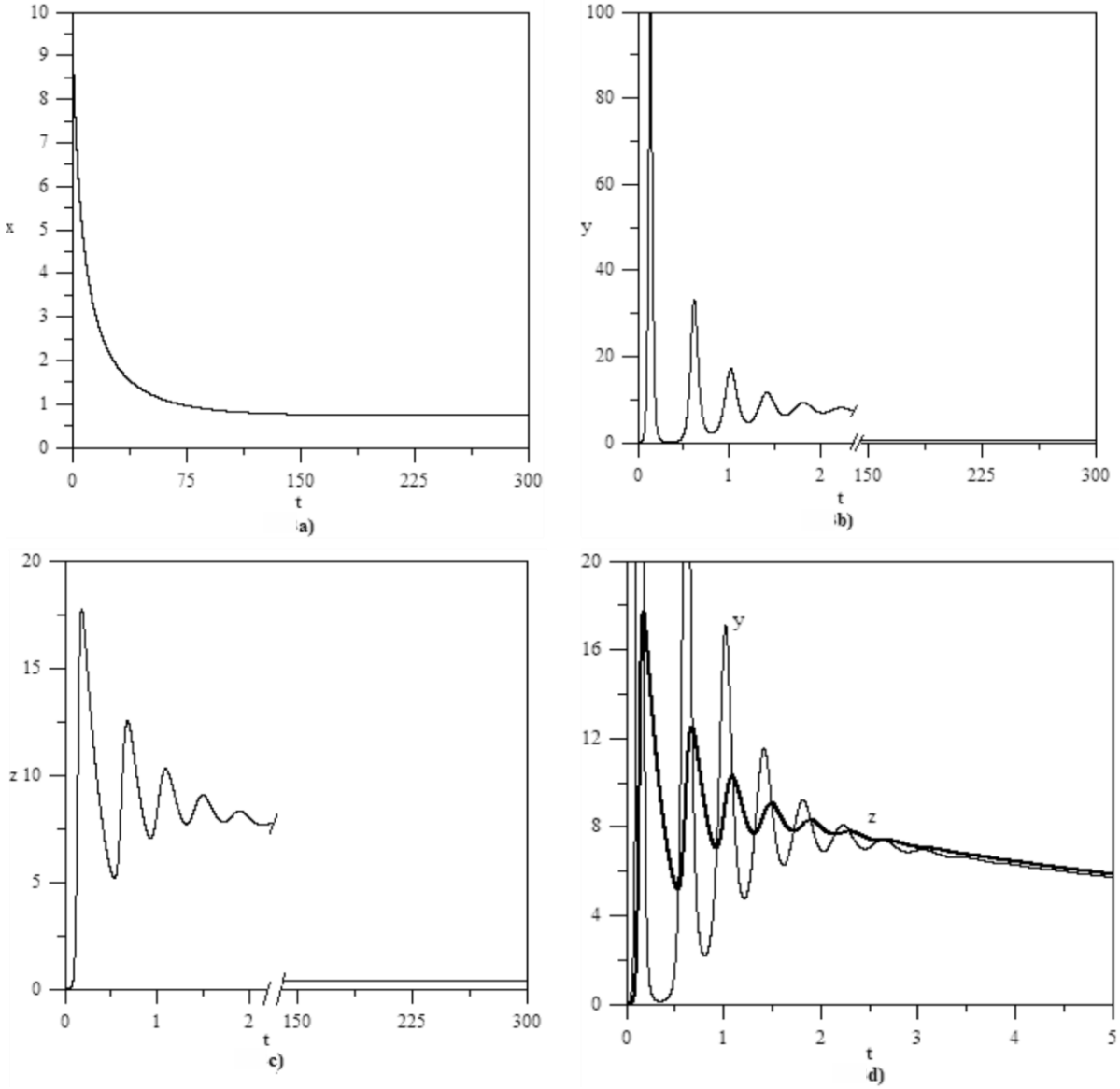

Figure 4.4(a, b, c, d): shows the numerical simulation of the model without the delay component and the reproductive number is not constant

Figure 4.4(a), the quantum of CD4+T cells approaches a constant value: 4.4(b) and 4.4(c) shows how HIV and CTL component in the blood fluctuates before assuming a common point, with time

Figure 4.4(d) depicts an escalation of the virus as CTL level decreases drastically

APPENDIX A.4

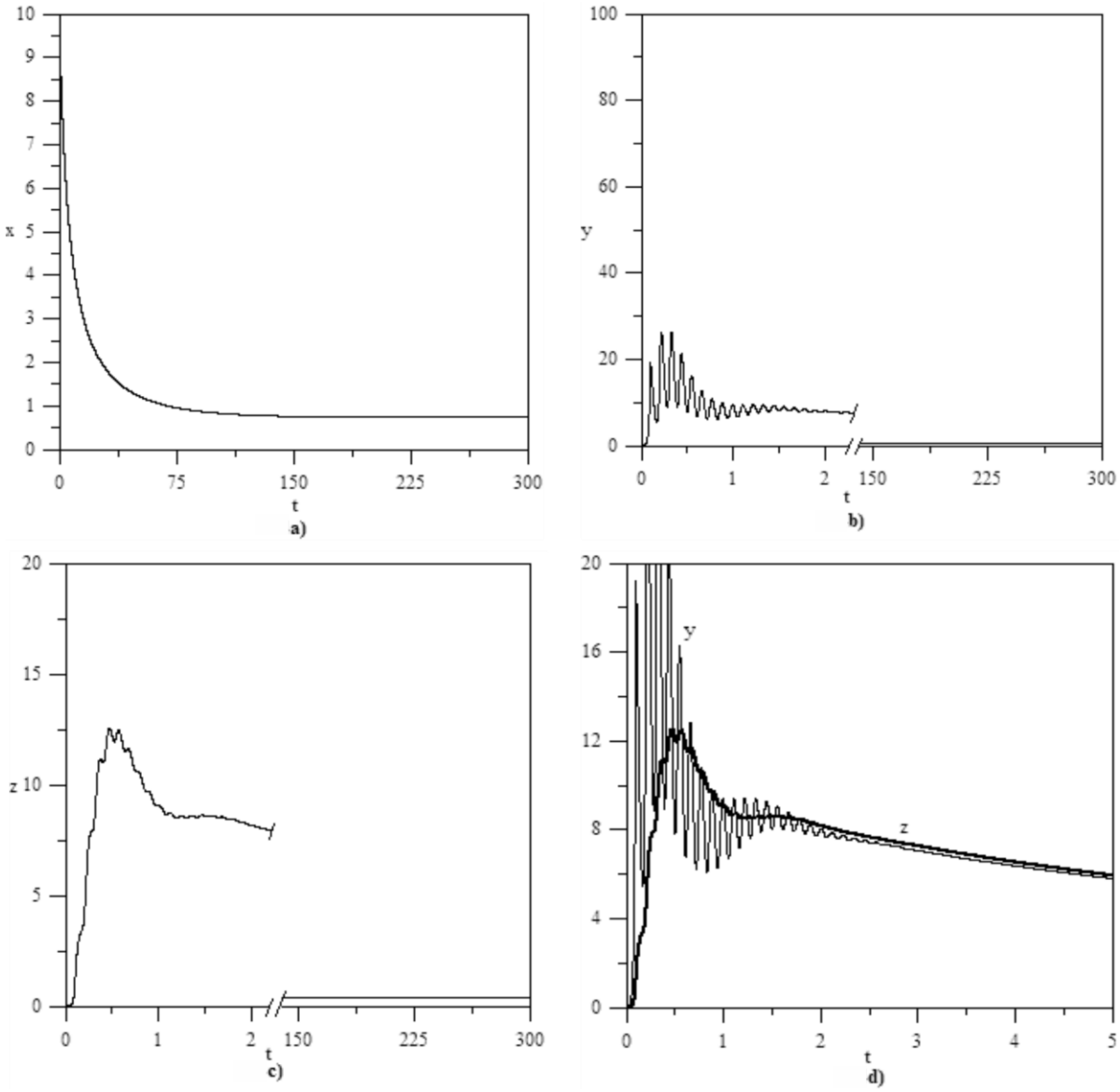

Figure 4.5(a, b, c, d) shows the numerical simulation of the model with delay whilst the reproductive number is not constant.

Figure 4.5(a) shows how the quantum of CD4+T cells decreases over time and assume a constant value: Figure 4.5(b) and 4.5(c) shows fluctuations of HIV and CTL in the blood. The Virus has reached an uncontrollable state as CTL decreases

Figure 4.5(d) shows an escalation of the virus component whilst CTL diminishes drastically for the interception of HIV.

APPENDIX A.5

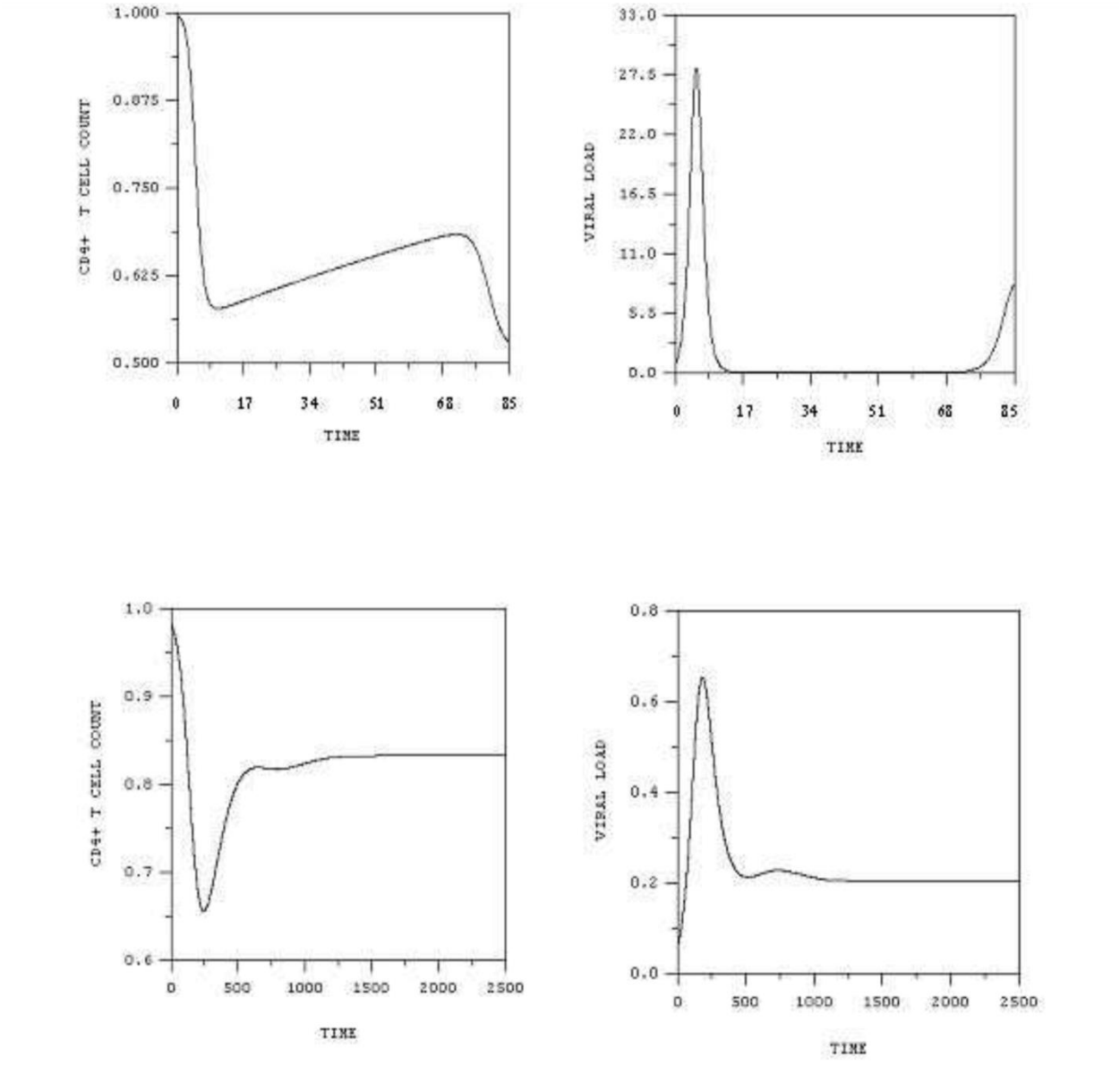

Figure 4.6 Plot for a full blown AIDS with low CD4+ cells and viral load

APPENDIX A.6

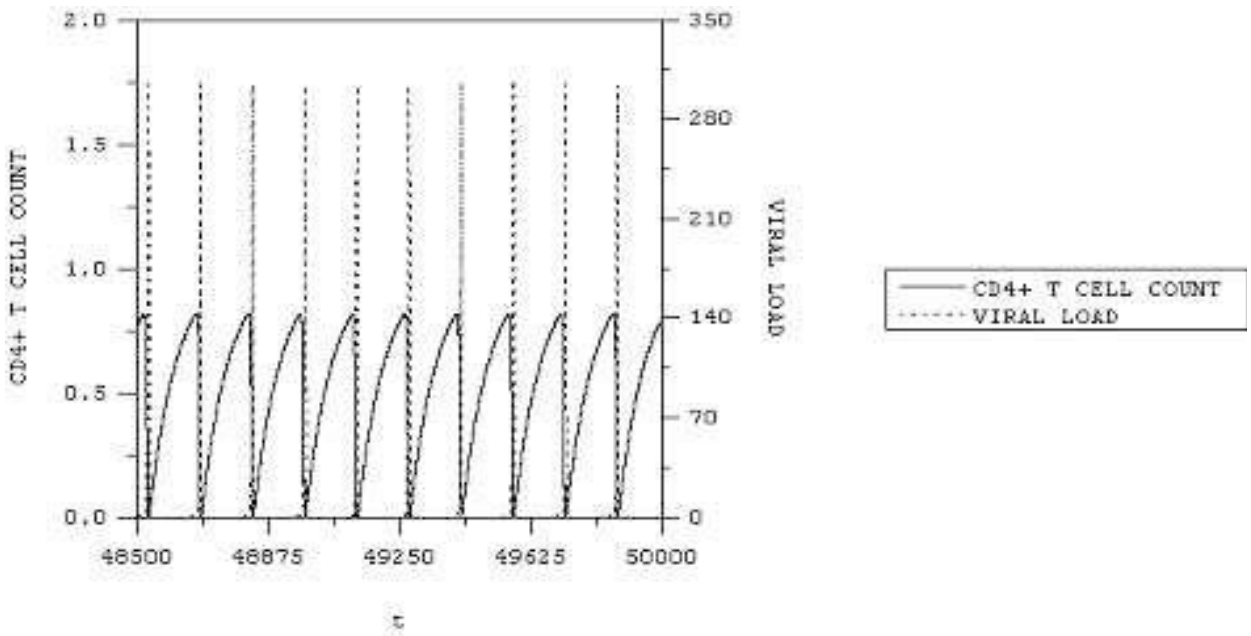

Figure 4.7: A plot of CD4+ T cells against viral load

APPENDIX A.7

Patient	CD4+Tcells (mm^{-3})	Viral load ($ml \times 10^{-3}$)
1	70	181
2	110	50
3	210	80
4	162	112
5	257	76
6	300	163
7	373	171
8	95	117
9	215	90
10	152	42
11	107	113
12	36	223
13	32	19
14	91	82
15	342	173

Table 4.2: HIV viral load of patients using the log value system of measurement

APPENDIX A.8

Variable	Category	% Frequency
Outcome of patients	Completed	180(70.3%)
	Lost follow up	76(26.9%)
Gender	Female	108(60%)
	Male	77(40%)
Age	≤ 25	8(4%)
	26-31	20(11%)
	32-37	52(29%)
	38-43	4(27%)
	44-49	28(16%
	≥ 50	24(13)

Table 4.3 Percentage viral load level after ARV administration