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A Within Host System Dynamics Model of HIV/AIDS, Tuberculosis and Malaria Treatment Policy

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A thesis submitted in Partial Fulfilment for the Award of the Degree of Doctor of Philosophy in Computer Science of University of Nairobi

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Declaration of Authorship

I, Mwangi Henry N., declare that this thesis titled, 'A Within Host System Dynamics Model of HIV/AIDS, Tuberculosis and Malaria' and the work presented in it are my own. I confirm that:

- Where any part of this thesis has previously been submitted for a degree or any other qualification at this University or any other institution, this has been clearly stated.
- Where I have consulted the published work of others, this is always clearly attributed.
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Dedication

To my late dad Peter Mwangi Njoroge. You left when I was just about to turn the corner, Aug-5-2015

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Abstract

Simulation and Modelling have a good history of application in numerous decision support health cases where the objective is of a managerial or policy nature. Information and Communication Technologies(ICT) in health care decision support with the application of simulation methods is receiving attention as indisputable advantages of these methods are getting widely recognized. Cutting edge eHealth researches have led to significant technological achievement, covering an expansive range of health services. Understanding the dynamics of disease is of crucial importance particularly in terms of risk assessment and evaluation of intervention policies against a large-scale epidemic outbreak. However most of the information is available after the spread itself, and preemptive assessment is far from vital.

Chronic diseases such as HIV, TB and Malaria e.tc. are widely studied and modelled. Apparently the researches carried out have been on the pathogenesis of the diseases individually i.e. HIV alone, TB alone and Malaria alone. Others researches have focussed on HIV and TB or HIV and Malaria but none has gone beyond trio infections which is quite common. With the advent of HIV, PLHIV are more prone to cofactors with the resultant of immune activation. Immune activation leads to the increase of HIV viruses as a result of bursting of resting TH1 cells once they are activated since HIV resides in resting TH1. This research aimed at studying immune activation for people living with HIV when they are attacked by other diseases like TB and Malaria which is quite common. The research was bordering on cells of the immune system that conduct adaptive immunity.

Immune system is quite complex to understand even so when the system is attacked by pathogens. As such, System Dynamics Modelling was applied to improve the understanding of immune system behaviour for people living with HIV in light of Malaria and TB. To understand the full range of immune cells and their activities, behaviour of pathogens and communication of immune cells to resist attack, field studies were carried out. Problems associated with the immune system inability to curb pathogens as a result of immune activation, how the HIV virus takes advantage of activated cells through attack by mycobacterium and merozoites were sought after in the field studies. The Research presents the overall architecture of the HTM system which constitutes cells, agents of the immune system like interleukins, interferons, natural killer cells as well as information flow. Qualitative research was done using causal loop diagrams as well as simulation through stock and flow diagram to capture the complex and dynamic nature of the immune system. The use of CLD provided deeper understanding of the structure of the cells of the immune system while simulation through stock and flow diagram provided the dynamic behaviour of the same.

The results of the study show that activation of the immune system by TB and Malaria for people living with HIV have overwhelming influence in their health. The study reaffirms the need to maintain rested TH1 cells, as wells develop policies

or regimens to deal with synergistic activities of TB and Malaria to PLHIV. The developed HTM system demonstrates the dynamics arising from the complexity, delays and non-linearlity which characterize the immune system. Based on the results of the simulations experiments, the suggested intervention that could improve the lives of PLHIV include the following: designing of relevant health IS, strengthening of healthcare system, adoption of ICTs innovations to improve efficiency and improving literacy levels.

The HTM model and the causal loop diagrams presents significant knowledge in terms of structure and the understanding of HTM system. The model captures requisite information requirements, key activities of the immune cells which represents the adaptive nature or collapse of the immune system. The model provides tools that tests different policies thus making it useful for strategic planning and policy debate.

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ABM-Agent Based Modelling

AIDS-Acquired Immune Deficiency Syndrome

ART-Anti-Retroviral Therapy

ARV-Anti-Retro-Viral

ARC-AIDS Related Complexes **BOT**-Behaviour Over Time **CD4**-Cell Differential Cells

DOTS-Directly Observed Treatment, Short-course

DSM-Dynamic Synthesis Methodology

EU-European Union

GRASP-Goals, Resources, Actions, Structures, and People

HAART-Hyper-Active Anti-Retro-Viral Therapy

HIV-Human Immuno-Deficiency Virus

HTM-HIV, Tuberculosis and Malaria **ICAD**-Inter-agency Coalition on AIDS and Development

ICAP-International Center for AIDS Care and Treatment Programs

ICT-Information and Communication Technology

IDU-Injection Drug Users

IVV-Independent Verification and Validation

LTB-Latent Tuberculosis

LTBI-Latent Tuberculosis Infection

M.TB-Mycobacterium Tuberculosis

MCM-Managing from Clarity Methodology

MDRTB-Multi-Drug Resistant Tuberculosis

MI-Malaria Intervention

MIT-Massachusetts Institute of Technology

NGO-Non-Governmental Organizations

OI-Opportunistic Infections

PLHIV-People Living with HIV

SD-System Dynamics

SIER-Susceptible, Infected, Exposed, Recovered

SIR-Susceptible, Infected, Recovered

SIS-Susceptible, Infected, Susceptible

TB-Tuberculosis

UK-United Kingdom

V&V-Verification and Validation

WHO-World Health Organization

Definition of theoretical terms To put this research into context, the following terms used in this thesis are defined.

1. **Modelling**: This is the process of generating abstract, conceptual, graphical or mathematical models. Science offers a growing collection of methods, techniques and theory about all kinds of specialized scientific Modelling (Forrester 1961).

2. **Triad-infection**: According to Szekely (2010), public health triad (or simply, the triad) describes the interactions among humans, animals, and the environment using health-related consequences but in this thesis, it means presence of three diseases within a host.

3. **Systems Dynamics** is a of study of information feed-back characteristics to show how a system structure, amplification and time delays interact to influence the success of an enterprise using computer simulations (Forrester 1961).

4. **HIV/AIDS**: PubMed, 2011 defines Human immunodeficiency virus infection / acquired immunodeficiency syndrome (HIV/AIDS) is a disease of the human immune system caused by the human immunodeficiency virus (HIV). Human immunodeficiency virus (HIV) is a blood-borne virus typically transmitted via sexual intercourse, shared intravenous drug paraphernalia, and mother-to-child transmission (MTCT), which can occur during the birth process or during breastfeeding. HIV disease is caused by infection with HIV-1 or HIV-2, which are retroviruses in the Retroviridae family, Lentivirus genus (Bennett et al. 2013).

According to Bennett et al. (2013), the patient with HIV may present signs and symptoms of any of the stages of HIV infection. No physical findings are specific to HIV infection; the physical findings are those of the presenting infection or illness. Manifestations include the following:

- Acute seroconversion manifests as a flulike illness, consisting of fever, malaise, and a generalized rash
- The asymptomatic phase is generally benign
- Generalized lymphadenopathy is common and may be a presenting symptom
- AIDS manifests as recurrent, severe, and occasionally life-threatening infections or opportunistic malignancies
- HIV infection can cause some sequelae, including AIDS-associated dementia/encephalopathy and HIV wasting syndrome (chronic diarrhea and weight loss with no identifiable cause)

5. **Tuberculosis:** From PubMed, 2011 Pulmonary tuberculosis (TB) is caused by the bacteria Mycobacterium tuberculosis (M. tuberculosis). One can get TB by breathing in air droplets from a cough or sneeze of an infected person. This is called primary TB. Most people will recover from primary TB infection without further evidence of the disease. The infection may stay inactive (dormant) for years. However, in some people it can be reactivated. According to Center for Disease Control (CDC), TB disease symptoms may include:

   - A bad cough that lasts 3 weeks or longer
   - Pain in the chest
   - Coughing up blood or sputum (phlegm from deep inside the lungs)
   - Weakness or fatigue
   - Weight loss
   - No appetite

- Chills
- Fever
- Sweating at night

Additionally the following Conditions or activities that place healthy population to be at increased risk of TB:

- Spending spent time with a person known to have TB disease or suspected to have TB disease
- Having HIV infection or another condition that puts you at high risk for TB disease
- Having signs and symptoms of TB disease
- Being from a country where TB disease is very common
- Living or working where TB disease is more common, such as a homeless shelter, migrant farm camp, prison or jail, and some nursing homes
- Use of illegal drugs

6. **Malaria:** Malaria is caused by a parasite that is passed from one human to another by the bite of infected Anopheles mosquitoes. After infection, the parasites (called sporozoites) travel through the bloodstream to the liver, where they mature and release another form, the merozoites. The parasites enter the bloodstream and infect red blood cells. According to PubMed (2011), Malaria symptoms usually appear about 12 to 14 days after infection. People with malaria have the following symptoms:

   - abdominal pain
   - chills and sweats
   - diarrhea, nausea, and vomiting (these symptoms only appear sometimes)
   - headache
   - high fevers

- low blood pressure causing dizziness if moving from a lying or sitting position to a standing position (also called orthostatic hypotension)
- muscle aches
- poor appetite

In people infected with P. falciparum, the following symptoms may also occur:

- anemia caused by the destruction of infected red blood cells
- extreme tiredness, delirium, unconsciousness, convulsions, and coma
- kidney failure
- pulmonary edema (a serious condition where fluid builds up in the lungs, which can lead to severe breathing problems).

7. Thesis: According to oxford dictionary, thesis is a noun that refers to a proposition stated or put forward for consideration, especially one to be discussed and proved or to be maintained against objections.

8. Conditions of an infected person with triad disease: The symptoms of a triad infection are a combination of the above for HIV, malaria and Tuberculosis.

Chapter 1

Introduction

1.1 Background Information

Health care services' demand by population in general in variant age groups is on the rise as they are constantly seeking better and more access to health services (Altsitsiadis et al. 2009). Additionally age, modern lifestyle and the rising prevalence of diseases due to increased incidence rates, contribute to this demand. Also, people have become aware of their health needs and do not necessary depend on health care providers for their diagnosis. Additionally, health care providers face rising costs and rivally over both customers and resources, while capital risks are growing and legitimate frameworks are getting tigher. The resulting stress-equation that is shaping over the health systems is reflected in the underlying challenges to provide the best health care under the limited budgetary conditions (Altsitsiadis et al. 2009, EUnion 2010).

Information and Communication Technologies(ICT) in health care decision making with the application of simulation methods is receiving attention as indisputable advantages of these methods are getting widely recognized (Altsitsiadis et al. 2009, EUnion 2010). Cutting edge eHealth research has led to significant technological achievement, covering an expansive range of health services. Simulation and Modelling have a good history of application in numerous decision

support health cases where the objective is of a managerial or policy nature. Lack of these simulation tools suggest weaknesses (systemic) in the respective decision support system. eHealth applications are believed to bring a beneficial impact on both sides of this systemic problem (Altsitsiadis et al. 2009, EUnion 2010).

This research aims at combining existing theories particularly in understanding of triad infections of HIV, TB and malaria in selected regions of Kenya. Through simulation of HIV progression, we will shed light on the effects malaria and TB on HIV and making alternative choices where necessary in the model, to better understand HIV and subsequently improved policies will be suggested which otherwise would be unobtainable. Its is believed that the resultant of this study can be generalized to other regions.

Understanding disease dynamics is of critical importance especially in terms of risk assessment and policies intevention evaluation against a large-scale epidemic outbreak. However, the much needed information get available after the epedimic itself has occured, and preemptive assessment is far from vital (Borshchev & Filippov 2004). As such, health care systems and emerging diseases modelling have become areas of interest for research and professional development as well as policy evaluation. Also, and according to research carried out by Borshchev & Filippov, 2004 direct experiments with some diseases like HIV/AIDS and its transmission is not ethical and feasible beside being quite expensive. The author suggest that Simulation Modelling experiments strategically for real situation can uncover opportunistic disease characteristics posed to people living with HIV and also may generate insights on what are the underlying causes and what potential intervention strategies may be pursued.

In Africa, Tuberculosis comes in advance of others as an indicator of initial visible symptoms of HIV causing AIDs amongst PLWHIV (Corbett et al. 2006). Corbett et al., (2006) observe in their research that TB becomes extremely complicated with respect to infectiousness as most patients become infectious immediately after initial treatment even if they are HIV positive. According to Mukadi et al.,

(2001), Africa has about 16-35% patients dying while on anti-tuberculosis treatment compared with 4-9% in HIV negative patients.

Interventions in chronic diseases which includes HIV/AIDS, tuberculosis, pneumonia, malaria among many is quite complex. The level of infectiousness in the population is dependent on incidence of new cases and progression of disease, deaths, and the interventions ideally reduce mortality rates leaving more people with the disease alive and requiring care at a later point in time. In the same note, infected population prevented from advancing to a more serious stage of the illness will have fewer health care requirement at a later point in time. Also infected population kept from developing the disease altogether have even fewer needs and better prognoses (Altsitsiadis et al. 2009). What mix of preventive programs and more active treatment of those who already have the disease yields the best results for the community? How might screening programs that identify these illnesses at an earlier stage improve outcomes? To fully evaluate these interventions, it is necessary to be able to track the effects of interventions over time. ICT can play a major role in simulating this situations (Altsitsiadis et al. 2009, EU 2010).

Health policies were believed to be about the provision and funding of medical care (WHO, 2003), while medical care can prolong survival and improve prognosis after some illness, but more important for the health of the population as a whole are the social and economic conditions that make people ill and in need of medical care ICAD (2010).

These policies may have significant infrastructure costs, including costs of program personnel (administrators, consultants, clinical care specialists) and the costs of information systems that allow providers and patients to record and share data electronically. Adoption of the program leads to a shift in care patterns, typically toward greater intensity of planned, non-urgent care, which in turn, directly affects health care costs (Altsitsiadis et al. 2009). This shift in care is intended to reduce the incidence and progression of disease and consequent complications and deaths. Reductions in the health care costs associated with diseases, as well as productivity losses due to disability, ideally would offset the added costs of infrastructure and

greater intensity of planned care, resulting in a net savings for the community as well as improving outcomes for patients (Altsitsiadis et al. 2009).

The need for models for care delivery cannot be overstated. At a minimum, efforts to develop models requiring fewer health care professionals are needed (Joynt & Kimball 2008). The need for innovation extends beyond creating models to deliver care with fewer workers to creating models that can leverage new roles and technology to deliver care to more individuals at lower cost while preserving and hopefully improving patient quality, safety and satisfaction (Joynt & Kimball 2008)

The economic importance of outcomes to support better understanding of emerging diseases is growing especially as public health services are constrained by lack of resources. In general these outcomes can be partitioned into four elements: prediction, scenario Modelling, optimal control and greater understanding of processes (House et al. 2011)

Accoding to literature, pregnant mothers are more likely to be infected with malaria among PLWHIV (Tkachuk et al. 2001). Malaria parasitaemia and incidence of malaria attacks are high with HIV-induced immunosuppression. Additionally, malaria severity and its related deaths have sky rocketed in people living with HIV of all ages living in regions with unstable malaria transmission (Tkachuk et al. 2001). The simple fact that TB and malaria occur together geographically and that they leading causes of death amongst people living with HIV makes addressing TB/malaria/HIV synergy critical in any strategy that aims to reach those most in need (ICAD 2010). The situation is made even worse by the fact that these diseases are prevalent in regions hit by poverty and where social amenities are scarce (ICAD 2010, Howard et al. 2004, Hochman & Kim 2012). Millions of dollars invested in addressing HIV are wasted if patients put on ARTs die because they cannot access malaria/TB drugs regimens that costs as little as $20 per person. Progress towards universal treatment and care for people living with HIV will not be met if they are dying from TB and malaria (ICAD 2010, Howard et al. 2004, Hochman & Kim 2012). The continued disconnect between

TB, malaria and HIV policy and programming is ineffective, inefficient and fiscally misguided. Collaborative approaches could, quite simple and most importantly, ensure that more lives are save (ICAD 2010). A collaborative effort in Modelling TB/malaria/HIV trio-infections as much as it is complex system, as an enabling role in exploration, understanding and explanation of disease behavior is crucial. In order to render such explanations of TB, malaria and HIV complex models noble, then one must appreciate the role of complexity and chaos theory in shedding light to these complex systems.

1.2 Causes of Problems in Trio infection of HIV/AIDS, TB, and malaria

This section summarizes causes of problems and misunderstandings surrounding the trio-infections of HIV, TB and malaria. The problems are listed in order of their importance and priority.

According to ICAP (2007), Tuberculosis is a much more serious condition for persons with HIV infection. HIV attacks the immune system which is critical for preventing progression of LTBI to TB disease and in helping control disease once it develops. When people have both LTBI and HIV infection, their risk of progression from LTBI to TB is increased 50%-100% fold (ICAP 2007).

Analyzing the research carried out by Brieger (2011), the region of the world where there are high incidence rates of malaria is Africa and incidentally it coincides with the highest HIV prevalence. The situation is complicated further when some co-infections, like malaria pathogens infect those people ailing with HIV/AIDS. The Bio-Medical Journal cited by Brieger (2011) indicate that, "there is a strong evidence for a rise of biological interaction between malaria and HIV within the host". As noted by the study done by Barnabas et al. (2011), there isa strong evidence of reduced viral load as a result of malaria treatment and equivalently high viral load where no treatment is sought

Lund et al., (2012) allude that HIV is a retrovirus that primarily infects the CD4+ T-cells. The infection is initiated with the adsorption of the virus particle to the cell surface and the binding of the viral gp120 glycoprotein to the CD4 receptor in the cell membrane. This binding causes the viral envelope to fuse with the cell membrane and allows the virus proteins and genetic material to be released into the cell. The success of the virus in this way hinges on its ability to attack precisely those cells that are meant to orchestrate its destruction (Lund et al. 2012). In addition, the viral infection contributes to the proliferation of the CD4+ T-cells, thus increasing the target population.

From ICAP (2007), more than one third of the global population is latently infected with Mycobacterium tuberculosis (LTBI), the bacterium that causes TB disease: and for each second that passes, a new person becomes infected. About five to ten percent of HIV-negative people with latent TB infection ever have progression of their LTBI and become ill with TB disease. People with TB disease of the lungs (pulmonary TB) can spread infection to others via coughing which introduces microscopic particles containing Mycobacterium tuberculosis into the air (ICAP 2007). Others including those that have HIV or even malaria may breathe in these infectious particles and become infected. Each individual with TB disease will infect an average of 10 to 15 others if they go undiagnosed and untreated and the cycle of transmission continues. In 2004, there were 8.9 million new cases of TB and 1.7 million deaths due to TB.

1.3 Scope of the research

For the purposes of this thesis the research will concentrate on MDG 1 and 6. The unit of analysis will be an individual and the cases will be studied for a period of 3 Months.

1.4 System Thinking Adoption

Healthcare and care delivery is a complex system because of the many entities involved ranging from care givers, patients, reaction to drugs, drugs administration, adherence to medication e.t.c and keep on fluctuating every now and then. System thinking has been applied widely in tackling and gaining leverage to problems with excessive fluctuations or that have slow response to input and have seen to give remarkable results. The view of an organization as a system assist in solving problems from a broader perspective. Present-day health care problems can be easily investigated by adopting realistic approach because of their increasingly complex nature (Forrester 1961, Sterman 2000). As an example, Ford (1996) explained the dynamics of the US energy sector from the 1880s to the 1990s using dynamic reasoning pointing out various policies and pointed out how spectacular the outcomes were in the long-run, Rwashana & Williams (2008) used dynamic modelling to explain the impacts of immunization in Uganda and how it affects children whose mothers were not immunized or did not adhere to immunization program. In this study systems thinking will be adopted.

A particular approach to system thinking is System Dynamics was adopted. This approach, according to Forrester (1961),is mostly suited in the study of complex systems such as corporations, markets, industries, healthcare, education and economies. For that reason, System Dynamics is the most suitable system approach for investigating and gaining leverage for system that witness fluctuations and are marked by delays and as such trends of activities that surrounds HIV progression, care delivery, dealing with adherence to drugs, opportunistic infections like TB, malaria among others could be best addressed using this methodological approach.

Of particular importance to modelling are the stages of SD as indicated in Figure 3.2, that involve; defining the purpose of the model, defining the model boundary and identify key variables, describing the behavior or the reference modes of the key variables and diagramming the basic mechanisms, the feedback loops, of the system, development of Dynamic hypothesis that explains the problem cause.

The third stage is building of the model of the system at the root of the problem identification then testing to ensure that it reflects the real world behavior. This is then followed by validation of the model behaviour to confirm that the model alternative policies serves to alleviate the problem. The final step to this methodology is solution implemetation (Forrester 1961).

1.5 Problem Statement

The tragedy of increased deaths due to HIV is well documented (WHO 2004, WHO 2005). Various research have also been carried out to shed light about the disease awareness, and spread and more so Modelling HIV/AIDS and opportunistic infections in-order to understand intervention points and proper regimes at various stages (Sharma et al 2005, Kamal et al, 2007). Most of the research done so far have been on HIV and co-infections Modelling but none if any has shed light on triad infection of HIV, malaria, and TB.

HIV/AIDS since the time of its initial description more than a two and a half decades ago has relentlessly spread all over the world with no sign of abatement. In 2004, there were more than 4.9 million new infections in sub-Saharan Africa and South-East Asia, the same areas that TB has been flourishing unhindered since ages. It's also evident that the same areas habor the vector that spread malaria (plasmodium falciparum) Sharma et al. (2005).

1.6 General Objective

The general objective of this thesis was to Model the Triad Infection of HIV/AIDS, Tuberculosis and malaria using System Dynamics Approach.

1.6.1 Specific Objectives

1. To identify and define factors (variables) that influence immune reactivation for people infection with HIV/AIDS infected persons in the light of TB and malaria to provide variables for the model.

2. To design a system structure model of Trio-infections of HIV/AIDS, TB and malaria.

3. To implement the System Dynamics simulation model for trio infection of HIV, TB and malaria

4. To test and validate the simulation model as a tool to support enhanced understanding of the HIV/AIDS disease progression and co-factors in malaria and TB

1.7 Justification

Advent of HIV/AIDS pandemic has led to a dramatic increase in TB cases. According to Sharma et al. (2005), 9% of all TB cases has been attributed to HIV/AIDS as also 12% of the deaths. TB incidence has gone up by 6 percent due to HIV/AIDS influence, observes Sharma et al (2005). Similarly about 5% Malaria deaths are due to HIV infection in sub-saharan Africa as there is also an estimated 28% increase in Malaria incidence due to HIV according to (Kamal et al, 2007). Human immunodeficiency virus/acquired immune deficiency syndrome (HIV/AIDS), tuberculosis (TB), and malaria are three of the world's leading causes of morbidity and mortality.

Along with the direct health effects, HIV/AIDS, TB, and malaria have far-reaching socioeconomic consequences, posing what many analysts believe are threats to international development and security (Kendall 2011). Because HIV/AIDS cripples the immune system, resurgence of opportunistic diseases is quite common, which results to an increased morbidity and mortality worldwide as observed by Sharma

et al (2005). Similarly malaria and HIV co-infections are a global concern for health organizations (WHO 2006). Deaths due to any of the three diseases, is quite common, partly due to bias of health workers diagnostic tests in favor of their less than perfect clinical judgment, lack of right treatment regimens, or the intervention points or even interaction of drugs once admitted when treating any of the diseases with no information about the others (Mukadi et al. 2001) These diseases are intricately linked to malnutrition, unemployment, alcoholism, drug abuse, poverty, and homelessness (Sharma et al. 2005). As such researchers as indicated in table 1.1 below shows their work that has aided in understanding of HIV/AIDs. Great deal of research has been done by various authors as indicated in table 1.2 below. That withstanding, there is no research that has combined the three diseases to shed light on the dynamics of these triad synergy that has been disastrous to human beings.

In this research therefore, we aim at developing an SD model that will provide insights into dynamics of the immune systems as a result of HIV/AIDS and how TB and malaria impacts on people living with HIV. This will be followed by providing intervention points to curb the opportunistic infections by providing the various regimes at each point.

Table 1.1 summarizes research done on Modelling of HIV/AIDs.

In their research, Lund et al. (2012), used System Dynamics Modelling to demonstrate how it can be used to understand complicated mechanisms related to how the body organs work in particular absorption of glucose, release of insulin etc. In the same breath, Culshaw (2006) research on AIDs, demonstrates the limitations, expectations, and future directions of mathematical methods in Modelling health care systems. She opines that the mathematical Modelling of single causation of AIDS i.e. HIV misses "prediction power" which is important in showing the progression of HIV to AIDS. Additional variables have been used in Modelling HIV progression in particular immune, susceptible, infectious and recovered individual to represent the population. One key thing that Culshaw (2006) pointed out was that of mathematical methods failure to provide understanding of disease mechanisms as well as the nature of the immune system. Culshaw (2006) suggested

Table 1.1: HIV/AIDs Models

Author	Title of Paper	Year of Publication
Ole Lund, Jakob L. Laugesen, and Erik Mosekilde	Concepts in Mechanism Based Modelling	2012
Rebecca V. Culshaw	Mathematical Modelling of AIDS Progression: Limitations, Expectations , and Future Directions	2006
Adams B.M. *et al.*	HIV Dynamics: Modelling, Data Analysis, and Optimal Treatment Protocols	2004
Dominik Wodarz and Martin A. Nowak	Mathematical models of HIV pathogenesis and treatment	2002
Tomas Hraba and J. Araslov Dolezalf	A Mathematical Model and CD4+ Lymphocyte Dynamics in HIV Infection	1996

other framework such as cofactors of HIV to explain immune dysfunction. Results from this were experimental to health care systems and to academicians. The intention of developing the model was to provide laboratory level experiments where various healthcare policy options can be tested to gain sufficient insight into the response of the regimens before the actual implementation can be done. The findings of the study showed there is a lot that policy-makers, consultants, clinicians, researchers in the health industry as well as counselors, or generally, the health sector can do to improve efficiency to higher levels even when they are constrained by their resources thereby eliminating the tendious process of soliciting funds from government financing bodies or donor agencies.

The findings of the study would also provide a basis for educating health sector participants in managing fluctuations in patient health and reaction to the same, in imaginative and collectively beneficial ways. A relatively more stable health sector should therefore improve the care providers performance and patients response to drugs without necessarily compromising on the adherence to the same.

Through simulations, the model would make known a host of different factors that

Table 1.2: TB Models

Author(s)	Title of Paper	Publication Year
Hughes *et. al*	Modelling TB in In areas of High Prevalence	2006
Colijn *et. al*	Mathematical models of TB Accomplishments and future challenges	2006
Carlos Castillo-Chavez Baojun Song	Dynamical models of TB And their Applications	2004
Baojun Song *et al.*	Tuberculosis models with fast and slow dynamics the role of close and casual contacts	2002
E. Jung *et al.*	Optimal control of Treatments in a Two-Strain TB Model	2002
Debanne *et al.*	Multivariate Markovian Modelling of TB: Forecast for the US	2000
Travis C. Porco and Sally M. Blower	Quantifying the Intrinsic Transmission Dynamics of TB	1998

brings together the reference mode indicated in figure 2.6. This factors could be social, economic, political, or structural. System thinking and in particular with application to HIV progression in the light of OI will further our understanding into the real cause and how these factors interact. The simulations will also rid care givers of the many unpleasant surprises and unexpected consequences they face when rendering their services to people living with HIV

1.7.1 Model Boundary, Key Variables and Stakeholders

Literature shows the top level variables that have been accepted widely in Modelling healthcare system are: Susceptible population, Infected Population, Recovery or Removed from the population. In addition to these there are other variables like drug toxicity that play a major role in affecting morphology of other drugs.

Adherence to policies is also important since it affects the subsequent stages. Nutrition also impacts on how the patient responds to drugs. Literature shows that good nutrition can rid the patient of majority of the OIs The model boundary and stakeholders are discussed in chapter 4 and immune system boundary is presented in figure 4.1

1.8 Summary of contributions

The major contribution of this research was the TB, malaria and HIV/AIDs Trio-infection model that constitute a novel scientific knowledge. As presented in figure 2.5 in chapter 2, the stakeholder will be the Government who are the financing agents and who develops the policies. With the different modeled scenarios and subsequent regimens, the Government can direct the limited resources appropriately.

Still with the model, drug manufacturing companies can know the appropriate all encompassing drug to be used to cater for cases of adherence as the has been cited in WHO (2006) as the disturbing problem posed by drug toxicity. In the same token, the ministry for medical services and ministry for public health and sanitation can use the model to facilitate campaigns and where to focus the on as pertains pathogenesis of HIV as well are reaching out to the communities

This tool shall be used as a trial in training situations for decision makers use to identify intervention points on Trio-infections

It added on existing literature on the new understanding of HIV with cofactors through the papers (Mwangi et al. 2015*b*,*a*).

Chapter 2

Literature Review

2.1 Introduction

Disease like HIV/AIDS are chronic in nature and requires patient to be followed medically for the rest of their lives (WHO 2007). The particular component of treatment and care of PLHIV is provision of ART, that is presumed to increase the longevity and quality of life of HIV-infected patients, as well as reducing the onward transmission of the virus. World Health Organization has contributed a lot in promoting a public health approach of PLHIV through ART. This is done through promotion of the rational selection and sequencing of different drug classes into first and second-line regimens with salvage options; simplified and standardized clinical management; and standardized record keeping in order to preserve therapeutic options, minimize drug toxicity and side-effects, maximize adherence and to support the goals of ART. The goals of ART are:

- clinical: This is through perpetuation of life and improvement of its quality;
- immunological: This is promoted to avoid o=opportunistic infections onset through quantitative and qualitative immunological reconstitution;

- virological: The aim here is to reduce or halt completely disease progression and prevent delay in the development of disease resistance through reduction of viral load;
- epidemiological: aimed ideally at the prevention of onward HIV transmission through reduction of its epidemiology(WHO 2007, 2006).

Medical history, examination findings, exact history of ART, laboratory results, results of other medical procedures and social circumstances need to be documented for the entire treatment period, which may be years or even decades long (WHO 2007).

WHO (2007) points out that optimal HIV-related treatment and care for PLHIV should be delivered by clinical teams. The core clinical team providing basic medical care-management of a patient should ideally consist of a physician (often an infectious disease specialist) who know the history of the patient or can interpret the same, a nurse and a social worker or a non-medical service provider. Each of the team members mentioned above has distinctive roles in providing treatment and care, and their services should be complementary - each has a role to play. A network of other specialists and self-help groups should be available in supporting PLHIV.

Despite remarkable successes in some areas, there are still more challenges in meeting the primary objective of HIV burden due to the chronic nature of the disease, OIs, adherence to regimens, drug resistance, ineffective management of OIs and compromised quality of life among others. These complex problems have persisted for decades and attempts to resolve them have been proving resistant. In an attempt to resolve them various methodologies have been used to model them in order to understand them better.

2.1.1 Prevalence of TB in patients with HIV infection

According to WHO stop TB strategy:

- TB bacilli infect about one-third of the world's population with the majority of infections being latent - they remain within the host until the immune system is activated when they burst from the host cell to infect other resting cells where they remain inactive- rather than active TB.
- Someone in the world is newly infected with TB every second and the number can rise depending on the congestion of the area the carrier is in.

About every 5-10% of HIV-negative people who are infected with TB bacilli become sick or infectious at some stage during their lifetime, with the highest risk period for active TB being in the two years after they were originally infected with TB bacillus (Copley et al. 2008).

In PLWHIV, however, the risk of developing active TB once infected increases to 10-15% per year. This has led to explosion of TB in sub-Saharan Africa and the resurgence of TB in many developing countries. Meanwhile TB is curable despite its' requiring strong national program for its control and long period of treatment.

2.1.2 Prevalence of Malaria in patients with HIV infection

Research by Amuta et al. (2012), WHO (2007) indicates that Malaria affects 40% of the worlds population putting 3.2 billion people at risk in 107 tropical countries. Amuta et al. (2012) alludes that it is one of the leading causes of death worldwide, especially in the developing world. They continue to say approximately 500 million clinical cases and about 3 million deaths occur every year due to malaria, 90% of such deaths occurring in sub-Saharan Africa. Additionally from the same authors, they conclude that those who are at risk are young children, pregnant women and HIV/AIDS patients whose immunities are compromised. This information indicates that Malaria and HIV prevalence coincides in sub-Saharan Africa. Some of the similarities between HIV and Malaria are: a) There is no effective vaccine for immunization of both of the two diseases. b) Just like HIV, Malaria parasite can be transmitted through blood transfusion and communal use of syringes by drug addicts and c) As HIV transforms into AIDS, a person become susceptible

to other infections like Malaria which make HIV even worse (Amuta et al. 2012, Onifade et al. 2007). Malaria treatment in areas where it overlaps with HIV can be complicated. Clinicians may miss opportunities to identify HIV in early stages or later when HIV status is confirmed, but not undertake appropriate diagnostics to differentiate Malaria from other causes febrile illness in PLWHIV. Additionally, Malaria is the most important of all tropical diseases and and it constitutes the most public health problems facing people in sub-Saharan Africa. In general, socio-economically, malaria and HIV/AIDS are exacerbated by ignorance and reinforced by poverty (Onifade et al. 2007, Amuta et al. 2012). They often affect the poorest segments of the population, which may be more vulnerable to disease due to lack of access to education, information and state services (Amuta et al. 2012).

2.2 Epidemiology of HIV-TB-Malaria

HIV, the etiologic agent of AIDS and AIDS related complexes (ARC) does not constitute a single illness but rather encompasses a wide range of clinical diseases including specific life threatening infections and neoplasm associated with a profound and irreversible acquired disorder of cell-mediated immunity (Onifade et al. 2007). The fact that 40% of the world's population become infected with malaria putting 3.2 billion people at risk in 107 tropical countries and that 68% of all PLWHIV reside in sub-Saharan Africa implies that this region bears the greatest burden of the epidemic (WHO 2009, Onifade et al. 2007, Amuta et al. 2012). This fact is also reinforced by the socio-economic situation of these regions since the epidemic thrives in poorest segments of the population that are vulnerable to diseases as a result of lack of access to education, information and state services. Coupled with this is the WHO (2007) observation that TB latently infect about one-third of the world's population and that every second, someone in the world will be newly infected with TB. These new infections have 10-15% chances of developing to active TB per year. This has led to explosion of active TB in sub-Saharan Africa and the resurgence of TB in many developing countries, a disease that WHO thought was already contained (WHO 2009, 2007, 2009).

PLHIV may often experience symptoms like OIs that spur them to seek medical care without their knowledge that HIV/AIDS battle is setting on Brieger (2011). It has been recorded in Kenya and Uganda that 75% of these may report fever, and occassionary many receive presumptive treatment for Malaria but few are actually tested for the same (Brieger 2011). This reflects the normal bias of health workers trusting their clinical judgment as opposed to diagnostic tests (Brieger 2011). According to Snchez (2010), global health scholars have been re-conceptualizing and redefining HIV/AIDS and TB into one disease category TB/HIV with the hopes of integrating preventive and treatment efforts based on the fact WHO research result that "At least one third of the 33.2 Million of PLWHIV worldwide infected with TB are 20-30 times more likely to develop TB than those without TB (WHO 2009)".

2.3 Modelling of Healthcare Systems

Researchers in HIV/AIDS have asserted that deaths due to the disease is as a result of not the disease itself rather the opportunistic infections (Sharma et al. (2005), Mukadi et al. (2001)).

Attempts to reduce deaths and stigma due to this syndrome has been studied using various methods: Mathematical Reed et al. (2008), Jong1995), Agent Based Modelling Wooldridge (1997), Getchell (2008), Dimitri (2009)), Discrete Event Borshchev & Filippov (2004), Simpson et al. (2007)). Apparently these methods have been based on the available data which have is very scarce and inconsistent to a great extent (Salomon et al. n.d.). Opportunistic Infections caused by immuno-suppression is quite volatile as there are many variables involved ranging from immune cells, age, geographical region among others. Yet most of the methods that have been used to study OI related to HIV are linear as support by *Statistical Research* (2004). Mathematical method is such a methodology (Reed et al. 2008, Mart & de Jong 1995, Borshchev & Filippov 2004). In order to reach better decisions and administration of proper regimens, there is a need to understand the interrelationships between variables related to OIs and those of HIV/AIDS through

visualizing the variables over time in order to perform the tradeoffs between the competing regimens.

The following is a discussion of various approaches for Modelling healthcare systems.

2.3.1 Mathematical Methods

1. **HIV Models**

   Ever since the discovery of HIV as the primary virus associated with AIDS, and its assumption as the etiologic agent of AIDS, mathematical models have been constructed to determine rates of progression to AIDS, optimal drug regimens, and the effects of the intracellular latency period on progression to disease.

   A key conceptual distinction among mathematical models is based on population averages and individual-based simulations. In individual-based simulations, each individual in the population is modeled as a discrete entity, and characteristics are determined separately for each individual. In models based on population averages, it is assumed that all individuals in the population have identical characteristics (Johnson 2004).
   The most common Modelling approach is in fact somewhere between individual-based simulations and population averages; most models divide the population into cohorts of individuals, and individuals in the same cohort are assumed to all have the same characteristics. The characteristics used to define cohorts in models of HIV/AIDS are usually factors such as age, sex and level of sexual risk behavior. Cohorts are also usually defined according to disease status: susceptible, infected (possibly further split according to stage of disease) or resistant (Johnson 2004).
   Stochastic models are often used with individual-based simulations. These models allow events such as HIV infection and death to be simulated by random processes.

Deterministic models, however, calculate expected numbers of events in cohorts of individuals. They are therefore used with models based on population averages, or models that are based on the division of the population into cohorts of individuals with the same characteristics. Deterministic models generate unique solutions, because they are based only on average values of random processes. A stochastic model, however, generates different solutions each time it is run, because the answers depend on the actual simulation of the random processes (Johnson 2004).

We can also distinguish between compartmental and distributional models. In distributional models, individual characteristics are treated as continuous variables that can take on any value within a specified range. In compartmental models, individual characteristics are treated as discrete variables, which can only take on a finite number of values. For example, in a distributional model, an HIV-positive individual's CD4 count might be allowed to take on any value between 0 and 2000. In a compartmental model, however, individuals would be classified according to the range in which their CD4 count falls: $CD4 > 500$, $CD4 < 200$, or CD4 between 200 and 500, for argument's sake. Models that are based on population averages or division of the population into cohorts are by definition compartmental models, while individual-based simulations can be distributional or compartmental (Johnson 2004).

Events such as infection and death can be modeled as occurring over a time interval or at a point in time. In discrete time models, numbers of events are calculated over each time period. The time period can be a year, a month, a day or any other chosen frequency. The choice of time period will depend in practice on the type of phenomenon that is being modeled. If, for example, we are modelling the risk of HIV transmission during acute HIV infection, when viral load changes very rapidly over the course of a few weeks, it will be necessary to use weekly or daily projection intervals. If, however, we were Modelling HIV survival in adults, it would be acceptable to use yearly projection intervals, because the time from HIV infection to death is

usually around 10 years, and the mortality rate does not change substantially from one year to the next. In continuous time models, events are modeled as occurring at a point in time. These models are specified in terms of differential equations. The discrete time model is often an approximation to the continuous time model, and may require simplifying assumptions (for example, in deriving multiple decrement tables, actuaries often make the assumption that events are uniformly likely to occur over the course of a given year). Generally, the shorter the time interval in the discrete model, the closer the model results will be to those of the continuous time model (**?**).

2. **Malaria Models**

   Malaria is a killer disease frequently found in the tropics and is manifested by frequent fever with muscle stiffness, headache, severe chills, shivering and sweating though these symptoms vary widely. Its caused by a parasite of the genus Plasmodium which is transmitted by Anopheles female mosquito as it feeds on blood to its developing eggs. Malaria can also be transmitted by infected blood transfusion or sharing of needles by the drug addicts.

   Malarial infection occasionally leads to complications affecting the brain, lungs, kidneys and other organs. It is lethal not only because it digest the red blood cells' haemoglobin, but also changes the adhesive properties of the host cell. This cause the infected cells to stick to the walls of the blood vessels blocking the blood flow and can be dangerous if its the brain capillaries where it would lead to celebral malaria.

   According to WHO (2006), every year 300 to 500 million people get infected and develop malaria and 1.5 to 3 million of these die and its most often children. Other group of people at risk are pregnant women as pregnancy lowers malaria immunity.

   An important dimension of malaria is that in highly endemic regions, mostly in tropical Africa, people are infected so frequently that they develop a degree

of acquired immunity, and may become asymptomatic carriers of infection (Bailey 1982)

Malaria control has been facing various challenges, the greatest of which is the emergency of antimalarial drug resistance. This has affected its spread in new areas where it was once eradicated. Additionally population movement has introduced resistant parasites to areas thought to be free of drug resistance.

Mathematical models have been used in studying the dynamics of malaria transmission as early as 1911 by Ross, and Macdonald later in 1957. Ross and Macdonald model was extended by Aron and May in 1982. Their model was as shown below.

$$\frac{dx}{dt} = (ab\frac{M}{N}y(1-x) - rx)$$

$$\frac{dy}{dt} = (ax(1-y) - \mu\, y))$$

where x is the proportion of the human population infected;
y is the proportion of the female mosquito population infected;
N is the size of the human population;
M is the size of the female mosquito population;
$m = \frac{M}{N}$ is the number of female mosquito per human host;
a is the rate of biting on man by a single mosquito(number of bites per unit time);
b is the proportion of infected bites on man that produce an infection;
r is the per capita rate of recovery for humans($\frac{1}{r}$ is the duration of infection in the human host);
μ is the per capita mortality rate of mosquitoes ($\frac{1}{\mu}$ is the average life time of a mosquito)

This model (Ross-Macdonald) assumes that the total number of mosquito and that of humans is constant (that birth and deaths balances out). Consequently this highly simplified model does not cater for developmental period of young mosquitoes into adults that transmit the infection. These elements

were factored in by Anderson & May (1981) who described the dynamics of the parasites that infect the host with inhost reproduction. They observed that microparasites reproduction within host is impractical to keep tract of. It follows that their model does not make a clear distinction among various infected categories of human and mosquito to host take account of the different developmental stages of the parasite. Malaria models have been extended to co-infection models. There is a common denominator in the above two models (Malaria and HIV).

Firstly the diseases disproportionately affect the poverty stricken regions in sub-Saharan Africa with limited access to health-care and health-care infrastructure hence perpetuating poverty. Secondly they are synergized by common geographical distribution (Hochman & Kim 2012).

Thirdly, the Mathematical models used to model these diseases compromise on the detailed and dynamic complexity. Literature suggests that most of the models use SIS, SIER, or SIR model (S-Susceptible, I-Infected, E-Exposed and R-Removed) without putting into consideration drug interaction, nutrition,behavioral factors, as well as delays in disease progression etc.
These implies that a more plausible methodology that can wholly address this factors need to be considered.

3. **Tuberculosis Models**

Tuberculosis (TB) being one of the major and chronic throug curable airborne bacterial infection caused by mycobacterium tuberculosis and is a major cause of morbidity especially in poor and developing countries with limited health-care resources and weak health-care systems. Though it is curable and preventable, it continues to claim millions of people annually (WHO 2009, 2007).

Tuberculosis is the highest killer of young and middle-aged adults among all infectious diseases as report by WHO in 1999. As much as its curable and preventable, it claims 5000 people daily. In addition, it strikes the most

vulnerable in the society and oftenly if left untreated, victims lose weight, weaken and eventually waste away.

Understanding of TB and its epidemiology is very important. This is aided by addressing the broad range of sociocultural, behavioral and structural issues pertinent to TB control. TB infections continue to decline in industrialized countries inspite of disproportionately affecting low-income groups, substance users, persons from TB-endemic regions, the elderly, and residents of congregate families (like nursing homes and prisons).

TB is a communicable disease caused by M. tuberculosis. Even though it can affect other organs of the body, the risky parts are the pulmonary and laryngeal TB since transmission from one person to another is more plausible. Its transmitted when a susceptible individual inhales air containing droplet nuclei carrying the tubercle bacilli. Once inhaled, the droplet nuclei eventually reach the lungs replicates and over time spreads throughout the body.

When the immune system is competent, it limits the multiplication of the bacteria though some remain dormant but viable a condition known as latent TB infection (LTBI) An individual with LTBI has an estimated 10% lifetime risk of developing active TB disease. However children under the age of 4 and individuals with weakened immune system due to malnutrition, diabetes, certain cancers, those recently infected with M. TB and most importantly HIV/AIDS have a much greater risk of developing active TB. HIV co-infection is the strongest known risk factor for developing active TB disease.

Mathematical Modelling have been widely used in Modelling TB in areas of high HIV prevalence in Harare, Zimbabwe Hallett et al. (2006). In this case, discrete event simulation was used to measure progression of HIV for patients with M.TB. The model used scheduled events that are executed in chronological order using a linked list. The events were: Birth, Natural death, TB development, Treatment, No treatment, and Death from TB. The

goal of the model was a geospatial discrete event simulation of TB transmission in the district which would allow a full assessment of the effectiveness of contact-tracing and case-finding strategies that make of geographical information.

Another area where mathematical Modelling have been used is in Modelling "sexual behavior change" association with declining HIV prevalence in Uganda, Kenya, Zimbabwe and urban Haiti Hallett et al. (2006). The main idea here was to determine how HIV prevalence affected changes in sexual risk behavior. The model showed dropping of sexual risk behavior with knowledge of HIV prevalence though the results could not be replicated. Roeger et al. (2009) developed a model of HIV and TB coinfection at the population level. The model implored the impact of factors associated with coinfection on prevalence of the two diseases. Differential equations were used to model the joint dynamics of HIV and TB. In this model, the population was divided into compartments: susceptible, Latent, Infectious, Treatment and AIDS. In this model, transmission paths for either of the disease were assumed like IV drug injections, breast feeding, MDRTB, and infection at birth.

Generally mathematical Modelling have yielded some quantitative results that have improved our understanding of immunological phenomena of infectiousness, it is still in its infancy (Perelson 2004). However, the vast majority of these models have been lacking in predictive value, owing to a lack of complete understanding of the disease mechanism, as well as the fundamental nature of the immune system (Culshaw 2006). It is thus imperative that an alternative framework is needed wherein non-HIV-mediated mechanisms of immune dysfunction are considered, either as cofactors of HIV or alternate mechanisms (Culshaw 2006).

To offer tractability, mathematical methods compromise on detailed and dynamic complexity which would offer realism in the understanding of disease infections. The utility of mathematical model lies in quantitative prediction of HIV progression (Culshaw 2006). In addition to this and according to

Culshaw (2006), the models cannot be applied to individual patient since these models involve a lot of parameter estimation which is critical for their success and also that different patients have different progression of HIV, live in different regions geographically, are in different age groups, different cultural regions,etc all of which contribute to diseases infectiousness. Literature also indicate that interaction of drugs in case of co-infections affects authenticity of drug effectiveness and this is hardly address by majority of these (Culshaw 2006).

2.3.2 Agent Based Modelling

An agent is an "encapsulated" computer system situated in some environment and capable of flexible, autonomous action in that environment in order to meet its design objectives (Wooldridge 1997).

According to Laskowski et al. (2011), Bonabeau (1999), ABM is systems Modelling, approached from the ground up or from the perspective of its constituent parts in order to build an aggregate picture of the whole. Systems are modeled as a collection of agents (people and objects)and their individual characteristics, behaviors, and interactions. In the most general context, agents are autonomous decision making entities able to assess their situation, make decisions, and compete with one another on the basis of a set of rules. ABM's conceptual depth is derived from its ability to model emergent behavior that may be counter-intuitive or, at minimum, its ability to exhibit a complex behavioral whole that is greater than the sum of its parts. ABMs are particularly well suited to system Modelling in which agent behavior is complex, nonlinear, stochastic, and may exhibit memory or path dependence. In his conclusion, Laskowski et al. (2011) ABM is a decision support tool available to healthcare practitioners and policymakers in order to qualitatively assess the relative impact of various infection control strategies.

As indicated here ABM is modeled ground up but it does not evaluate the structural elements of the constituent part. In addition ABM is inclined to qualitative research. According to Bonabeau, (1999) ABM is more of an art than science and

derives its popularity on social systems, they most often involve human agents, with potentially irrational behavior, subjective choices, and complex psychology, in other words, soft factors, difficult to quantify, calibrate, and sometimes justify.

2.3.3 A System View of Fluctuation in HIV treatment

Adherence to treatment is a classical problem in system literature. Sections 2.1 blamed fluctuations to external factors, however, the systems view of adherence. System thinking views causes of organization output instability as caused by interractions within the organization as opposed to outside circumstances like the competitors, the press, the markets, the economy or the government. "System thinking show that there is no outside; that you and the cause of your problems are part of a single system" Senge (1990). Systems thinking therefore would not attribute variations in treatment to "outside factors" but to challenges of the industry's management.

The view that excessive variations or inconsistent reaction to therapy are internal problems of healthcare industry is not naive. The view of system thinking is that feedback control structure of a system constitute its dynamic behaviour. This view does not mean ignoring effects of external factors such as treatment cycles and changes in treatment policies; it does mean that the way that the system responds to these supposedly external factors depends on the dynamic structure of the system itself. For that reason, a system's dynamic structure can be conceptually designed in such a way that the "external" factor will eventually not adversely affect the performance of the system. This argument is amplified in system dynamics literature, for example in Senge (1990). At first, the argument may appear to go against conventional wisdom but it does not necessarily do so. It actually gives the conventional wisdom great insight and more often than not challenges it to view an organization's problem from a wider perspective.

2.3.4 The System View

In order to elucidate a good understanding of how system thinking would be applicable to the healthcare industry, we first provide a technical definition of a "System". A system is "a collection of parts organized for a purpose" Coyle (1996). According to Schoderbek & Kefalas (1980) a system is a "set of objects together with relationship between the objects and between their attributes, connected or related to each other and to their environment in such a manner as to form an entirely or whole." Though similar but different in details, Coyle's(1996) definition sound more appealing and therefore will be adopted in this study.

When an an organization is viewed as a system, it is easier to solve organizational problem in a broader perspective; the problem solving adopts a broad look at the organization rather that an overly fixated to a particular problem in question. This holistic view is considered to be the most realistic for the solution of present day organizational problems because of their increasing complexity Forrester (1961). The system approach contrasts with the ABM method, whereby an entity is examined primarily from the viewpoint of its constituent element. Nevertheless, system thinking supplements rather than replacing the ABM thinking.

In adopting Systems thinking to problem-solving, various system approaches are used depending on the nature of the system in which the problem occurs. From Schoderbek & Kefalas (1980), the various system approaches, may be summarized as follows:-

1. General System Theory:- Framework for viewing complex phenomena as wholes with all their interrelated and interacting parts, which was formulated by an interdisciplinary team of scientists in the 1950s

2. Cybernetics:- the science of control and communication in the animal and the machine; it uses information feedback loops as the means of system control

3. System dynamics:- the science of feedback behavior in multiple-loop non-linear social systems; it can be seen to be an extension of the cybernetic approach to social systems, albeit at a higher resolution level.

4. System analysis:- a systematic examination of a problem of economic choice in which each step of the analysis is made as explicit as possible; it involves problem formulation, search of relevant data, building a model and exploring its consequences, and deriving conclusions.

5. Operation research: - application of quantitative techniques to decision-making regarding organizational operations; it comprises linear and dynamic programming, decision trees, queuing theory, transportation method, network analysis and simulation models.

The choice of a systems framework depends on the complexity of the system in question. For system that are probabilistic(with many states of nature) and fairly complex such as inventory levels and sales, operations research may suffice. However, for systems that are probabilistic and exceedingly complex such as human beings, corporations, industries, health, and economies, cybernetics and system dynamics are most suitable. Between the two extremes are systems of somewhat intermediate complexity such as management information systems and development projects where systems analysis and systems engineering are the most suitable approaches Schoderbek & Kefalas (1980)

From the above mentioned system approaches, systems dynamics suits the system understudy for it involves viewing social-economic systems of the size and complexity comparable to that of healthcare industry.

2.3.4.1 SD Principles

In System Dynamics, a system is viewed as being controlled by a process of information, action and consequences(i.e. results of actions), in order to maintain purpose. In the system, "Information produces actions which have consequences,

generating further information and actions, and so on" Coyle (1996). This continual sequence is what is technically referred to as feedback in the system and experts control on the system. An SD study of an organization's problem, therefore aims to capture this feedback control process, thereby Modelling the organization as a feedback system.

A fundamental principle of SD is the idea of proportional control, whereby control action is proportional to the discrepancy between the current and the target states of the system, in view of the purpose of the system. SD Modelling is therefore "an application of the attitude of mind of a control engineer, to the improvement of dynamic behavior" in system Coyle (1996). It involves interpreting a real life system into computer simulation models that allow one to see how the structure and decision-making policies influences the system create its behavior.

A basic motive of SD Modelling is "to improve a situation by suggesting how people can act upon the system" (Forrester 1991). Although every system may have specific attributes, SD studies have revealed certain attributes that are common to all complex systems. From Coyle (1996), Forrester (1991) fundamental principles of systems from the stand point of SD can be summarized as follows:-

1. Systems are seen as feedback processes having a specific and orderly structure. From the structure of the particular system arises its dynamic behavior.

2. Simple systems consist of one level variable on the feedback loop. Walking, warming ones hands beside a stove, picking things up and driving a car may be approximated as simple systems. Complex systems have many level variables and a network of feedback loops. Corporations, cities, economies, healthcare and governments are complex systems.

3. A complex system behaves in many ways quite the opposite of the simple systems from which experience has been gained. Most of intuitive responses have been developed in the context of simple systems, where the intuitive lesson that cause and effect are closely related in time and space has been grasped. However, in complex systems, cause and effect are often not closely

related in either time or space because of the multiplicity of the interacting feedback loops.

4. Complex systems are counter-intuitive. That is, they give indications that suggest corrective action which will often be ineffective or even adverse in its results. They have a tendency to present apparent causes that are in fact coincident symptoms. Conditioned by training in simple systems, people apply the same intuition to complex systems and are led into error. The outcome lies between ineffective and detrimental.

5. SD Modelling helps to unify decision makers knowledge of a complex system, enhances their mental perception models of the problem in question and reveals the few policy areas which are leverage points for the system improvement. A general characteristic of systems is high resistance to policy changes. Perhaps as many as 98% of the policies in a system have little effect on its behavior because of the ability of the system to compensate for changes in most policies.

Following the guidelines given in WHO (2006, 2007), a HIV therapy is a very complex system. Perhaps, HIV response to ARVs variants and behavior of the immune system are a manifestation of some of the counter-intuitive behavior of HIV progress and hence subjecting the patient to OIs.

One of the key strength of SD Modelling is that it takes into account the delays in the flow of matter and information through the system. Delays are hold-downs that inhibit instant flow of material or information through a system. Insights from SD models "often have to do with delayed and counter-intuitive effects of feedbacks. Delays mean current information may provide misleading signals" Kummerow (1999).

HIV therapy, for example, takes on average 10 years to be symptomatic. This is regardless of the environment the patient is in whether developed or developing countries. Once the CD4 cells reduce to a significant level, the patient can start therapy to try to raise its level. During this period little is known about the significant behavior of the immune system, ""just about lowering the CD4 count".

2.3.4.2 System Dynamics Modelling Process

System Dynamics (SD) was developed by Professor Jay Forrester at MIT during the 1950s and consequently laying the foundations of the discipline and later defined the methods and techniques associated with it Forrester (1961).
System Dynamics is a theory of the structure of systems and their resulting dynamic behavior whereby the structure includes not only the physical aspects of processes but also importantly the policies and traditions both tangible and intangible that dominate decision making Deakins (2001). Elsewhere System Dynamics is defined by Wolstenholme (1990) as "rigorous method for qualitative description, exploration and analysis of complex systems in terms of their processes, information, organizational boundaries and strategies; which facilitates quantitative simulation Modelling and analysis for the design of a system structure and control". While Robberts (1978) describes System Dynamics as "the application of feedback control system principles and techniques to managerial, organizational and socio-economic problems".

System Dynamics is a methodology that applies system thinking methods. System thinking methods facilitate the understanding of system by focusing on relationships that link the parts of the whole that on parts themselves. In order to understand the systems interrelated parts, there is need to understand the cause-effect linkages. System thinking methodologies benefit managerial decision making through the provision of tools that enable them to comprehend complex systems, share the observations and experiences related the complex systems as well as providing a clear understanding which enables the testing of the dynamic behavior Richie-Dunham & Rabbino (2001), Sterman (2000). As enthused by Maani & Cavana (2000), System dynamics Modelling has the following advantages. It employs the use of causal-loop stock and flow diagrams which show the nature and direction of relationship within the system being modeled. This enables a deeper understanding of the system. Decision rules or policies can be varied as they are formulated during simulation as opposed to being specified as constant thus incorporating feedback effects of past relation. Both linear and non-linear relationships

can be included. Physical and information delays can be easily incorporated in the model. Soft behavioral relationships for which adequate statistical data may not be available can be modeled.

System Dynamics has a very strong mathematical foundation that make it a powerful method encompassing a body of knowledge, a theory of representation and a methodology for designing and analyzing complex feedback systems and their dynamic behavior (Sterman 2000). System Dynamics provide tools which help better understanding of complex management problems by looking at an organization as a system of interacting parts as opposed to focusing on isolated events and causes Williams (2000) As expressed by Richardson & Pugh (1981), the following tools are supported by System Dynamics approach to expound on the system Graphical notation are used for representing the system architecture The problem can be studied in-depth by showing how particular set of events is part of a longer term pattern of behavior Circular chain diagrams of cause-and-effect are used to present relationships that are difficult to describe verbally. Use of feedback loops which facilitates the understanding of causes of the patterns of behavior in management systems. Stocks and flows help describe how a system is connected by feedback loops which create the non-linearity found so frequently in modern day problems. Computer software is used to simulate a system dynamics model of the situation being studied. Running "what if" analysis to test certain policies on such a model can greatly aid in understanding how the system changes over time.

As stated by Affeldt (1999) System Dynamics can be used to clearly demonstrate the systemic consequences and actions once the framework for the SD simulation has been properly constructed.

Hirsch (1979) outlines the following strengths of applying SD Modelling in healthcare The process of developing the model involves decision makers who must use the model. Models can be developed by starting with the causal loop diagrams which consist of the important variables which makes it very useful in poor data environments. The developed models help decision makers identify necessary data

that should be available but is not being collected. The SD methodology employs different types of variables to describe real world phenomena

2.4 System Dynamics Methodological Approaches

There are varied approaches to SD for Modelling real world problems in varied disciplines as suggested by Coyle (1996), Wolstenholme (1990), Williams (2000). This section reviews some of the different SD Modelling approaches.

2.4.1 Structured Approach to System Dynamics

System Dynamics "is a method of analyzing problems in which time is an important factor, and which involves the study of how a system can be defended against, or made to benefit from, the shocks that fall upon it from the outside world" according to Coyle (1977). Coyle (1977) further identifies five structured stages to SD analysis Problem recognition which involves identifying the problem and the different stakeholders. Problem understanding and system description which involves creation of an influence diagram and representation of the forces at work in the system. Qualitative analysis where views of experienced people are gathered thus generating insight towards solving the problem. Construction, testing and debugging of a simulation model. Policy testing and design which involves the exploration of the different system behavior as well as policy design by optimization thus leading to a further understanding of the problem.

2.4.2 System Dynamics approach as a tool for system thinking

Wolstenholme (1990) defined SD as "a rigorous method for qualitative description, exploration and analysis of complex system in terms of their processes, information, organizational boundaries and strategies; which facilitates quantitative

simulation Modelling and analysis for the design of a system structure and control". Accordingly, the development of a system thinking and Modelling involves five major steps Problem structuring which involves the collection of preliminary information and identification of problems; Causal loop Modelling which involves the main variables, preparation of reference modes, development of influence diagrams, identification of system archetypes and development of intervention strategies; Dynamic Modelling which involves the development of system maps, stock and flow diagrams, simulation mode, validation of the model, sensitivity analysis, design and analysis of policies and development and testing of strategies; Scenario planning and Modelling which involves the planning, construction, simulation of various scenarios as well as evaluation of policies and strategies; and Implementation and organizational learning which involves the preparation of reports, communication and development of a micro world and learning laboratory based on the simulation model.

2.4.3 System Dynamic Methodology as an Iterative process

SD as described by Richardson & Pugh (1981) begins and ends with understanding and goes through an iterative and non-linear process which results in increased understanding of the problem at hand. This Modelling approach consists of the following six stages; problem definition, system conceptualization, model formation, simulation, policy analysis and policy implementation as indicated in figure 2.1

2.4.4 Managing from Clarity Methodology (MCM)

Richie-Dunham & Rabbino (2001) proposed a Managing from Clarity as a methodology that uses SD and system thinking approaches to map out dynamics around resources. Modelers use exper intuition, implicit understanding of the system and

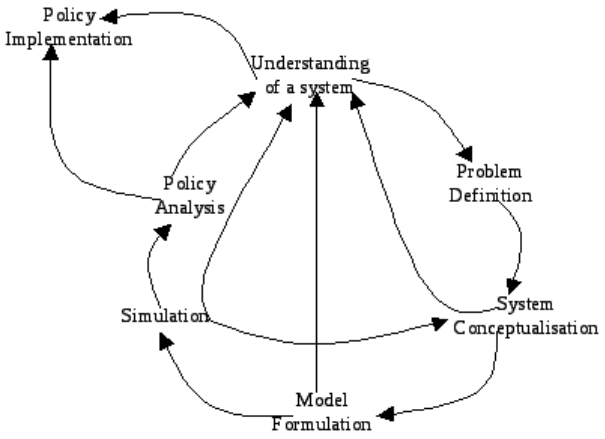


FIGURE 2.1: System Dynamics Methodology Process [Adapted from (Richardson & Pugh 1981)]

relies heavily on SD stock flow Modelling language. The MCM methodology approach uses the following stages form Modelling: Building a GRASP map which consist the organization's overall Goals, Resources, Actions, Structure and People where the cause and effect linkages are qualitatively described; Quantification of key resource dynamics which involves the exploration of unintended consequences of policies that affect these resources and quantitative testing of the recommended strategies, hypothesis and utilization of resources over time; Integration and validation of the map; Scenario planning and strategic foresight which provides tools for integrating strategies and selection of the best strategies and structures designed, designing future key assumptions thus providing a deeper understanding of future trends that might impact the organization; and Learning interfaces which are designed to communicate the strategies of the organization to the stakeholders.

A system dynamics (SD) study adopts the case study research design; it aims to do an in-depth elucidation of one entity "the system in focus". The SD Modelling process involves conceptualization and quantification of the phenomena underlying the problem behavior.

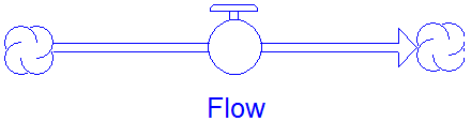
2.4.4.1 Elements of System Dynamics Model

Stella (Structural Thinking Experimental Learning Laboratory with Animation) software version 9.0.2 was used to develop the model. The software was sought after because it provides the modelling environment for dynamic systems. It has a very user friendly graphical user interface environment for carrying out quantitative study especially studying interaction of structural variables of the model. There are three basic elements used in System dynamics namely stock, rate and the converter. Stella software implements this basic components using the following four components

a. Stock also know as the level is a generic symbol for anything that accumulates. They collect whatever flows into them, net of whatever flows out of them. They can be physical in nature such as population, cash, water or non-physical such as reputation, learning, quality, anger or even trust. System survival is dependent on stock and so they play an important role in management of dynamic system. The symbol of a stock is shown in the figure below

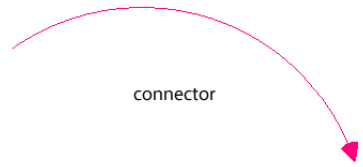
Stock

b. The second component of Stella is the flow. The job of flows is to fill and drain accumulations or stocks. Maani & Cavana (2000) defines flows as outcome of decisions by managament or external forces outside management control. Flows can only be observedby accumulations or averaging and not by a single point in turn. Sometimes flows can be physical or non-physical in nature just like stocks.



c. The third component in the stella software is the Converter or auxilliary variable. Anything that is input or manipulated in the model is represented by a converter. They may be constants, grahical relationships and behavioural relationships. Converter are used to define derived variables as well as construct relationship that can be derived from flow equations. Converters are especially useful for modularizing complex flow equations into solvable components. They can also be used to solve algebraic equations like sums, divisions that represent exogenous inputs as well as serving as substitutes for stocks or flows that may not be represented for simplicity

d. The fourth item for developing models maps using Stella is the connector. The symbol for a linker or connector is an arrow that demonstrates information passing between converters, stock and converters, stocks and flows and converters and flows. They serve as inputs and outputs and not at any time as inflows or outflows. Stella linkers come in two types: the "solid line" for converting the resulting decision into an action that eventually changes the flow volume and the "information connector" generally a dashed liine which provides information that is used to derive a decision.



2.4.4.2 Types of equation supported

This section highlights types of equations that are used in stella software.

Stock equations are represented by two equations as shown below:

$$S(t) = S(0) + \int_0^t (bx - dx)dt \tag{2.1}$$

Equation 2.1 in Stella is simplified as equation 2.2 and 2.3

$$S(t) = S(t - dt) + (I - O)dt \tag{2.2}$$

$$INITS = 0 \tag{2.3}$$

Equation 2.1 represents stock at time *(t)* which is equal to the stock at previous time $t - dt$ plus inflows *(I)* and outflows *(O)* during the period of time (dt). Equation 2.3 gives the initial value of the stock.

Flow equation is generally a policy statement in the system reflecting the rate at which the system will change during the forthcoming simulation interval of time. For example

$$Births = (Population * BirthFraction)/Time \tag{2.4}$$

This implies that the number of births of the specified interval is equal to the population multiplied by birth rate. Converter equation is an intermediate variable, constant or a graphical relationship showing a plot of the variables or factors

under consideration. In this case Births is measured in terms of the number of people who are born per year.

System Dynamics is iterative in nature with distinct phases. According to Coyle (1996), Forrester (1961), Pidd (1998) the process entails the following stages: -

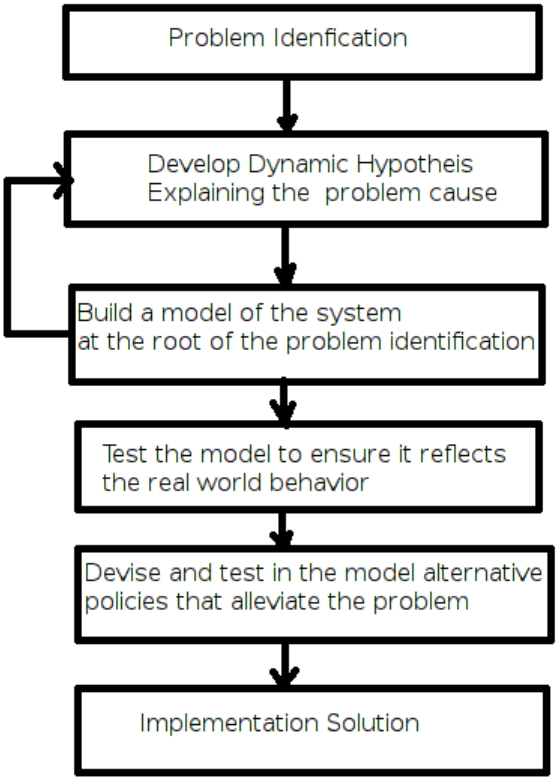


FIGURE 2.2: System Dynamic Process as derived from Forester (1991)

a. Identification of the problem;

b. Development of a dynamic hypothesis explaining the cause of the problem drawing influence diagrams, either as causal-loop diagrams or level-rate diagrams;

c. Qualitative analysis of the problem examining what the participants in the system feel is the problem with the system and establishing whether any bright ideas on the system can be borrowed from the modelers previous experience with similar systems;

d. Building a computer simulation model of the system at the root of the problem drawing detailed influence diagram(s) using computer code and formulating necessary difference equations;

e. Testing the model to be certain that it reproduces the behaviour observed in the real world;

f. Devising and testing in the model, alternative policies that alleviate the problem; and

g. Implementing the solution recommended.

The process is similar to the case study process of of the previous Modelling methodologies (i.e. unsystemslike) approach to problem investigation. However, the details "conceptualization and quantification of the variables" are a complete paradigm shift from the the above approaches. If applied to an industry, the SD Modelling procedures are likely to capture more variables than those that have hitherto been captured in mathematical Modelling. SD Modelling of healthcare activities is therefore expected to add significantly to the insights mathematical and ABM Modelling has so far given regarding the healthcare cycles.

An SD study need not cover all the seven stages listed above. "The problem is sometimes solved at stage 3 [qualitative analysis], and there is no need to go on to the other stages," Coyle (1996) except, of course, the last one i.e. the

implementation of the solution recommended by the qualitative analysis. At the qualitative analysis stage, great insight may be gained by a comparing the pattern of the problem behavior with generic patterns of similar systems, technically known as system archetypes. From Braun (1988), Senge (1990), eleven system archetypes are explained as follows: -

a. *Balancing Process with a Delay:* A person, group, or organization acting towards a goal adjusts their behavior in response to delayed feedback. If they are not conscious of the delay, they end up taking more corrective action than needed, or (sometimes) just giving up because they cannot see that any progress is being made.

b. *Shifting the Burden:* A problem symptom can be resolved either by using a symptomatic solution or applying a fundamental solution. Once a symptomatic solution is used, it alleviates the problem symptom and reduces pressure to implement a fundamental solution, a side effect that undermines fundamental solutions.

c. *Eroding Goals*: A gap between a goal and an actual condition can be resolved in two ways: by taking corrective action to achieve the goal, or by lowering the goal. When there is a gap between a goal and a condition, the goal is lowered to close the gap. Over time, lowering the goal will deteriorate performance.

d. *Escalation:* This archetype occurs when one partys actions are perceived by another party to be a threat, and the second party responds in a similar manner, further increasing the threat. The two balancing loops will create a reinforcing Figure-8 effect, resulting in threatening actions by both parties that grow exponentially over time.

e. *Success to the Successful:* If one person or group (A) is given more resources than another equally capable group (B), A has a higher likelihood of succeeding. As initial success justifies devoting more resources to A, further widening the performance gap between the two groups over time.

f. *Tragedy of the Commons:* This archetype identifies the causal connections between individual actions and the collective results (in a closed system). If the total usage of a common resource becomes too great for the system to support, the commons will become overloaded or depleted and everyone will experience diminished benefits.

g. *Fixes that Fail:* A quick-fix solution can have unintended consequences that exacerbate the problem. The problem symptom will diminish for a short while and then return to its previous level, or become even worse over time.

h. *Limits to Growth:* A reinforcing process of accelerating growth (or expansion) will encounter a balancing process as the limit of that system is approached. Continuing efforts will produce diminishing returns as one approaches the limits.

i. *Growth and Under-Investment:* This applies when growth approaches a limit that can be overcome if capacity investments are made. If a system is stretched beyond its limit, it will compensate by lowering performance standards, which reduces the perceived need for investment. It also leads to lower performance, which further justifies underinvestment over time.

j. *Accidental Adversaries:* When teams or parties in a working relationship misinterpret the actions of each other because of misunderstandings, unrealistic expectations or performance problems, suspicion and mistrust erode the relationship. If mental models fueling the deteriorating relationship are not challenged, all parties may lose the benefits of their synergy.

k. *Attractiveness Principle:* The result sought by a firm and which is the target of a growing action may be subject to multiple slowing actions, each of which represent an opportunity and an opportunity cost to managers. Insight into the inter-dependencies between the slowing actions is a critical insight into deciding how scarce resources should be utilized to reduce or remove the slowing actions.

Six of the archetypes listed above appear to be most relevant to the problem of HIV handling and management. The six archetypes are: balancing process with a delay, shifting the burden, eroding goals, limits to growth, escalation and fixes that fail. This archetypes also guided in generating figure 2.6 captioned reference modes indicating behavior overtime of the high level variables derived from the conceptual model in figure 2.5 called causal loop diagram. Table below gives brief descriptions of the archetypes and examples of situations in which such archetype may apply with regard to the system under research.

System Archetype	**Dynamic Theory**	**Example**
Balancing with Delay	A person, group, or organization acting towards a goal adjusts their behavior in response to delayed feedback. If they are not conscious of the delay, they end up taking more corrective action than needed, or (sometimes) just giving up because they cannot see that any progress is being made.	Once infected with HIV virus, the virus attacks the CD4 helper cell. These cells production rate is slow compared to the rate of attack, hence the rate of reduction during the incubation period needs to be monitored so as to know when therapy should start. The question is how many people go for tests?.
Shifting the Burden	A problem symptom can be resolved either by using a symptomatic solution or applying a fundamental solution. Once a symptomatic solution is used, it alleviates the problem symptom and reduces pressure to implement a fundamental solution, a side effect that undermines fundamental solutions.	When affected PLHIV do not adhere to the ARV therapy, the HIV virus become resistant to drugs. This leads to the exposure to OIs hence which later leads to AIDS. Once this happens we shift the burden to trying to contain the OIs when the viral load is very high and at this point there is no return.

Eroding Goals	A gap between a goal and an actual condition can be resolved in two ways: by taking corrective action to achieve the goal, or by lowering the goal. When there is a gap between a goal and a condition, the goal is lowered to close the gap. Over time, lowering the goal will deteriorate performance.	PLHIV have to reach a certain CD4 threshold to start therapy. When they start therapy, there are specific ARVs they are supposed to start with. Depending on the strains of the virus this threshold may be brought forward or delayed. Delaying HIV therapy may deteriorate the patient condition hence compromising the efficacy of the drugs
Escalation	This archetype occurs when one partys actions are perceived by another party to be a threat, and the second party responds in a similar manner, further increasing the threat. The two balancing loops will create a reinforcing figure-8 effect, resulting in threatening actions by both parties that grow exponentially over time.	This is quite perfect in this case in the sense that inclination to managing HIV may subject the patient to drug toxicity thereby increasing viral load hence subjecting the patient to OIs. This will cause sudden drop in CD4 count hence subject the patient to AIDS and threatening any action forthwith

Limits to Growth	A reinforcing process of accelerating growth (or expansion) will encounter a balancing process as the limit of that system is approached. Continuing efforts will produce diminishing returns as one approaches the limits.	When viral load continues to increase and CD4 count continue to reduce, and there is initiation of HAART, this lower viral action and allow production of more CD4 cells hence balancing the process.
Fixes that Fail	A quick-fix solution can have unintended consequences that exacerbate the problem. The problem symptom will diminish for a short while and then return to its previous level, or become even worse over time.	Once the Patient is in symptomatic state, any treatment, any quick fix will seem to work as the AIDs virus attacks other organs leading to general failure and worsening the situation

TABLE 2.1: Six System Archetypes

Simulation Modelling has been used widely in strategy implementation, risk analysis, policy design and analysis in many areas including health care management. Generally, health management systems include but are not limited to billing, administrative, staffing management, patient management, hospital management, pharmacy, consulting, disease screening, and emergency (Rwashana & Williams 2008). Literature shows that computer models are used widely in systems management to provide insights in the general view of the working system. On the other hand mental models are structurally and dynamically impoverished and characterized by short-time horizons, narrow boundaries, open loops, and poor understanding of time delays (Meghan et al. 2011). Simulation Modelling applied

in health care play a major role in decision making at all levels (Meghan et al. 2011, Homer & Hirsch 2006, Altsitsiadis et al. 2009) as it provides quantitative information that provides clear understanding of the problem.

System Dynamics has previously been used in health care system Modelling in the following areas

a. Disease transmission and public health risks assessment. This aimed at Modelling of infectious diseases and the impact of varied intervention strategies to limit their spread in human populations. Examples of diseases modeled here target those disease that develop over a long period of time to accommodate new knowledge regarding transmission mechanisms of the disease. Variables of interest here include AIDS incubation period, stages of the disease, stage at which treatments starts, and survival periods (Atun et al. 2011, Corbett et al. 2006, Mukadi et al. 2001).

b. Screening for diseases: Modelling at this level is used as a tool for detecting the disease before it causes harm, its impact on transmission, evaluating social, medical, and financial consequences of different screening strategies. Such tools have been used previous to analyze cervical cancer among others. This tool was used in UK department of Health.
Variables of interest here are transmission of the disease, sexual behavior of the susceptible population, treatment effectiveness, and population groups (Atun et al. 2011, Corbett et al. 2006, Mukadi et al. 2001, Graham et al. 2007).

c. Managing waiting lists. Literature shows that this issues has been widely studied in various contexts using SD because of their political nature. Variables influencing size and length as well as those related to policy decisions, for example, cause of waiting lists escalation were used in the UK to study its impact on shifting elderly community care responsibility from department of Health to the Local Government Social services (Atun et al. 2011, Corbett et al. 2006, Mukadi et al. 2001, Homer & Hirsch 2006)

d. Pedamallu et al. (2010) used SD to model intentional HIV transmission using Cross Intentional Analysis. In their study, they used variables such as: Health Infrastructure, Work colleagues, Family Members, HIV+, and Other Infrastructure. This research showed identification of important factors that result in non-disclosure and could invoke new intervention policies and regulations to prevent the intentional transmission of HIV/AIDS in different countries and societal environments. This research is inclined to bringing out knowledge about intentional transmission and though it achieved its purpose, it lack recommendations about eradication of such habits or policies leading to the same.

e. In another research carried out by Rifat, Reda and Richard (2008) on TB transmission in settings of high MDRTB and explosives epidemics of HIV, they found out that if MDRTB treatment is done at the right time, a substantial numbers of deaths will occur while a significant number of deaths can be avoided if effective treatment policy such as the WHO DOTS is adopted. They also found out that HIV has an impact on MDRTB and TB deaths. They failed to point out the probable intervention points for the same, neither did they show the point where ARV and TB therapy can be adopted to reduce deaths (Rifat et al. 2008).

2.5 Conceptual Framework

In summary, the following table, Table 2.2 gives a comparison of the above methodologies based on the attributes pertinent to complex systems. The attributes used are; support for multiple theories, support for multilevel policy development by stakeholders, handling of emergent behaviors, support for incorporation of high dimensionality, ability of handling complex behavior, ability to deal with scenarios, path dependency, predicting people behavior, subjectivity to boundaries and dynamic analysis.

TABLE 2.2: A comparative analysis of the above Modelling methodologies against some selected attributes adapted from Marcus Carley, 2007.

Attribute	**System Dynamics**	**Mathematical**	**ABM**	**Regression**	**Game Theory**
Multi-theoretical	Yes	N/A	Yes	N/A	No
Multi-Level	Yes	Yes	Yes	Yes	No
Emergent Behavior	Yes	No	Yes	No	No
High Dimensionality	Yes	No	sometimes	No	No
Capable of expressing non-linear behavior	Yes	No	Yes	No	No
Enable analysis of hypothetical situations	Yes	No	Yes	Limited	Limited
Path Dependent	No	No	Yes	No	No
Predict people behavior	Yes	Yes	Yes	Yes	Yes
Boundaries are subjective	Yes	No	Yes	No	No
Enable Dynamic Analysis	Yes	No	Yes	No	No

Now, based on the above attributes, the research adopted the System Dynamics methodology as it seems most suitable for the subject understudy.

The health system is a highly structured functional process with differing viewpoints from the stakeholders to the medical practitioners, care providers and to the patients.

A Stakeholder is defined as any functional agent who has an interest in the proposed or current system. A stakeholder may be a customer/patient, care provider (doctor, nurse, pharmacist and clinical officer).

A conceptual framework is a written or visual representation that explains either graphically or in narrative form, the things to be studied - the key factors, concepts or variables and the presumed relationship among them Huberman (1994) In order to develop the conceptual framework, the research integrated framework resulting from viewpoint of the financiers and that emanating from the mathematical view

of disease progression. As such, figure 2.1 is the financiers framework. It indicates the means through which funding is generated in macro-organizations, persuasion, government funding or soliciting payment from the patients.

Once the funds are got, the immediate outcomes are access, Quality and Efficiency from the service providers while the goals are health status, financial risk protection and customer satisfaction to the patients or community.

Immediately below the Figure 2.3 is the relation amongst the financing instruments and their goals

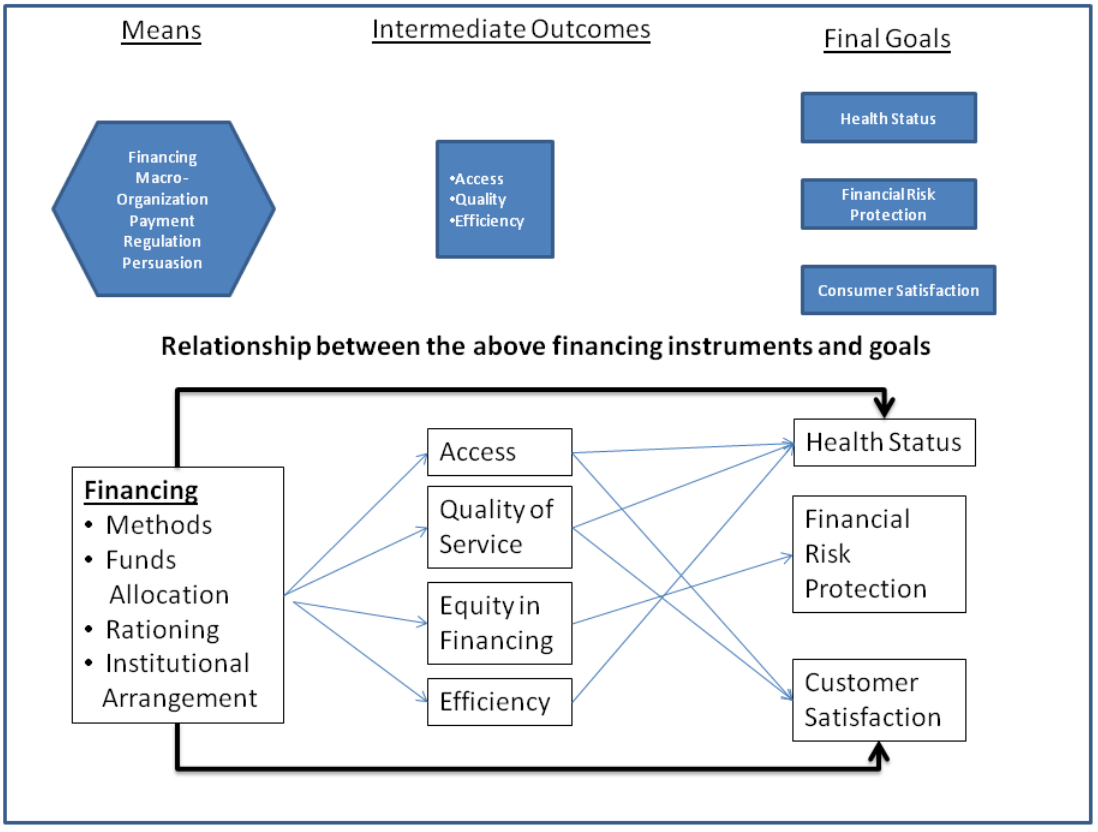


FIGURE 2.3: Interactions that occur between the financing Institutions

Figure 2.5 is the conceptual framework derived from the mathematical and ABM discussed in section 2.2 above. In this case, the population is partitioned into cohorts' Susceptible, Infected, Exposed, or Recovered and Removed depending on a given disease progression (Gautam et al. 2009, Roeger et al. 2009, Kermack & McKendrick 1991).

In order for the cohort to be consistent with SD, the cohorts are further partitioned

into inputs, processes, and output as indicated in the Figure 2.4 in page 52. The figure also indicates the relationship among immediate variables that are important in the consideration of triad-infection. The input to the system are identified as

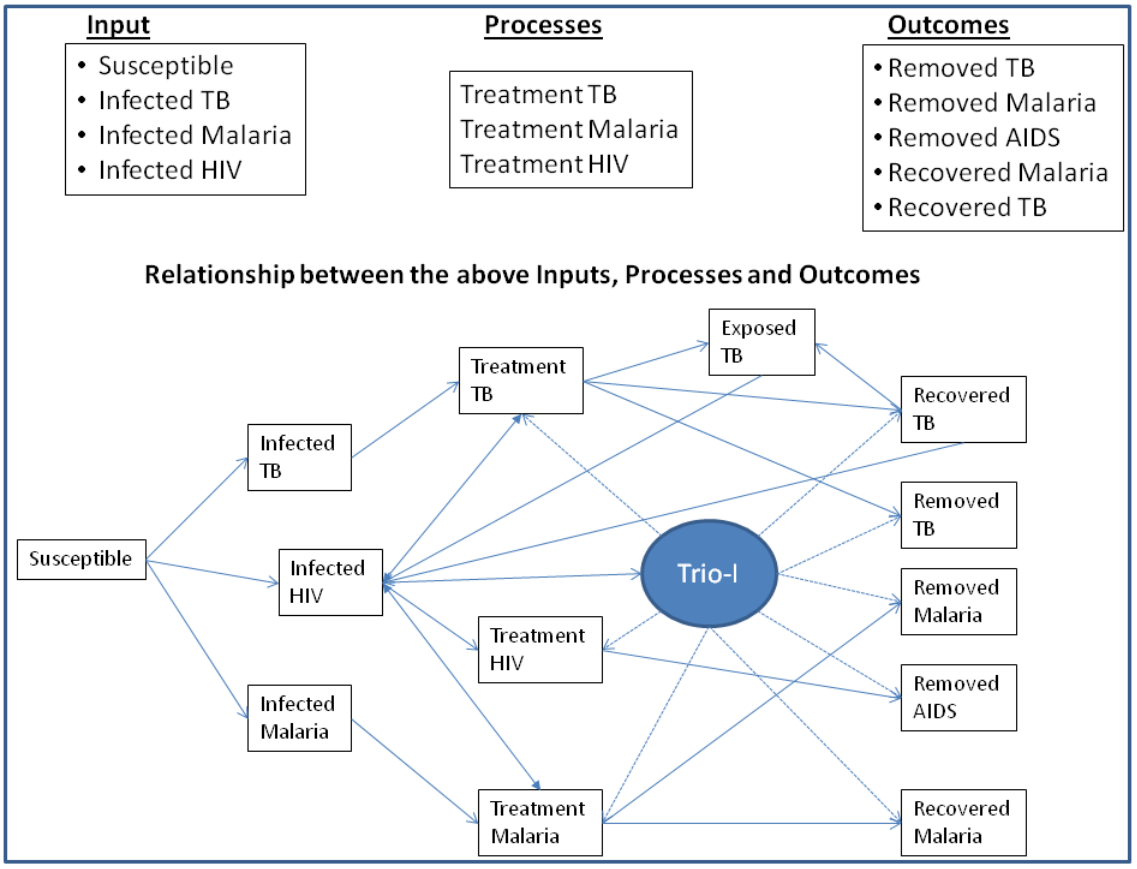


FIGURE 2.4: Emerging triad-Infection conceptual framework

the susceptible population, Infected TB, Infected Malaria, Infected HIV. The main process here is the treatment to the three disease. The outputs are: Recovered TB and given TB is never fully treated, another cohort is introduced (Exposed TB), Recovered Malaria, Removed TB, Malaria and AIDS (fully blown HIV). During the interaction process, the three diseases may meet thereby exposing the patient to trio-infection. This leads to the introduction of this cohort that calls for the intervention dependent on what infection should be treated first.

Finally the combined conceptual framework 2.5 derived from Figures 2.4 and 2.6 presents the variables and the anticipated relations. The circled sections indicates where the concentration of this research i.e scenarios and policies generated from simulation of model consistent with the methodology adopted (stage 6 of system

dynamics - testing and validation).

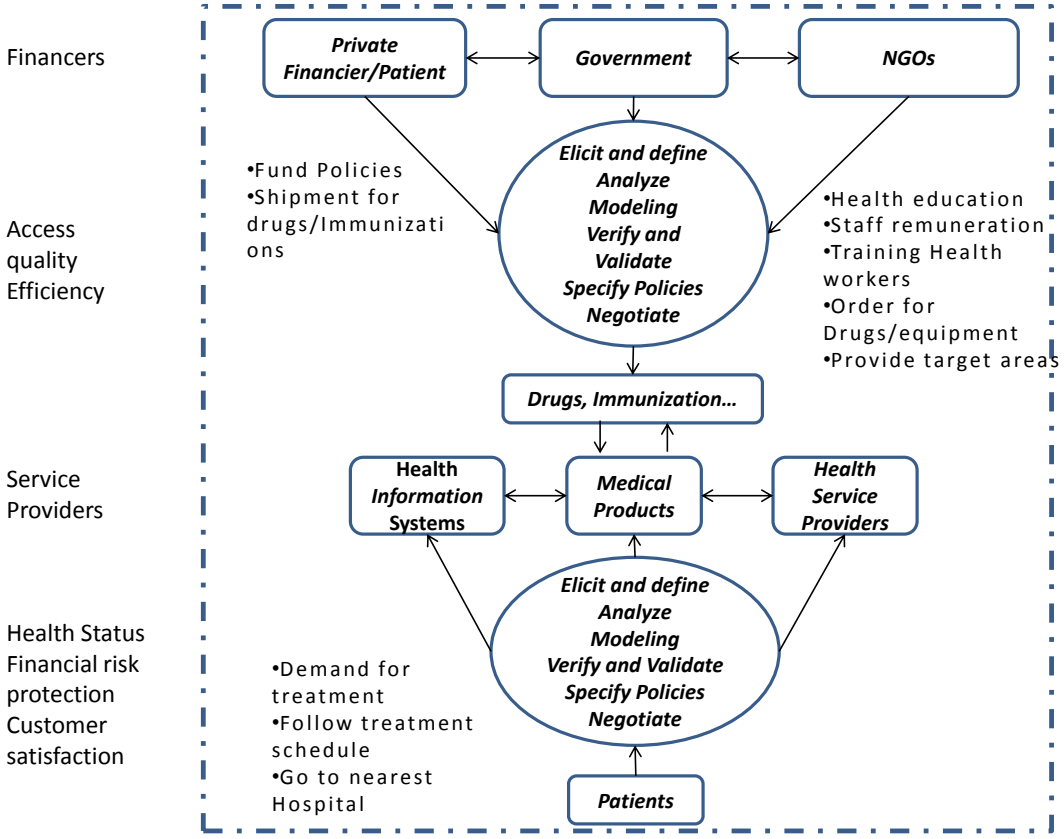


FIGURE 2.5: Conceptual model for this research

The upper circle indicates the model contribution aimed at elucidating scenarios aimed at generating the best policies for harnessing where best the financiers can invest in such the diseases can controlled particularly in PLWHIV. The model also indicates whether the intermediate goals of access, quality and efficiency are achieved in the process with the ultimate goals of improvement of health status, financial risk protection and customer satisfaction.

2.5.1 Reference Modes

The following (Figure 2.6) describes behaviour over time emanating from the descriptive model shown in Figure 2.7 representing the high level variables which are defined in Chapter 4. The Figure 2.6 was arrived at by using the archetypes

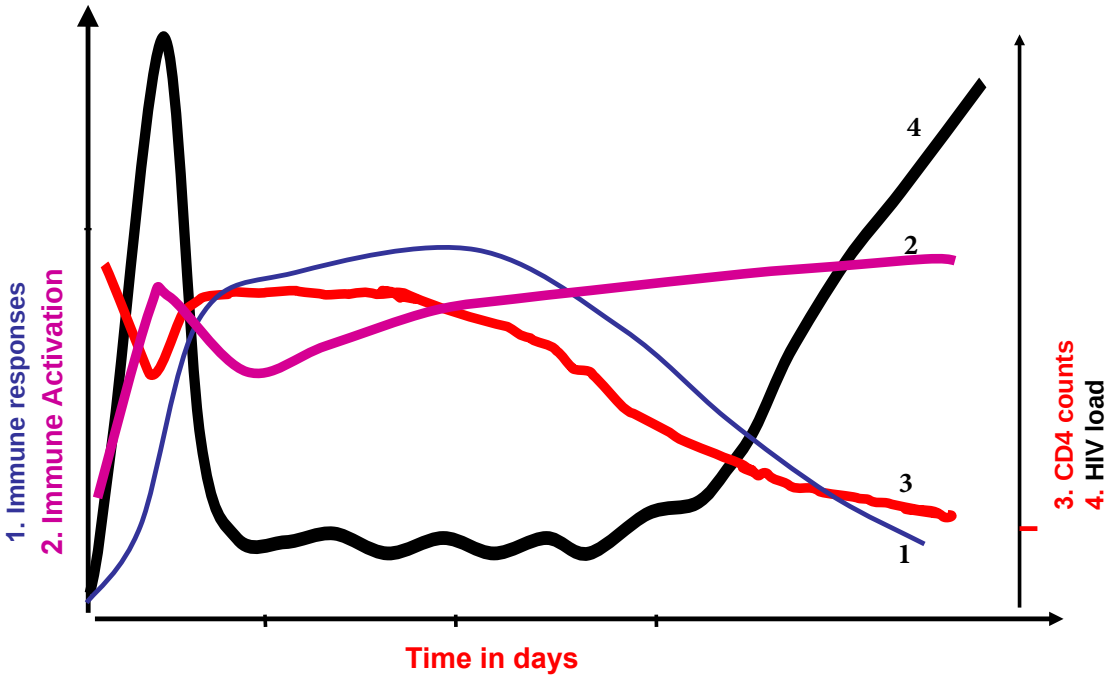


FIGURE 2.6: Reference Modes

described earlier in this Chapter together with discussions from the FGD. As System Dynamics models represent problems patterns not systems, the first step in the Modelling process is to define the problem the model will represent. This problem definition is named the reference mode. A reference mode is derived from historical information and is often described graphically. While reference mode is meant to consist of historical data, historical data may not be the only starting point for constructing a reference mode, but represent an abstract concept that must be developed very carefully to infer future trends. It represents a fabric of trends representing a complex pattern rather than a collection of historical time series. A reference mode, therefore, is not historical data, it is an abstract concept that must be arrived at through a careful analysis of the historical data and the future that can be inferred from it (Saeed 1998). With reference to the defined problem, it is apparent from the Figure 2.7 that healthy population continues to be susceptible to HIV, Malaria and TB over time. Opportunistic Infections (TB

and Malaria) represented by graph 2 comes into play when HIV reaches asymptomatic stage. From there on, the host becomes subject to multitude of such OI till death.

HIV behavior over time is represented by the viral load (curve 3). This continues manifesting in the life of the host exponentially after infection up to a an equilibrium point. During this time, the host immune system produces antibodies to fight the disease and the virus is replicating relentlessly. Over time, the patient starts becoming weak as HIV becomes asymptomatic during which the patient starts receiving ARVs. The accumulation of these drugs in the body is represented by curve 1. Accordingly, the host does not receive the drugs immediately based on CD4 cell count. As can be seen in reference mode 6, its not until the CD4 count reaches a particular level that the patient start receiving ARVs.

Also, when the host is subject to OI and various interventions regimes applied accordingly, the patients start responding to curative interventions represented by curve 4, indicating reduction in infectiousness

2.5.2 Basic Mechanisms and the Feedback of HIV Progression with OI

This is used to highlight the set of variables associated with the causal links of the model (Berard et al. 2008). This dynamic hypothesis representation shows the feedback loops of the model. This model Figure 2.6 is deemed complex because of feedback loops that illustrate the micro-structure of the system. A complex system is structured with feedback loops interactions. Reinforcing feedback loops labeled *Ri*, amplify the reinforcing macro-behavior of the system, and balancing feedback loops labeled *Bj* introduce inertia toward equilibrium, thus limiting the actions of the reinforcing loops. Feedback loops within systems do not behave in isolation, they generate alternative feedback interactions at different points over time and as a result of time delays in the system. The relationships among variables captured from multitude of literature can be represented as follows (Figure 2.7).

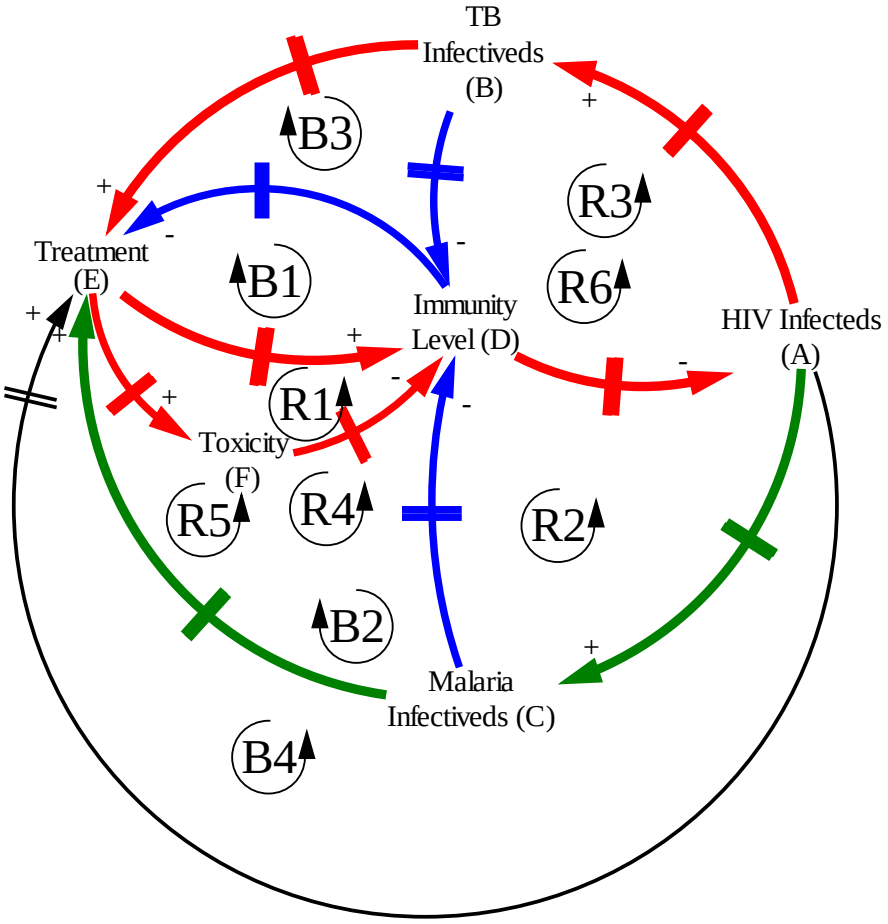


FIGURE 2.7: Trio Infection Dynamic Hypothesis

Reinforcing loops are 6: R1-R6 and described as follows

a. Loop R1 of length 2 Immunity Level (D), Treatment (E) and Toxicity (F) This loop, called the toxicity loop shows the impacts of consistent consumption on regimens leading to toxicity in the patient system and subsequent compromisation of immune system that can lead to collapse of the same

b. Loop R2 of length 2 Immunity Level (D), HIV Infecteds (A), and Malaria Infectiveds (C) Loop R2 presents the reinforced activity of Malaria and HIV pathogens to the immune system effectively causing to fail. This is a case where the HIV patient is not aware of malaria attacks. The loop is called HIV-Malaria synergy loop

c. Loop R3 of length 2 Immunity Level (D), HIV Infecteds (A) and TB Infectiveds (B) Loop R4 presents the impacts of HIV and TB pathogens on the immune system. The collaboration of HIV and TB to attack the immune system will lead to its collapse. The loop is called called HIV-TB synergy loop

d. Loop R4 of length 3 Immunity Level (D), HIV Infecteds (A), Treatment (E) and Toxicity (F) Loop R5 presents the impacts of hyperactive antiretroviral regimens to the people living with HIV. This leads to increased toxicity. The loop is called HIV-treatment toxicity loop.

e. Loop R5 of length 4 Immunity Level (D), HIV Infecteds (A), Malaria Infectiveds (C), Treatment (E) and Toxicity (F) This loop presents the synergistic activities of malaria, HIV and toxicity to the immune system complementally rendering the immune system into fail. It presents a case where the patient is taking malaria drugs and HAART regimens that raises the toxicity of the body.

f. Loop R6 of length 4 Immunity Level (D), HIV Infecteds (A), TB Infectiveds (B), Treatment (E) and Toxicity (F) On the same note, this loop presents the activities of TB, HIV pathogens, and their respective treatment on the immune system that subsequently render it completely ineffective

Balancing loops are three: B1, B2 and B3 described as follows.

a. Loop B1 of length 1 Immunity Level (D), Treatment (E) This balancing loop presents the effects of treatment on immunity, that an increase in treatment increases immunity that prompts reduction of treatment overtime. It is called treatment loop.

b. Loop B2 of length 3 Immunity Level (D), HIV Infecteds (A), Malaria Infectiveds (C) and Treatment (E) This loop, presenting the effects of HIV on Malaria implies that, a compromise on immunity by the HIV virus exposes the patient to malaria infections that prompts increase in treatment that

raises the immune level of the patient. The loop is called HIV impact on malaria pathogens

c. Loop B3 of length 3 Immunity Level (D), HIV Infecteds (A), TB Infectiveds (B) and Treatment (E) Loop B3 presents the impacts of HIV virus on TB pathogens indicating that a lowered immunity due to HIV virus leads to increase in viral load that predisposes the patient to TB infection that leads to seeking treatment which then leads to seeking treatment. Increase in treatment leads to improved immunity. The loop is called HIV impact on TB pathogens

d. Loop B4 of length 2 Immunity Level (D), HIV Infecteds (A) and Treatment (E) This loop presents HIV aware patient who is handling the situation by taking ARV regimens. It is called HIV treatment loop

Chapter 3

Methodology

3.1 Research Philosophy

This section discusses our belief about methods that were used to collect data, analysis and used with relation to HIV, TB and Malaria. The term epistemology (facts or what is known to be true) as in contrast to doxology (what is believed to be true) encompasses the various philosophies of research approach. The purpose of science, then, is the process of transforming things believed into things known: doxa to episteme. Positivist - sometimes called scietific and interpretivist also called antipositivist are two major research philosophies that have been outlined in the Western tradition of science according to Galliers (1991).

3.1.1 Positivism

Positivists philosophizes that reality is stable and can be observed and described from an objective standpoint Levin (2005), that is without meddling with the phenomena understudy. They contend that phenomenon should be segregated and that observations should be repeatable. This is followed by manipulation of reality in various ways through each one of the single independent variables or constituent factors so as to identify regularities in, and to form relationships

between, some of the constituent elements of the social world. Predictions can be made on the basis of the previously observed and explained realities and their interrelationships. "Positivism has a long and rich historical tradition. Positivism is engraved in our society that knowledge claims not grounded in positivist thoughts are simply dismissed as ascientific and therefore invalid" Hirschheim & Klein. (1989). Incidentally this is supported by Alavi & Carlson (1992) in a review of IS research articles, established that all the empirical studies were positivist in approach. In addition positivism has had a particularly successful association with the natural and physical sciences. Meanwhile, there has been much deliberations on the issue of whether or not this positivist view is exclusively suitable for the social sciences as alluded by Hirschheim & Klein. (1989). Many authors however calls for a more pluralistic attitude towards IS research methodologies (as observed by e.g. (Bjrn-Andersen 1985, Kuhn 1970, Remenyi & Williams 1996). While we put a comma on this debate, it is central to our study since it is also the case that Information Systems, dealing as it does with the interaction of people and technology, is considered to be of the social sciences rather than the physical sciences Hirschheim & Klein. (1989). Indeed, some of the difficulties experienced in IS research, such as the apparent inconsistency of results, may be attributed to the inappropriateness of the positivist paradigm for the domain. Likewise, some variables or constituent parts of reality might have been previously thought unmeasurable under the positivist paradigm - and hence went unresearched (after Galliers (1991)).

3.1.2 Interpretivism

This view contend that only through the subjective interpretation of and intervention in reality can that reality be fully understood. The study of phenomena in their natural environment is key to the interpretivist philosophy, together with the acknowledgement that scientists cannot avoid affecting those phenomenon they study. They admit that there may be many interpretations of reality, but maintain that these interpretations are in themselves a part of the scientific knowledge they

are addressing. Interpretivism has a tradition that is no less glorious than that of positivism, nor is it shorter (Muhl 2014).

It is apparenet that these two research traditions started in Classical Greek times with Plato and Aristotle (positivists) on the one hand, and the Sophists (anti-positivists) on the other. This was followed by long, dark periods in European scientific thought, with the resurgence of the discipline in the sixteenth and seventeenth centuries. Since then, well known positivists have included Bacon, Descartes, Mill, Durkheim, Russell and Popper. On the opposing side we have Kant, Hegel, Marx, Freud, Polanyi and Kuhn (Hirschheim & Klein. 1989). Vreede (1995) alludes that in both Organisation Science and Information Systems research, interpretive research used to be the norm, at least until the late 1970s. Since that time, however, the positivist tradition has taken a firm hold with (Dickson and DeSanctis, 1990), Orlikowski (1991) noting that about 96.8% of research in the leading IS journals conform to this paradigm. Pervan (1998), in a review of 122 articles in the GSS literature, observes that only 4 (3.27%) could be described as interpretivist. It has often been observed (e.g. Benbasat et al. (1999)) very accurately that no single research methodology is intrinsically better than the other, with many authors calling for a combination of research methods in order to improve the quality of research (Kaplan & Duchon 1988). Equally important, some institutions have tended to adopt a certain "house style" methodology Galliers (1991); this seems to be almost in defiance to the fact that, given the richness and complexity of the real world, a methodology best suited to the problem under consideration, as well as the objectives of the researcher, should be chosen (Benbasat, 1984, Pervan, 1994b). In this research, we have tried to avoid what may be characterised as methodological monism, i.e. the insistence on using a single research method. This is not due to an inability to decide between the various merits and demerits of the various alternatives, but in the believe that all methods are valuable if used appropriately and that research can include elements of both the positivist and interpretivist approaches, if managed carefully. To do all that this research entails as outlined in the objectives in chapter one compelled

interprevist view. However, recognising the lack of objectivity sometimes associated with interpretivist research methods, we adopted positivist, quantitative approach to the development of our key research instrument. These various elements of our research approach are further elaborated in the following section on research design.

3.1.3 Dynamic Synthesis Methodology

This methodology was proposed by Williams in 2000. The methodology integrates System Dynamic Modelling and Case study Research method. In agreement with Williams (2000), research designs that extensively combine both system dynamics and case study research is strong. The triangulation of methods though not new has not been applied in healthcare system Modelling. Dynamic Synthesis Methodology is such a methodology.

The methodology Williams (2000) uses a research design that combines two powerful research strategies namely: qualitative (case research method) Galliers (1985), Yin (2003) and the quantitative (System Dynamics Modelling-Forrester (1961), Richardson & Pugh (1981), Sterman (2000)) techniques to provide solutions to problems. Qualitative analysis provides a deeper understanding of the ways in which individual variables behave and impact organizational phenomenon. Simulation Modelling provides an opportunity to study situation through experimentation that might otherwise be impossible to analyze, while case studies Yin (2003, 1984) capture reality in greater detail and enables analysis of more variables than is possible using other research strategies as also observed by Galliers (1985).

The combination of qualitative and quantitative research methods increases robustness of the results and subsequently strengthening the findings through cross validation with the case study results. The SD model is based on the field study results which provides descriptive model on which the SD conceptual feedback structure is developed.

The feedback structure model is develop with the help of causal loop Diagrams. Causal loop diagrams are converted to stock and flow diagrams which are a formal quantitative model of the problem in question. Mathematical relationship between and among the variables which enable the simulation of the model are defined after which simulations of the key variables are run.

This methodology is comprised of six stages as indicated in the figure 3.2 below.

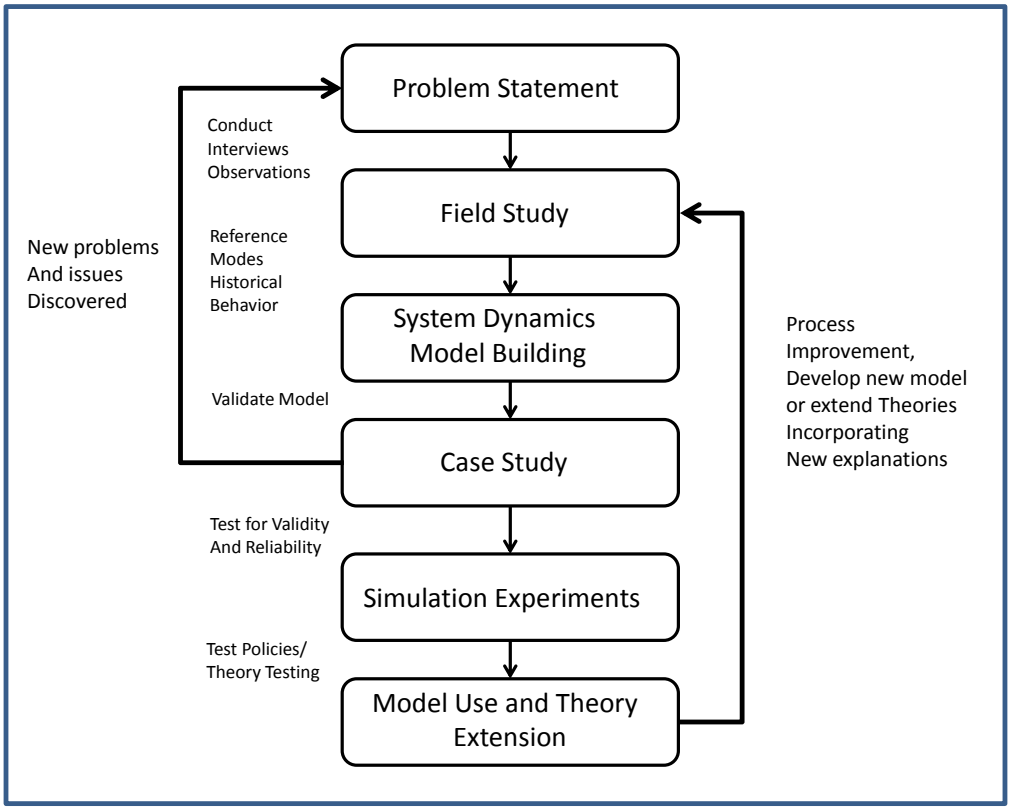


FIGURE 3.1: Dynamic Synthesis Methodology [Adapted from Williams (2000)]

Stage 1: Problem Statement

The problem is clearly stated at this stage. System dynamics refers to the problem to be solved while case study refers to the questions to be answered. The problem should be clearly stated as it is important early phase of Modelling.

Stage 2: Field Study

Field study and supporting data collection methods provide invaluable insights and discoveries during SD research. In the research, both quantitative and qualitative

data will be collected. Quantitative data can be collected through surveys, observation, program evaluation, case studies, and field experiments. Qualitative data collection methods which will predominate this research where data collection, analysis and field studies often take place concurrently, has been used by management consultants to understand problems in organization and gain insights in expected improvements to achieve organizational effectiveness Sterman (2000) Input and output information to activities identified in causal loop diagram in figure 1.2 resulting field studies are used to identify activities, resources and products used by the process. Data on processes, resources and product are used to develop the generic model Williams (2000)

Stage 3: System Dynamic Model Building

System Dynamics model development is a system stage process that begins and ends with understanding as explained by Richardson & Pugh (1981) also in figure 3.1.

The results of the field study are used to develop the descriptive model on which SD conceptual feedback structure can be developed which is done by the use of causal loop diagram Williams (2000).

A feedback loop is a control system which has input and output to the system where the output of the system is fed back into the system as part of its input Sterman (2000). Feedback may be reinforcing (R) or balancing (B) loop. Maani & Cavana (2000) defines a reinforcing loop as a positive feedback system that represents a growing or declining action while a balancing loop is a negative feedback system that is self-regulating and seeks stability or aims for a specified target. The causal loop diagram is converted into stock and flow diagrams which are defined by mathematical equations. Simulation can be run on the important variables and once confidence is gained through validation and ownership by the stakeholders, then the model is available to test hypothesis and policies of interest.

Stage 4: Case Studies

Case studies is an exploratory (single-in-depth study) research strategy involving empirical investigation of a particular phenomena within its real life context using

multiple sources of evidence as claimed by Yin (2003), Williams (2000). Case studies are used to validate SD model and provide a deeper understanding of the problem being investigated. They provide valuable insights and discoveries during the SD research.

Stage 5: Simulation Experiments

Simulations models are abstracts of the real worldview of the system or problem being solved. Shanon as cited by Williams (2000) defines simulations "The process of designing a model of a real system and conducting experiments with this model for the purpose of understanding the behavior of the system and/or evaluating various strategies for the operation of the system". The model is used as a vehicle for experimentation in a "trial and error" way to demonstrate the likely effects of various policies.

Stage 6: Model use and theory extension

As stated by Williams (2000) building valid and credible process model is an important aspect of a researcher's representation of the actual system being studied will be the next stage. For the us to determine the accuracy of the model, three terms are important to describe:- Verification, validation and credibility of the model. Verification is the process of determining that a simulation computer program (or model) performs as intended. Verification checks the translation of the conceptual model (e.g. influence diagram, flowcharts and assumptions) into a correctly working program or pseudo-code in the Dynamic Synthesis Methodology. Validation is the process of determining whether the conceptual model (as opposed to the computer program or model) is accurate representation of the system under study. As suggested by Law & Kelton (1991) a model is "'valid' if the decisions made with the model are similar to those that would be made by physically experimenting with the system. A model is credible when a simulation model and its results are accepted by managers/customers as being valid, and used as an aid (tool) in making decisions. The following questions are used in determining whether the model is valid or not:

a. Does the model represent the system correctly?

b. Does the system match the requirement?

c. Do the specifications match the requirements?

The most common approach for checking the validity of a model as argued by Sargent (1994), is for the model development team to decide as to whether the model is valid or not. Another approach suggested is often called independent verification and validation (IVV), which users to evaluate third party independent of both the model development team and model users to evaluate the model. Sargent however discourages the third party approach which uses a scoring model stating that this method tends to be objective, may cause over confidence in the model and that it is difficult to determine how passing scores are determined.

Some of the validation techniques for verifying and validating the sub models and overall model suggested by Sargent (1994) are:-

a. Animation: The model operational behavior is displayed graphically as the model moves through time.

b. Event validity: Events of the simulation model are compared to those of the real system to determine if they are the same.

c. Historical data validation: Part of the data that is collected is used to build the model and the other part is used to determine if the model behaves the same way the system does

d. Parameter variability sensitivity analysis: This involves changing the values of the input and internal parameters of a model to determine the effect upon the model behavior and its input.

The following validation techniques as expressed by Coyle (1996) are used as a test for confidence in the model:-

a. The influence diagram should correspond to the statement of the problem

b. The equations correspond to the influence diagram which includes checking for syntax errors, missing parenthesis, variables that are not defined and documented.

c. The model should be checked for dimensional validity either by hand or software.

d. The model should be subjected to test such that the model does not produce any ridiculous values and that its behavior is reasonable.

This research used Dynamic Synthesis Methodology (DSM). This is firstly because the System Dynamics as a methodolgy for modelling complex system has gone through various evolution meant to improve the methodology. Secondly is that such improvements have been set out to add value to the quantitative nature of the methodology. With Dynamic Synthesis Methodology, the improvements have not only been to the quantitative value but also the qualitative nature of the methodology especially the case study addition. The following Table 2.2 summarizes the choice of DSM methodology as the method of choice for this research.

HIV management is a dynamic and complex system which displays fluctuations. Its complexity is even reinforced owing to the fact that HIV weakens the immune system and exposes it to other opportunistic infections particularly TB and malaria. Sterman (2000) suggested characteristics that make systems dynamically complex and some of these can be found in the system under study

3.2 Comparative Evaluation of SD Modelling Approaches

In this section we highlight some of the SD Modelling approaches and the different stages analysis. As claimed, SD method should be able to capture concepts related to the model of interest. The SD methods discussed in section 3.1.1, 3.1.2. and 3.1.3 pioneered by Richie-Dunham & Rabbino (2001), Wolstenholme (1990), Coyle

TABLE 3.1: Dynamic Complexity of Trio-Infections

Characteristic	Description	Examples
Dynamic	Changes in system occur at many time scales and are difficult to predict	The cells under attack by HIV virus oscillates such that sometimes they are high, other times the are low. There is time delays between on set to therapy using ARV and stabilization of CD4 cells. The situation become even worse when OIs sets in
Tightly Coupled	Actors in the system interact strongly with one another	When under ARV, there are situation as indicated by WHO (2006, 2007) PLHIV react to drugs even before OIs sets in.
Governed by Feedback	Actions feedback on themselves	As PLHIV continue their therapy, drug toxicity sets in and viral load increases thereby reducing CD4 count and making therapy ineffective hence subjecting the patient to OIs.
Non-Linear	Effects is rarely proportional to cause. Cause and effect relationship is not proportional	While some PLHIV react positively to ARV, others do not at all. There are other cases of discordant where parties involved may not be affected equally under the same conditions
Policy resistant	Many seemingly obvious solutions to problems fail or actually worsen the situation	Even with education, thereby boosting awareness about the calamity of HIV, cases of the same continue to increase.
Characterised by trade-offs	Time delays in feedback channels means the long run response is often different from the short-run	Successful administration of ARV is only time bound. Recurrence of immunodeficiency is not guaranteed as there is no cure.

(1977) fail in guiding the researcher on how to carefully collect data that is relevant to the problem under investigation (Trio-infection fluctuations) as presented in Table 3.1

All the Modelling approaches described in Sction 3.1 other than MCM, have more or less the same approach to Modelling other than being broken down in diverse stages. They all start with defining and understanding the problem. Once identified, qualitative methods are drawn before constructing the quantitative Modelling of the problem. The DSM beat all the mentioned SD Modelling approaches in that

it triangulates case study with simulation to provide deeper investigation of the problem understudy. Combining Simulation (SD) and case studies methods as

TABLE 3.2: Dynamic Complexity of Trio-Infections

Research Approaches	Coyle (1996)	Wolstenholme (1990)	Richie-Dunham & Rabbino (2001)	Williams (2000)
Problem Definition	✓	✓	✓	✓
Qualitative Analysis	✓	✓	✓	✓
Model Building	✓	✓	✓	✓
Case Studies	✗	✗	✗	✓
Simulation Experiments	✓	✓	✓	✓
Test and Design Policies	✓	✓	✓	✓

proposed by the DSM methodology is beneficial as the strength of the case study enables the collection of data in its natural setting as well as on-site collection of information of the current system, owners and user requirements and specifications used to develop a generic model.

It is evident from Sub-section 3.1.3 that SD Modelling approach is a thorough method which uses tools that analyze and present the dynamics of a problem faced by complex systems as well as managerial decision making process. The following chapter provides an analysis of various stages of DSM and proposed method used to conduct research

3.3 Research Design

This section discusses the research design adopted in this work. We will start by extending and discussing figure 3.2 following the work of Williams (2000). This extension is given in Figure 3.2. As outlined in Figure 3.2, DSM presents six stages.

In the first stage "problem statement", a though investigation on literature was done inorder to define the factors that define the pathogenesis HIV, TB and Malaria. In addition to this, interviews were conducted through focus group

discussions to personnel handling these diseases particularly from Kenya Medical Research Institute(KEMRI). KEMRI is a research body in Kenya that does research on tropical diseases including Malaria, Tuberculosis and HIV among others. It hosts researchers that have travelled widely and who are well versed in pathogenesis of these diseases and many others. Other than the researchers, we also interviewed pharmacist who handle and transcribe medicine to the diseases. Results from these interviews were used to enrich the descriptive model (Figure 2.7 and improve Figure 2.6 representing BOT (behavior over time).

Field studies through FGD were carried out to determine the challenges facing HIV service providers and their activities particularly when handling patient with OI and the coverage of care centers. From the Figure 3.2, this was stage II.

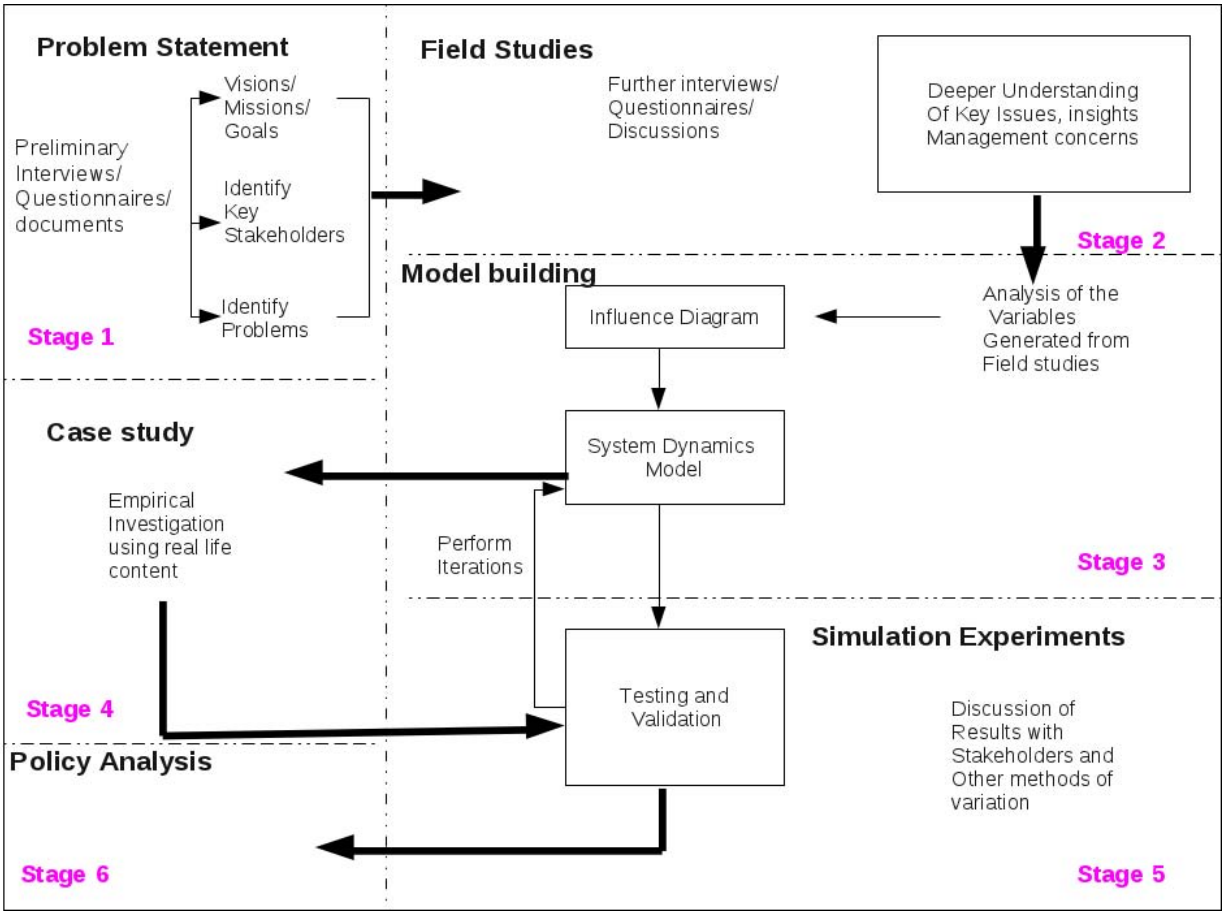


FIGURE 3.2: Research Design Framework [Adapted from Williams (2000)]

The particular information that we sought regarding HIV, TB and Malaria pathogenesis was captured through factors like CD4 count, viral Load copies, macrophages,

red blood cells, cytolytic cells, natural killer cells, Current ART, Resistance (genotype or phenotype) and previous ART regimens and reason for changing. This information was necessary in order to model the progression of HIV, TB and Malaria.

In order to measure the accessibility to treatment, the following data was collected at the clinical level. Number of patients seen, number of patients seen who are eligible for care, patient seen for care initiating HAART, number of patient seen interrupting ART, patients seen while at HAART including cause of death (whether due to accident, overdose or suicide), patients who died in the first 12 months on initiating HAART and number of deaths due among all HIV patient.

Information about ARV that we collected include: Type, size, dosage, major side-effects as well as resistance profile. This information was important so that we can measure the drug decay as well as administration during test and validation in stage 5 according to the research design in figure 3.3. The following data was collected in order to measure the prevalence of TB on PLHIV: number of registered TB patients, number of registered TB patients test for HIV, number of TB patients testing positive for HIV, number of HIV patients seen for treatment and care who are screened for TB symptoms, number of HIV patients who have TB infection, number of HIV patients who are newly diagnosed with TB disease; number of HIV patients newly diagnosed and registered with TB disease who have CD4 350 cells/mm3, number of HIV patients newly diagnosed and registered with TB disease who have CD4 ¡350 cells/mm3, number of HIV patients newly diagnosed with TB disease who have received TB therapy, number of HIV/TB patients who are receiving TB treatment, number of HIV/TB patients receiving both TB treatment and ART, number of HIV/TB patients in each category of TB treatment outcome, number of HIV/TB patients who have died, including cause of death (e.g. TB-related deaths, other HIV/AIDS related mortality or non-HIV/AIDS related mortality such as accident, over- dose or suicide).

Similarly, the following information was collected with regard to Malaria and HIV:- number of registered Malaria patients, number of registered Malaria patients test

for HIV, number of Malaria patients testing positive for HIV, number of HIV patients seen for treatment and care who are screened for Malaria symptoms, number of HIV patients who have Malaria infection, number of HIV patients who are newly diagnosed with Malaria; number of HIV patients newly diagnosed and registered with Malaria who have CD4 350 cells/mm3, number of HIV patients newly diagnosed and registered with Malaria who have CD4 ¡350 cells/mm3, number of HIV patients newly diagnosed with Malaria who have received Malaria treatment, number of HIV/Malaria patients who are receiving Malaria treatment, number of HIV/Malaria patients receiving both Malaria treatment and ART, number of HIV/Malaria patients in each category of Malaria treatment outcome, number of HIV/Malaria patients who have died, including cause of death (e.g. Malaria-related deaths, other HIV/AIDS related mortality or non-HIV/AIDS related mortality such as accident, over- dose or suicide).

The resulting information was used to develop the descriptive model (causal loop diagrams) which was presented to the stakeholders as identified in table 4.1 for improvements. Consequently a comprehensive causal loop diagram was developed and used to design the quantitative model for simulation in chapter 5. An empirical investigation using data from one referral hospital and dedicated dispensaries was carried out to populate the model (Stage 4). This was followed by scenario building in stage 5 and testing of various policies as well as validation. Finally intervention strategies were proposed according to the research design's stage 6 towards eradication of OIs for PLHIV

3.4 Architecture of Triad-Infection and System Boundaries

The successful development of a conceptual model is preceded by establishing the model boundary, flow of information, and key processes in the triad management and control system. The high level map of aggregation and information flow is as indicated in Figure 3.3 in Page 74, that outlines the types of different organizations,

activities, stakeholders and respective flow of information. Subsequently, the figure shows the points where data was collected from. The major subsystems are as follows:

a. Community sub-system that represent the population that benefits from the HIV services. The community is tasked with the duty of taking care of PLHIV and report cases and incidences concerning the same.

b. Healthcare sub-system. This provides palliative care to PLHIV and other services to the general population. It is also concerned with management of the resources like clinical officers, doctors, nurses, drugs, immunizations and related equipments.

c. Health Management sub-system. Tasked with management, monitoring and evaluation of HIV and related services at the national level

d. Drugs and Immunization Sub system. Responsible for management and delivery of quality drugs and immunization services.

Figure 3.3 shows the model bounday, key processes, flow of information and the main sub-systems. These were necessary for the development of the conceptual and simulation models of the HTM system. This map (Figure 3.3), also known as high level map shows the overall architecture of the model, information on the boundary and levels of aggregation developed. It also shows the number and types of different sectors or agents, key processes, activities and flow of information. The diagram however does not show the influences and causality thus necessitating the development of the causal loop diagram which provide deeper understanding of the HTM system.

a.) Health Information Subsystem.

This subsystem is tasked with monitoring HIV, Tuberculosis and malaria patients as well as related services like capturing, storing, processing, and communicating timely information to decision makers for better coordination

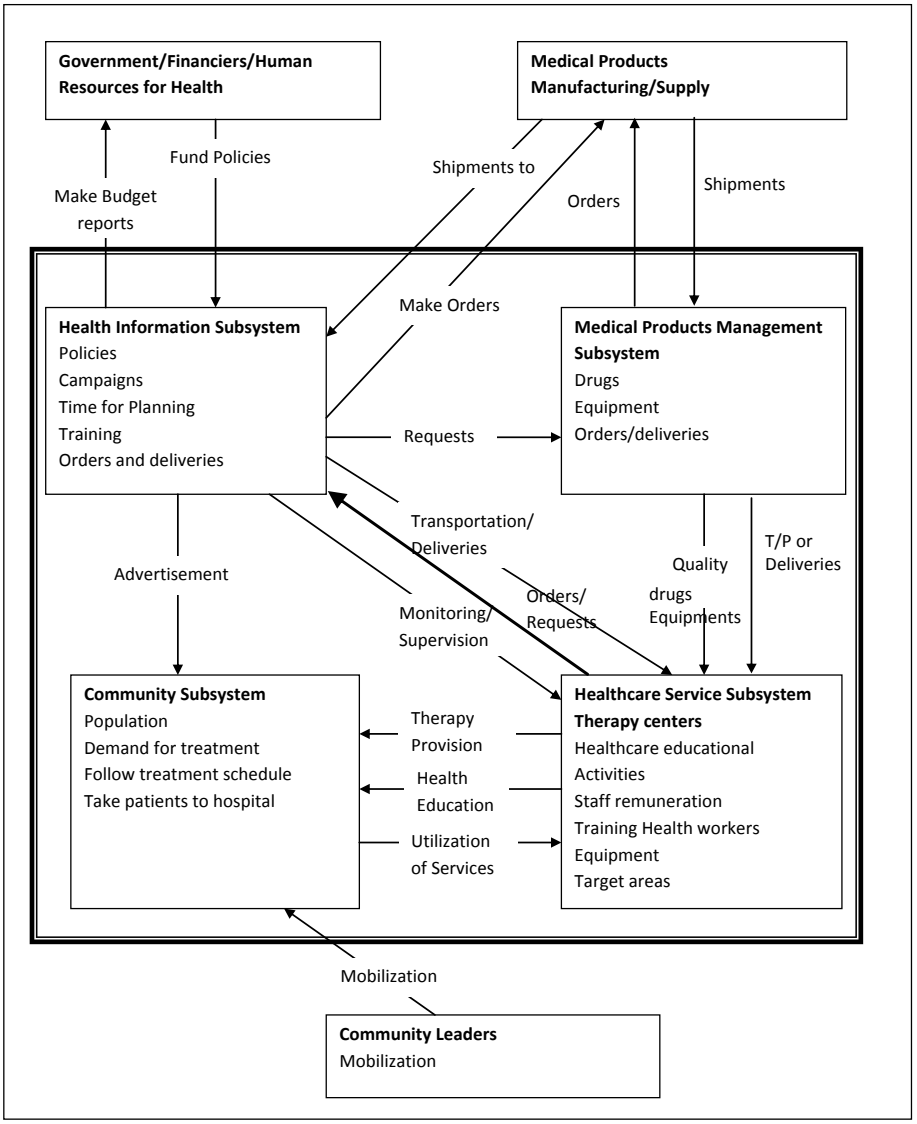


FIGURE 3.3: Model boundary for HIV Management and Control of OI System

of healthcare at both the individual and population levels as well as sending reminders.

b.) Medical Products Management Subsystem
This subsystem's responsibility is deliver quality drugs and immunization services to patients. It also does simple tests to confirm the patients ailments like the tuberculin skin test, blood test for malaria parasites among others.

c.) Community Subsystem.
This subsystem represent the population that benefits from treatment services as well research on various diseases. It also represent the researchers who carry research related to population and health status of the same.

d.) Healthcare Subsystem.
This module represent healthcare workers that provide healthcare services to ailing population. It is concerned with management of resources like clinical officers, doctors, nurses, drugs, immunizations and related equipments like test tools like microscopes among others

3.5 Field Studies

Field studies were conducted to determine the full range of activities and challenges associated with HIV management and control of OIs, examining acknowledged factors associated with the provision and utilization of HIV and related services. Secondary data from field study, interviews, and observation with the stakeholders was critical in revealing the historical, social, political and economical context within which the cases reside. This data was used to develop the preliminary descriptive model (causal loop diagram) in chapter one Figure 2.7. The stakeholders involved in this study were as follows (Table 4.1)

The methodology is comprised of six stages. In stage one information and problems related to HTM were collected from literature review and documents guiding the treatment of HIV, TB and malaria from WHO (2006, 2007, 2009) Kenya

TABLE 3.3: HIV Management and OI Control System Stakeholders

Stakeholder	Aspirations and Interest
Policy Makers	Reduce the disease burden and national mortality and morbidity
Policy Implementers	Provide HIV care to all nationalities to ensure the targets are met
District Health Services	Ensure that health facilities are well maintained and managed and that PLHIV are properly monitored
Health Workers	Work in well equipped health facilities with good remuneration
Community Leaders	Ensure that the members of the community have good health services, receive drugs/immunization and are in good health.
Customer/User	That ARVs/ARVs, HAART, Immunization or other drugs are accessible, well facilitated in a good environment provided with motivated health workers and effective care.

Aids Survey 2014. Issues related to HTM treatment and foregoing problems were summarised in the dynamic hypothesis (Figure 2.7) and BOT (Figure 2.6. The problems associated with HTM were cross checked by doing field studies in stage two. Here, structured interviews were used to guide in the focus group discussions. The discussant were drawn from Kenya Medical Research Institute which is a body engaged in research on infectious diseases like Tuberculosis, HIV, Malaria among others, College of Biological and Physical Sciences - University of Nairobi experts who teach and research on immunology, malaria, HIV and Tuberculosis, Institute of Infectious diseases and Tropical medicine - Jomo Kenyatta University of Science and Technology , Kenya Aids Vaccine Initiative researchers in development of HIV Vaccine as well as Daystar University School of mathematics and Engineering. Results from the field studies were used to concrete the dynamic hypothesis (Figure 2.7) and the behaviour over time (Figure 2.6 also called the reference modes. The factors that lead to progression of HIV to AIDs were critically explored and used to develop the causal loop diagram (Figures 4.1, 4.3, 4.4 and 4.5), which were results of literature and stakeholders for comments and improvements. Feedbacks from consultations were used to develop comprehesive causal loop diagram which was further used to develop the quantitative model (chapter 5) in stage three of the methodology. Discussion of results with stakeholders was done in stage five to

validate the model and finally proposition of strategies towards improvement of quality of life for people living with HIV were made.

3.6 Data Collection, Study area, and Procedure

Focus group discussions was considered in this research because of its strengths in collecting qualitative data and the nature of the reasearch, i.e. need to interact with researchers in HIV, Tuberculosis or Malaria or experts in the same. These is in agreement with Powell & Single (1996) who defines a focus group as a group of individuals selected and assembled by researchers to discuss and comment on, from personal experience, the topic that is the subject of the research, in this work cells that define HIV, TB and malaria as well as the cytokines and chemokines that are secreted and how they interract. More precisely Fern & Oaks (1982) specifies the approximate number of participants as six to twelve in his definition of FGD. Engagement of FGD was done in the month April 2014. This was part of the DSM methodology that requires both the qualitative and quantitative study in accordance with perception of many other researchers Sagoe (2012). The Dynamic Synthesis Methodology is underpinned by qualitative data collection methods which plays a significant role in the development of causal loop diagrams. Qualitative methods in part are significant in that they facilitate obtaining perceptions, opinions and attitudes as well as generation of recommendations about HIV, TB or Malaria in the specified environment which is a good representation of urban and sub-urban areas. The ideas generated here were used to enrich the other part which is causal loop diagram initially drawn from literature review. Causal Loop Diagrams is a foundational tool used in system dynamics in developing an understanding of complex systems, ability to identify visually and display intricate processes and root causes. Every system behaves in a particular manner due to the influences on it. Some of these influences can be changed, some cannot, and some can be minimized. Causal loop diagrams bring out the systematic feedback in

processes by showing how variable X affects variable Y and, in turn, how variable Y affects variable Z through a chain of causes and effects. By looking at all the interactions of the variables, the behavior of the entire system is discovered. With a CLD, a practitioner no longer needs to focus only on one interaction between two variables, but can focus on the entire system, along with its many variables and its many causes and effects. The result of this engagement were later used to develop the quantitative model in chapter 5. The quantitative model was developed in order to draw out these effects on the HTM model. The stakeholders engaged in focus group discussions are outlined in Table 3.3. The stakeholders provided different aspects of the HTM model. Firstly, the policy makers were engaged in order to provide information on how the results of the model would impact their decision making particularly in view of reducing national mortality and morbidity and checking on the disease burdens to the community. Secondly, were the policy implementers who takes part in care provision to people living with HIV. The category of stakeholders were particularly important as they are the ones who interact with the patient directly. Their role was to provide information about the behavior of patient part when they do not have any other infection and part when they are overburdened by other diseases like TB and malaria. Thirdly were the reasearchers in these fields i.e. HIV, Tuberculosis and malaria. A lot of work has been done and is still going on. In this research it was very important to tap into these areas as this work empasis was interactivity of the three diseases and how they impact the immune system. These stakeholders provided information about each player in terms of disease pathogenesis as well as the chemokines and cytokines that are secreted by the immune systems with a view to avert the pathogen intentions. Fourth category of stakeholders were the microbiologists, parasitologists and immunologists in training institutions. This category were particularly important as they are day in day out training students particularly in higher institutions of higher learning. On completion of the research, they are targeted consumers of the model aimed at helping the students understand the immune system and diseases and their interactivity better.

3.6.1 Sample selection

The purpose of the study was to get factors that facilitate progression of HIV to AIDS in the presence of cofactors Tuberculosis and Malaria. Therefore purposeful sampling was used to capture a homogeneous audience. We also did consider the knowledge level of the participants as well as our budget since alot of travelling was critical to the diverse audiences. Mini groups of four (4) people were used because the research required a deeper understanding of the factors influencing HTM. Also it was assumed that each member of the group had a greater deal to share about their expertise. Another reason for selecting small groups was perspective of multiple stakeholders' views on some research aspects did not intend to control adversely the passions of the audience when discussion starts. The participants were grouped according to their speciality i.e. HIV or Tuberculosis or Malaria but the for the last set was comprised of six (6) members, piggyback and on location focus group was adopted so that the research does not interfere with the primary purpose of the gathering. The reason for this was part to understand the factors influencing pathogenesis for each diseases while also addressing the interaction of the three diseases.

3.6.2 Strategies for Finding Participants

Because of the nature of the study, the researcher adopted a list of experts listed on doctors plaza in Kenyatta hospital, and purposeful random sampling of researchers from KEMRI, KAVI, University of Nairobi College of Biological and Physical Sciences and Daystar University, town Campus. Emails and phone numbers were used to first contact the group members as these were easier to get from the various instituions offices.

3.6.3 Coding

The objective of engaging FGD was to elicit as much knowledge as possible both technical and general about HTM. To achieve this, digital recording was used inorder to clarify points and to provide information for validating the data collected in the event of forgetting or losing the notes.

3.6.4 Data Management and Analysis

To analyze the qualitative data collected, thematic approach was used. These themes included general knowledge, technical knowledge about pathogenesis of each of the diseases under consideration i.e HIV, TB and malaria particularly the cells of the immune system that these diseases interact with. It was also important to have separate group discussions for the separate diseases as well as one that incorporated the three disease though it was the hardest to get these experts together as they are busy and travel alot depending on their current engagements. Since the groups were small, the researcher did three visits for each group. The first visit entailed an awareness of what causal loop diagrams entailed and letting the group members understand what the research was all about and signing the consent note. The second visit was a discussion of the pathogenesis of the disease in question taking notes and doing the recording at the same time. It is important to note that the researcher could meet the three groups in the same day. The third visit entailed a presentation using vensim - a software for developing causal loop diagram - to confirm that everything discussed is properly presented and clearing the over-presented ideas or variables. Three times may seem many but what came out from the group members was that they had never seen how variables could be related using causal loop diagram. Actually after discussion with one of the group which was composed of researchers who complimented their work with lecturing, was that they took some of the discussion to their immunology students who were very excited about the same.

3.7 Ethical Consideration

Because of the nature of the study and as a requirement by the National Council of Science and Technology, the researcher sought research clearance. Also human subject were involved and therefore need for ethical clearance which was sought and approved by University of Nairobi Ethical Review Board. This document are attached in Appendix C Page 193

Chapter 4

Results and Findings

4.1 Introduction

This chapter discusses the finding and results from the field study. The intention of the field study was to gain a deeper understanding of HTM system as explained in chapter 3. We will present a system diagram showing the main sub-systems that were used to develop the sectors of the simulation model of the HTM system. In addition we will also present the methods of gathering, analysis and interpretation of data from the field studies that were used. Finally, we shall present the research findings and conceptual model also known as causal loop diagrams resulting from the analysed data presented from Sections 4.2.1 to 4.2.5

4.2 Findings from the field Study

This section presents the findings from the study. These findings were as a result of discussions with stakeholders using the tools attached in Appendix A

4.2.1 Immune Subsystem

This subsystem was discussed by Immunologist with objective of identifying the cells of the immune system and how they mount response in the event of pathogens. Throughout the body are variety of cells each kind performing its' designated function. The immune system is made up of specialized cells called the immune cells.The blood is comprised of many red cells called erythrocytes. It also contain other cells called leukocytes and it is these cells also called the white blood cells (WBC) that work as part of the immune system. Blood circulates in the entire body and hence the WBC are located everywhere in our body. Certainly there are parts of the body where these leukocytes are concentrated like the spleen and the lymph nodes and it is from these sites that the immune systems launches resistance when attacked by pathogens. The pathogens are of four main types: viruses, bacteria, fungi and parasites - worms or protozoans. The immune systems can either be innate or adaptive. Innate immune response mount response as a result of skin cuts, abrasions, bites and wounds that provide pathogens entry through the skin. Pocking, touching, picking and rubbing the eyes, nose, and mouth accelerates pathogens to breach mucosal surfaces as is the case with breathing air, eating contaminated food and being around infected people. The innate immunity is ready to act immediately and avert the infections within a few days. The particular players in the innate immunity is the intact skin, mucus membranes and their secretions and normal microbiota participating as first line of defense while the second line of defense players are phagocytic white blood cells, inflammation and fever and antimicrobial substances (Howard et al. 2004, Perelson 2004).

Adaptive immunity or acquired or specific resistance, termed as the third line of defense is compromised of the specialized lymphocytes B cells and T cells as well as antibodies (Maarika 2010).

This study focussed on third line of defense particularly B cells and T cells. Based on discussion with the stakeholders, the resulting relationships between the cells of the immune system are shown in the Figure 4.1

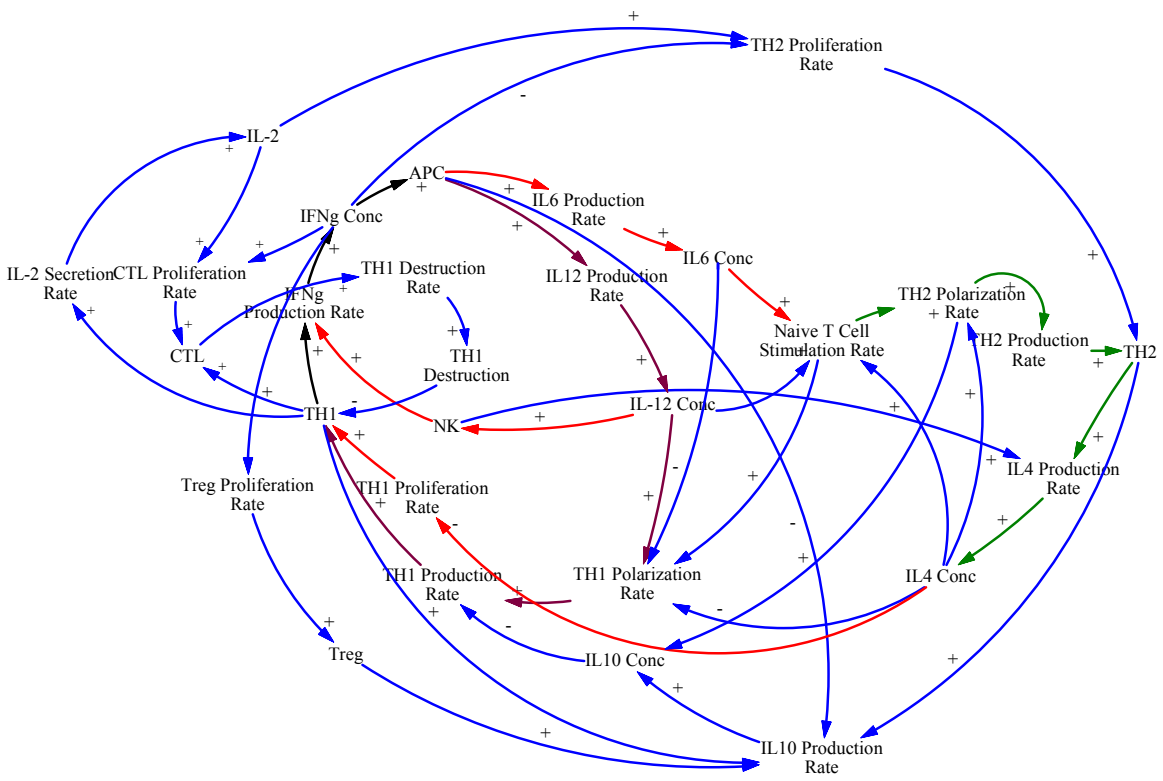


FIGURE 4.1: Immune System causal loop diagram

The Figure 4.1 is a indicator of the dominant loops of how the TH1 and TH2 cells influence the immune system during pathogen attack. The major activities of the T cells is to initiate elimination of modified or altered "self" cells. The T cell-mediated responses does its work through exciting or activating the Cytotoxic T cells popularly known as the CD8 or by having the T cells TH1 releasing cytokines as well as activating the macrophages that engulf the pathogens.

The Table 4.1 shows the relationships between variables and that play part in the sustaining immune system and are target of pathogens including viruses, bacteria, fungal etc attacks. The table indicates which variables were collected from the field and which were gathered from literature as well as unit of measure used in the model.

TABLE 4.1: Factors that influence the immune system functioning and the sources

Immune SubSystem		
Variable Name	**Reference/Source**	**Measure**
Naive-T-Cell	Literature	cells
Th1-Polarization	Field Studies	cells/day
Th1-Production rate	Literature	cells/day
Th1 Population	Field Studies	cells/day
Th1-Proliferation rate	Field Studies	cells/day
Th2-Polarization	Field Studies	cells/day
Th2-Production rate	Field Studies	cells/day
Th2 Population	Literature	cells/day
Th2-Proliferation rate	Literature	cells/day
Antigen Presenting Cells	Field Studies	cells/day
InterLeukin-6	Literature Review	mg
IL6 Production-Rate	Literature Review	mg/day
IL6 Conc	Field Studies	mg/day
InterLeukin-10	Field Studies	mg
IL10 Production-Rate	Literature Review	mg/day
IL10 Conc	Field Studies	mg
InterLeukin-4	Field Studies	mg/day
IL4 Production-Rate	Literature Review	mg/day
IL4 Conc	Field Studies	mg
InterLeukin-2	Literature Review	mg
IL2 Production-Rate	Literature Review	mg/day
IL2 Conc	Literature	cells
Treg Population	Literature	cells/day
Treg Proliferation rate	Literature	cells/day
IFNg	Literature Review	mg
IFNg Production Rate	Literature	mg/day
IFNg Conc	Field Studies	mg
CTL Population	Literature	cells
CTL Proliferation rate	Literature	cells/day
IL2 Conc	Field Studies	mg
IFNg Conc	Field Studies	mg/day

4.2.2 HIV Subsystem

The Figure 4.2 summarizes the factors that influences HIV pathogenesis as discussed by various researcher from Kenya Medical Research Institute as well as Kenya Aids Vaccine Initiative. The main interest here was to understand the cells of the immune system that contribute the most when it is under HIV attack. In addition was the interest to know which of these cells are related to TB and malaria pathogenesis. The Table 4.2 references the response from the field study

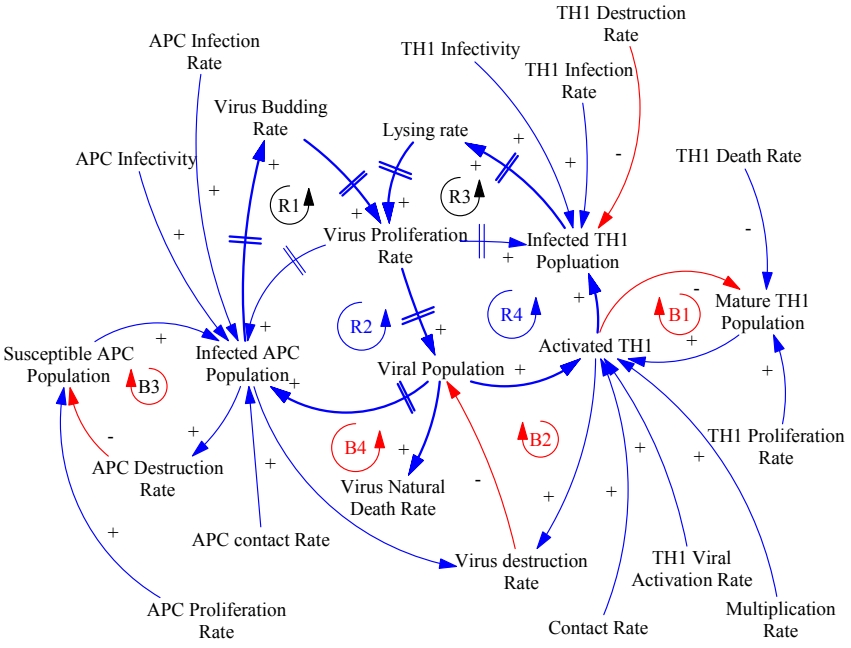


FIGURE 4.2: Factors that affects HIV pathogenesis

of the factors that influence the transmission of HIV virus, sustenance of the virus within the host as well as control. It also indicates which were confirmed from literature reviews as well as their unit of measure.

TABLE 4.2: Factors that helps in sustenance of control virus in the host body

HIV SubSystem		
Variable Name	**Reference/Source**	**Measure**
APC Infection rate	Literature	cells/day
Infected APC Population	Field Studies	cells/day
APC Contact Rate	Field Studies	cells/day
APC Destruction rate	Literature	cells/day
APC infectivity	Literature	cells/day
Susceptible APC Population	Literature	cells/day
Viral Pop	Field Studies	Virions
Virus Budding rate	Literature	Virions/day
Virus Proliferation rate	Field Studies	Virions/day
Virus lysing rate	Field Studies	Virions/day
Virus Natural death rate	Literature	Virions/day
Virus Destruction Rate	Literature	Virions/day
Activate Th1	Literature	cells/day
Th1 Contact rate	Field Studies	cells/day
Th1 Death rate	Literature	cells/day
Th1 Destruction rate	Field Studies	cells/day
Th1 Infection rate	Literature	cells/day
Th1 Proliferation rate	Literature	cells/day

4.2.3 Tuberculosis Subsystem

As with HIV subsystem, this tuberculosis subsystem was discussed with TB experts from KAVI researchers particularly because of the strong relationship between TB and HIV. Other than KAVI, researchers from KeMRI also looked into the initial factors which they made recommendations and verified the same as explained in Section 3.6. The reason for this subsystem was to identify the factors that contribute to progression of TB and their relationship with those of HIV as well as malaria. It came out from the FGD that Mycobacterium tuberculosis, the etiological agent of T.B. rarely causes disease in humans, it only does so to

individuals with weakened immune system. It emerged that Mycobacterium tuberculosis can remain dormant in the infected cells for decades without causing the disease. The Figure 4.3 summarizes these factors. The Table 4.3 shows field

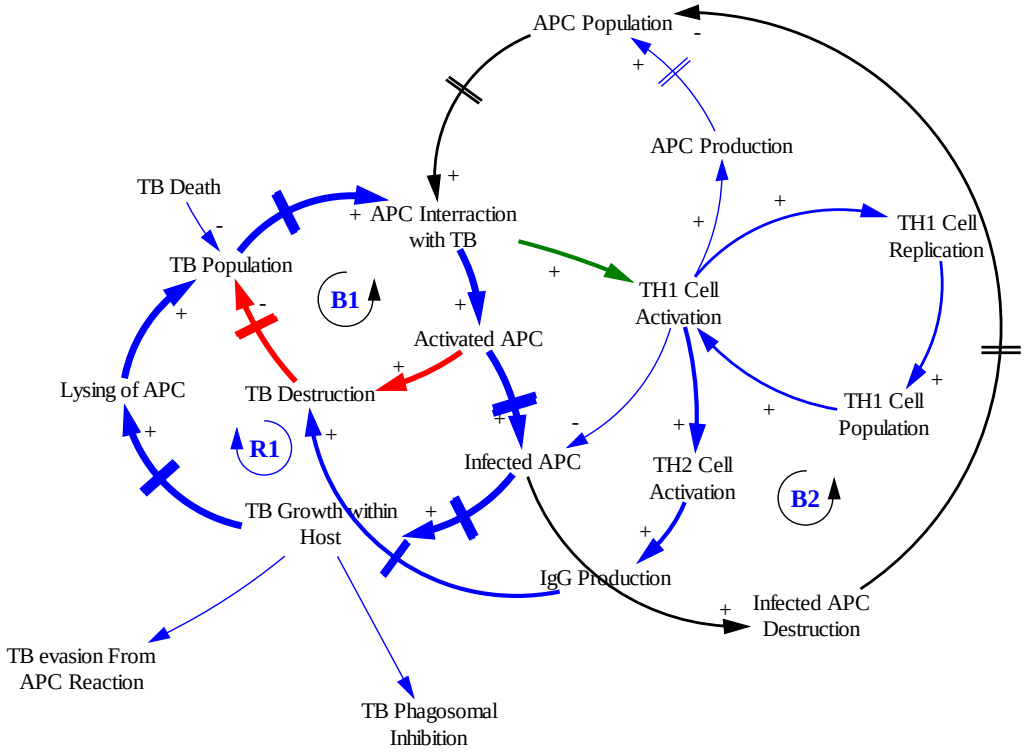


FIGURE 4.3: Factors that affects TB pathogenesis

study response of the variables that carry the heaviest burden in development of TB disease within the host. Included also in the Table 4.3 is also their unit of measure.

4.2.4 Malaria Subsystem

This subsystem was looked into by experts engaged in research from various parts of Kenya particularly the western regions like Kisumu and Kisii but based in Nairobi. We were interested in their input inorder to capture the pathogenesis of malaria within the host and at the same time relate them with those of TB and HIV pathogenesis. With regard to this, the Figure 4.4 summarizes the important

TABLE 4.3: Factors that influence TB growth and sustainance with the host

TB SubSystem		
Variable Name	**Reference/Source**	**Measure**
APC Population	Literature	cells
APC Production rate	Field Studies	cells/day
Activate APC	Field Studies	cells/day
APC Infection rate	Literature	cells/day
Infected APC destruction Rate	Field Studies	cells/day
Th1 activation rate	Literature	cells/day
Th1 population	Literature	cells
Th1 proliferation rate	Field Studies	cells/day
Th2 population	Literature	cells/day
Th2 Activation	Literature	cells/day
IgG Production rate	Literature	mg/day
IgG concentration	Field Studies	mg
TB Population	Field Studies	parasites
TB Natural death rate	Literature	parasistes/day
TB growth rate within APC	Literature	parasites/day

factors that contributes to the disease progression within the host. Response from the field on factors that influence malaria development in the host is summarized in Table 4.4 as well as the variables unit of measure.

4.2.5 Treatment Subsystem

Figure 4.5 shows the conceptual framework highlighting the interaction of drug in the host body. Table 4.5 presents the universal view of the variables representing the key variables associated with healthcare delivery but at cell level.

Table 4.4: Factors that infuence development of Malaria in Host

Malaria SubSystem		
Variable Name	**Reference/Source**	**Measure**
RBC Count	Literature	cells
Infected RBC	Field Studies	cells/day
Infected RBC destruction rate	Field Studies	cells/day
RBC production rate	Literature	cells/day
RBC natural death rate	Literature	cells/day
RBC contact rate with free merozoites	Literature	cells/day
Th1 production rate	Literature	cells/day
Activation of Th1 due to RBC	Literature	cells/day
Th1 Interaction with infected RBC	Field Studies	cells/day
Free Merozoites population	Field Studies	parasites
Merozoites lysing rate	Field Studies	parasites/day
Merozoites elimination rate	Literature	parasites/day
IFNg concentration	Literature	mg
IFNg secretion rate	Literature	mg/day
NK population	Literature	cells
NK stimulation rate	Literature	cells/day

Table 4.5: HTM Variables

Treatment SubSystem		
Variable Name	**Reference/Source**	**Measure**
Drug Concentration	Field Studies	mg
Drug absorption rate	Field Studies	mg/day
Drug excretion rate	Field Studies	mg/day
Drug volume of distribution	Field Studies	mg/day
Drug dosage	Field Studies	mg/day

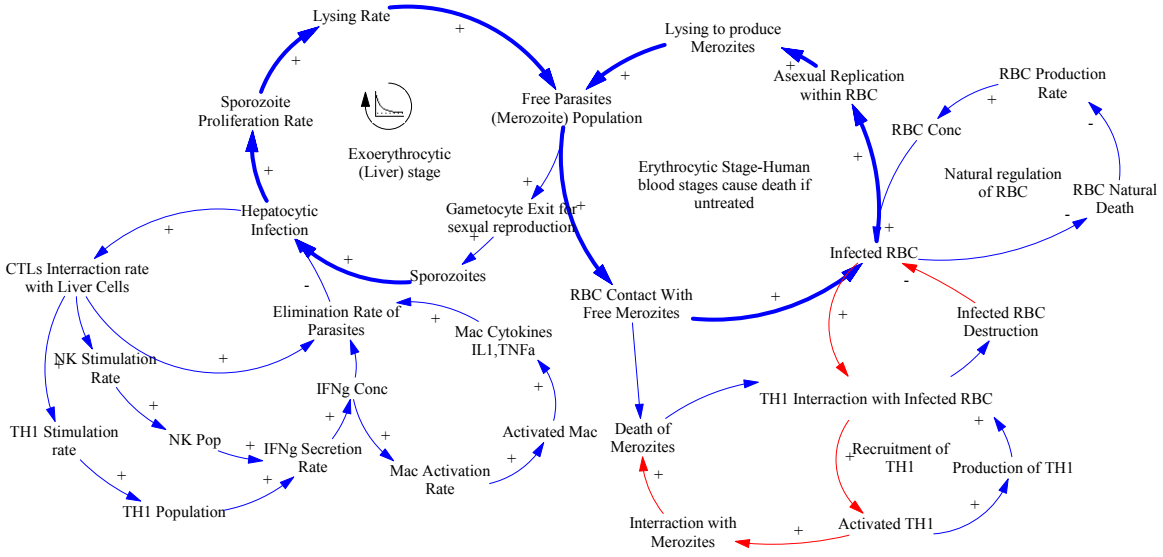


FIGURE 4.4: Factors that contributes to malaria pathogenesis

4.3 Conclusion and Summary of finding from the field study

Studies indicate that in order to reduce deaths and disease burden realted to HIV, there is need to increase and intensify treatment alloted to cofactors like TB and Malaria including funding on their research. As a summary the causal loop diagrams show the following as the significant as far as HIV and progression to AIDS is concerned:

a.) TH1 cells get activated by about all pathogens. TH1, being the host of the HIV virus, when it get activated, it replicates very fast with a view to outdo the virus budding - whose consequences are heavy viral load, having already

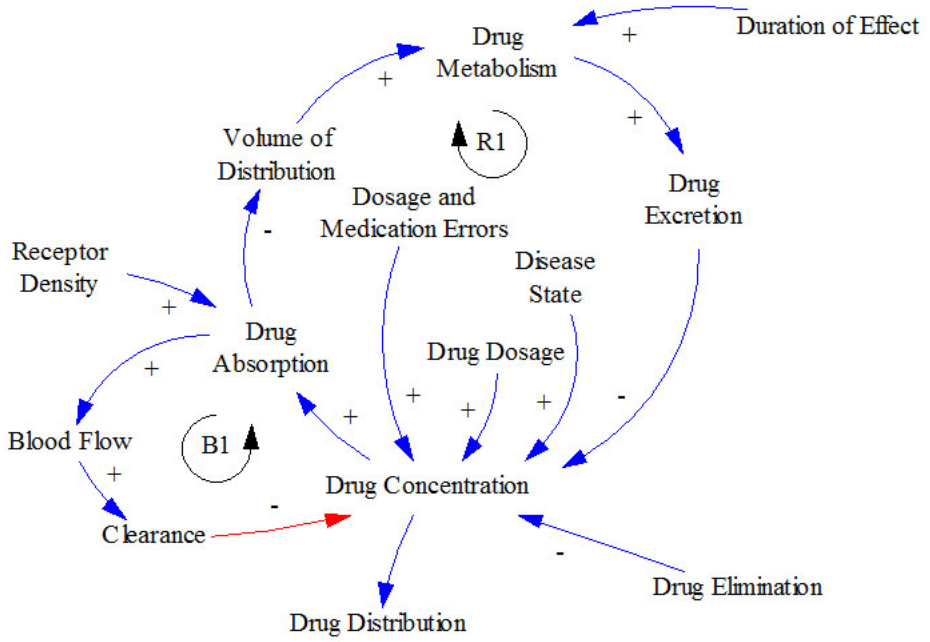


FIGURE 4.5: Drug interaction within host

undergone the reverse transcriptase phase. This means that care must be accorded PLWHIV to avoid other ailments that may subject the immune system to collapse as a result of virus replication.

b.) Access to Information. Alot of attention and information have gone to teaching on HIV. While this is important, focus should now be to coinfections having appreciated the fact that HIV infection among production age is growing by the day with about 30-40

c.) Motivation of health workers. As earlier noted in chapter 2, deaths due to HIV/AIDS are due to lack of testing so that the right medication is prescribed. To avert this standing, health care workers need to be well trained, remunerated and accorded managable workload.

Evaluation and analysis of figures and causal loop diagram in sub Sections 4.2.1, 4.2.2, 4.2.3, 4.2.4 and 4.2.5 indicate that causes of problems to the immune system due to HIV, Malaria and TB are due the following factors:

a.) The pathogenesis of HIV, Merozoites and TB are inherently comprised of feedback loops most of which are reinforcing loops

b.) Diseases pathogenesis is a complex dynamic system

c.) Factors contributing to the progress of the infections to disease are overly influenced by delays which overwhelms the health care personnel

d.) Analyis of factors of HIV, TB and Malaria clearly demonstrate that these diseases cannot be modelled using linear methodologies.

Causal Loop Diagrams presents the cause and effect linkages that benefit stakeholders and policy makers by enabling them comprehend complex systems as well as share observations that elicit deeper understanding of dynamic behaviour. The CLD described in this chapter are used to develop the simulation model in chapter five.

Chapter 5

Within Host HTM Simulation Model

5.1 Introduction

This chapter develops the simulation model for the HTM system. The model is based on the issues discussed in chapter four Section 4.2. The objective of the model was to show the relationship, trends and effects of the key variables associated with HTM system rather than predict the livelihood of the PLWHIV. This model like all continous System Dynamics Models is formalized and underpinned by mathematical differential equations

5.2 General Principles of HTM Formulation

The HTM model used the following system dynamics modelling principles in the formulation of equations in accordance with Barlas (2002).

a.) Equations were designed with meaning where variable naming as well as parameters correspond to real world meanings

b.) Units of equation were checked for equivalency for dimensionality consistency with the units on both the right and left hand side.

c.) Under extreme conditions, equations being tested must yield valid results

d.) The model was designed to provide realistic description of the real processes where the major focus of the model formulation was the realism and not the mathematical exactness

The model is based on the following equation formulation as alluded by Barlas (2002). *Linear Equation* which assume that the output is proportional to the input and *Non-Linear equation* that arise from the delay and dynamic feedback nature of the model where the output is a dependent on the product of a number of input variables.

The general form of the product formulations is brought out by the additive and multiplicative effect of formulations with the general form of the formulation taking the following form:

$$\begin{aligned} P = ((EffectOfX_1onP) + (EffectOfX_2onP) + ...+ \\ (EffectOfX_nonP) * Pnormal \\ P = ((EffectOfX_1onP) * (EffectOfX_2onP) * ...* \\ (EffectOfX_nonP) * Pnormal \end{aligned} \tag{5.1}$$

where the output P is additive or multiplicative function of $(X_1, X_2, ...X_n)$*Barlas* (2002).

In the event that the formulation is a multiplicative effect formulation, all functions *f()* yields unity *(1)*. Normalization is used to keep the different model parameters within the ranges of the function since absolute values would make it impossible to build robust experimental models. The model uses several of the multiplicative and effect formulation equations to represent feedback in the model Barlas (2002).

5.3 The HTM System Model

The HTM Model was constructed with a view of drawing deeper understanding and insights in the progression of HIV to AIDS when the immune system is under other attacks with TB and malaria under focus. The development of HTM model also intended to give insights in the issues that arise when cells of the immune system are activated and what cytokines the secretes and how this lead or not lead to providing conducive environment for HIV virus replicating. It also aimed at bringing out at what point should the care givers embark on therapy or disengage on the same. The Dynamic hypothesis outline in Figure 2.7 and the problem statement in Section 1.5 on Page 8. This model was developed based on the analysed data that was collected from the fields as reported in Chapter 4. The HTM model exemplifies key areas that can be focussed on including treatment, care services to people living with HIV as well as TB and malaria patients.

5.3.1 HTM intended Audience, purpose and use

Today, time is regarded as a competitive dimension.For example, speed or time-to-market is a critical factor in new product development and customer deliveries. Just-in-time manufacturing, set-up reduction, and quick response time are other examples of time-based management. Faster response time in healthcare processes corresponds to fewer bottlenecks, less deaths, fewer queues and better service delivery. One of the key objectives of healthcare system is to reduce time and increase speed. This objective is important today, as organizations must deal with 'critical' decisions rapidly Maani & Cavana (2000). This model was designed and developed with a distinctive purpose to aid healthcare providers, research in HIV progression, students of immunology as well as decision makers process of proposing policies that would enhance improvement of quality of life of people living with HIV.

The model objectives were designed based on the following questions

a.) What were the model objectives? What did the model intend to achieve?

(a) Pinpoint the relationship amongst TB, HIV and malaria

(b) Improve the quality of life of people living with HIV

(c) Identify intervention treatment points along the HIV progression

(d) Improve understanding of HIV and its impact on the immune system when other diseases are in the picture

b.) By how much should the life expectancy of people living with HIV range? By use of scenarios this was achieved to test and determine the performance range of the variables mentioned and described in Chapter Four (4)

c.) What constraints must the modeller work within? The modeller had to work within stipulated time frame, limited budget as well methodological approaches

5.3.2 Model Scope

The research revolved around the study of dynamics of cells attacked by HIV to assess its progress and those that TB and malaria pathogens infect and how they interact inorder that they propagate or delay HIV progression to AIDS as well as management of these cells by the immune system. The research also looked into therapies focussing on these diseases.

5.3.3 Model Assumptions

The following assumptions were made in the course of model development.

a.) Each disease has its own characteristics

b.) The model operation is based on peri-urban population

c.) The host lives in overcrowded regions

d.) The social ammenities like hospitals are a challenge to access

e.) Each disease has its own pathogenesis

f.) The host is already infected with HIV virus

g.) Time period is set in months and the model is set to run for three months

5.4 HTM System Model Development

System Dynamics Models are comprised of cause and effect equations as shown in Equation 5.1. Quantitative analysis in System dynamics is implemented using stock and flow structure which are designed by formulating mathematical equations that describe cause and effect relations for all variables. One of the strengths of System dynamics is its ability to deal with absence of statistical data. This section highlights the general principles that were used in the design of the HTM model.

5.4.1 Control Statements and variable definitions

The variables and their relationships were defined and modeled for quantitative analysis through simulation experiments. The complete listing of these variables is indicated in Appendix B. Euler method of integration was most preferred compared to Runge-Kutta integration method as it has built-in functions that generate integer flags of 0 - 1 which work like switches. For the Euler integration method, a small step of 0.0625 which is equivalent to 20 days was adopted as the dt. This was most preferrable because it provides a good compromise between the accuracy of the result and the speed of the simulation. It also gives the virus sufficient time to replicate with the host CD4+ cell.

In addition to this, the following control statements were used in the model development.

a.) Variables were given minimum and maximum values

b.) Stock cannot be negatives and so were set to have minimum values of zero (0)

c.) Soft variables like TH activation were represented as graphical inputs and unit of measure being unitless as they cannot be quantified.

5.4.2 Variables

This section outline the variables used in the design and development of HTM model

a.) Decision variables

Decision variables are used by policy makers to influence their decision and implementing strategic policies. In this model the decision variables are represented using sliders in the control panel within the range provided by the model. In this model, the decision makers were allowed to see the probable effects of their decision by altering the following parameters:

TABLE 5.1: Decision Variables

	Variable Description	**Value**	**Reference**
1	TH1	600	Bershteyn & Eckhoff (2013)
2	TH2	550	Bershteyn & Eckhoff (2013)
3	NK	150	Mukadi et al. (2001)
4	CTL	2000	Mukadi et al. (2001)
5	APC	600	Bershteyn & Eckhoff (2013)
6	Treg	2000	Mukadi et al. (2001)
8	Viral Load/Pop	$10^{-}6$	Mukadi et al. (2001)Bershteyn & Eckhoff (2013)
9	TB Pathogens Population	$10^{-}3$	Mukadi et al. (2001)
10	Malaria Parasite Population	$10^{-}2$	Mukadi et al. (2001)

b.) **Input Variables**

This section provides the initial values that were used in the model. Most of the values are based on WHO (2009), Bershteyn & Eckhoff (2013) as summarized in Table 5.2 and literature surveys. The variables are categorized as HIV, Treatment, Malaria and TB associated variables. The invocation of

TABLE 5.2: Immune System Input Variables

	Variable Description	Values	Reference
1	Viral Load	$10^{-}6$	Bershteyn & Eckhoff (2013), WHO (2009)
2	TB Pathogens	$10^{-}3$	Mukadi et al. (2001), WHO (2009)
3	Malaria Parasites	$10^{-}2$	Mukadi et al. (2001), WHO (2009)

immune system to action requires activation of Antigen presenting cells by presence of pathogens in the host.

Table 5.3 presents the input variables associated with the infection, development and budding of HIV virus in the host cells particularly TH1 and APC - the cells that manifest CD4 TB progression within the host is presented in the table 5.4 as suggested by literature and field studies especiall researchers in this domain. Key to this table is the Antigen Presenting Cells among them the macrophages - the cells that inhabit the tubercle bacillus- because of its richness in oxygen for aerobic activity of the bacteria. Table 5.5 give a list of variables that help in the pathogenesis of malaria derived from literature survey as well as research experts in the field of malaria. The table shows a dominant presence of the Red Blood Cells (RBC) which are

TABLE 5.3: HIV Sector Input Variables

	Variable Description	Values	Reference
1	Susceptible APC population	600	Bershteyn & Eckhoff (2013)
2	APC infection rate	Computed	Bershteyn & Eckhoff (2013)
3	APC destruction rate	Computed	Bershteyn & Eckhoff (2013)
4	APC infectivity	1/[10−3]	Bershteyn & Eckhoff (2013)
5	Virus initial Population	10−6	Bershteyn & Eckhoff (2013)
6	Virus Budding rate	5−1	Bershteyn & Eckhoff (2013)
7	Natural virus death rate	$5.6 * 10^{-3}$	Bershteyn & Eckhoff (2013)
8	Virus destruction rate	$5.6 * 10^{-6}$	Bershteyn & Eckhoff (2013)
9	Virus proliferation rate	5−3	Bershteyn & Eckhoff (2013)
10	Activated TH1	0	Mukadi et al. (2001)
11	TH1-virus contact rate	600/10−6	Bershteyn & Eckhoff (2013)
12	TH1 death rate	0.39	Mukadi et al. (2001)
13	TH1 infection rate	$6.5 * 10^{-4}$	Mukadi et al. (2001)
14	TH1 proliferation rate	0.1	Mukadi et al. (2001)

TABLE 5.4: TB System Input Variables

	Variable Description	Values	Reference
1	APC population	600	Mukadi et al. (2001)
2	APC Proliferation rate	0.1	Mukadi et al. (2001)
3	APC infection rate	Computed	Mukadi et al. (2001)
4	Infected APC destruction rate	Computed	Mukadi et al. (2001)
5	TH1 population	600	Mukadi et al. (2001)
6	TH1 Activation rate	Computed	Mukadi et al. (2001)
7	TH1 proliferation rate	0.1	Mukadi et al. (2001)
8	TH2 Population	550	
9	TH2 activation rate	Computed	Mukadi et al. (2001)
10	TB initial population	10−3	Mukadi et al. (2001)
11	TB natural death rate	10−1	Mukadi et al. (2001)
12	TB growth rate	0.1	Mukadi et al. (2001)

the cells of the immune system and hosts of the malaria causing parasites. From the table still are the Natural Killers (NK) cells. These cells are necessary for elimination of the cells that are attacked by pathogens and cannot recover. These cells are usually marked for the NK cells to identify them easily. The immune system is self sustaining. From that front, when it is down

TABLE 5.5: Malaria System Input Variables

	Variable Description	**Values**	**Reference**
1	RBC blood count	1200	Magombedze et al. (2011), Amuta et al. (2012)
2	RBC production rate	0.009	Magombedze et al. (2011), Amuta et al. (2012)
3	RBC contact rate with merozoites	0.05	Magombedze et al. (2011), Amuta et al. (2012)
4	RBC infection rate	0.008	Magombedze et al. (2011), Amuta et al. (2012)
5	RBC natural death rate	0.8	Magombedze et al. (2011), Amuta et al. (2012)
6	Merozoites initial population	4000	Magombedze et al. (2011), Amuta et al. (2012)
7	Merozoites lysing rate	16	Magombedze et al. (2011), Amuta et al. (2012)
8	Merozoites natural death rate	3	Magombedze et al. (2011), Amuta et al. (2012)
9	Merozoites elimination rate	0.85	Magombedze et al. (2011), Amuta et al. (2012)
10	NK population	150	Magombedze et al. (2011)
11	NK stimulation rate	0.6	Magombedze et al. (2011)

or defeated by pathogens, treatment is called for. The healthcare services or therapy represent care accorded people living with HIV and is interpreted at cell level as composed of the following input variables presented in table 5.6.

c.) **Output Variables**

TABLE 5.6: Health service delivery/treatment Input Variables

	Variable Description	**Values**	**Reference**
1	Drug dosage	100	PubMed2011
2	Drug Absorption rate	Computed	
3	Drug efficacy	0.01	PubMed2011
4	Drug excretion rate	0.693/16	PubMed2011

From the inputs described above, the model outputs is presented by the following output variables shown by table 5.7. These outputs are selected as Key Performance Indicators for the success of the HTM system.

TABLE 5.7: Health service delivery/treatment Input Variables

	Key Performance Indicator	**Variable Description**
1	TH1 Level	Number of TH1 cells in the host
2	APC Level	Number of Antigen Presenting Cells
3	RBC Count	Red blood cell count which are targets of malaria parasites - the merozoites
4	Viral Load	Indicator of HIV virus in the host - minimal
5	TB Level	Indicator of Tubercle Baccilus in the host - minimal
6	Merozoites Level	Malaria parasite in the host - Nil

5.4.3 HTM Model Sectors

The model was generally based on pre-existing models especially those proposed by Anderson & May (1981) although they are linear models. However the author laboured in developing CLD adding assumptions and accompanying relationships as there is no literature showing Modelling of interacting disease at cell level.

The HTM model is divided into Five sectors which interact as was indicated in the tabulated variables in Tables 5.3, 5.4, 5.5, 5.6 and 5.2

a.) **Immune System Sector**.

This sector presents the dynamics of the immune system and is central to the HTM model. Every other sector reflects part of the immune system. The APC, TH1, CTL and NK cells are particularly important as the play a major role in disease manifestation. APC presents the antigens to the TH1 that mobilizes the immune effectors through the chemokines that it produces. When CTL- the CD8+ and NK cells senses this chemokines, they replicate very fast and in multitudes. Replicating in huge numbers is one of the fighting mechanism that the immune system uses to guard the body against diseases. The APC also play part in this by engulfing the pathogens. CD8+ fight the pathogens by killing the free pathogens whereas the NK cells task is to kill the infected TH1, TH2 and APC. The Immune System has nineteen stocks representing the activated TH1 cells, Activate APC, resting APC that are constantly generated by the body, CTL cells, IFNg, IgG, IL10, IL12, IL2, IL4, IL6, infected APC, NK cells, infected TH1, Resting TH1, Naive TH, TH2, TNF, and Regulartory T cells. To mount fight against pathogens, TH1 must be activated first. This model assumes that the host already has HIV, therefore activation of TH1 is as result of more infections due to malaria and TB as per the model. Hence the Equation (5.2) demonstrate this.

$$Actd\_TH1\_Cells(t) = Actd\_TH1\_Cells * (t - dt) + (activating\_TH1 + replicating\_self - TH1\_Infection) * dt \tag{5.2}$$

where Actd_TH1_Cells(t) is initialized to zero (0). As mentioned above activation of TH1 is as result of presentation of pathogens by the APC. This is represented in the Equation (5.2) by $activating\_TH1$ and is given by the Equation (5.3) as well as $self\_replicating$ cells since upon attack, they divide very fast which is represented above by $replicating\_self$ and given by

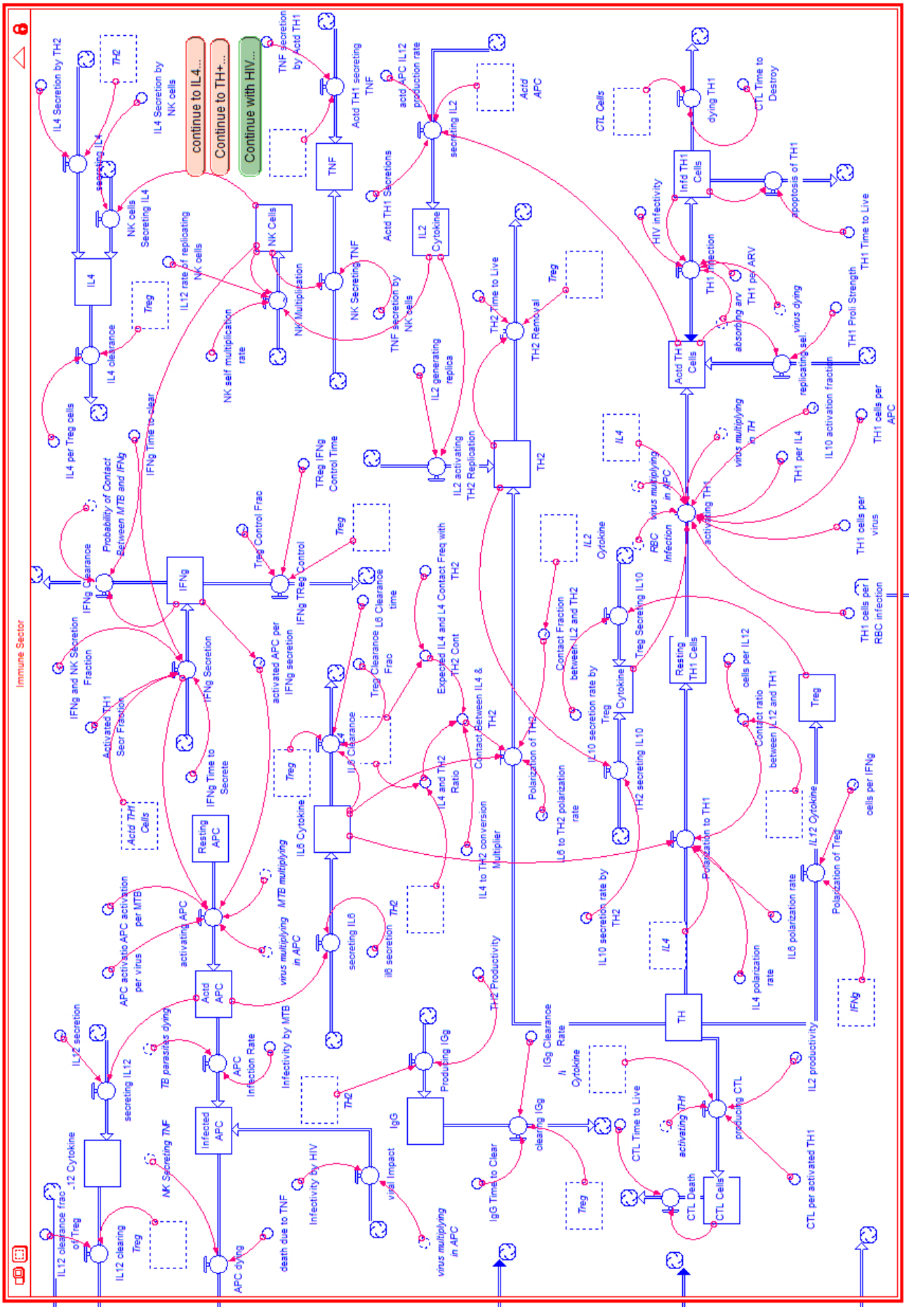


FIGURE 5.1: Immune Sector

equation (5.4).

$$activating\_TH1 = RBC\_Infection * TH1\_cells\_per\_RBC\_infection + virus\_multiplying\_in\_APC * TH1\_cells\_per\_APC + TH1\_cells\_per\_virus * virus\_multiplying\_in\_TH1 - IL10\_activation\_fraction * IL10\_Cytokine - IL4 * TH1\_per\_IL4 \quad (5.3)$$

It is important to also point out that activation of TH1 is indirectly influenced by IL10 which is secreted by regulatory T cell and TH2 to control for over production of TH1 through self replication or reinforced activation by APC. From the relationship in Equation (5.3) the component $virus\_multiplying\_in\_APC * TH1\_cells\_per\_APC$ signify TH1 activation due to HIV virus invading APC and the
$TH1\_cells\_per\_virus * virus\_multiplying\_in\_TH1$ signify activation of TH1 as a result of HIV virus replicating in TH1 and the negative set of
$IL10\_activation\_fraction * IL10$ and $IL4 * TH1\_per\_IL4$ are due to controlled production by regulatory T Cell and Th2 cells. The units for the relationship is
$cells/day$

TH1 increment is also directly influenced by replicating itself as shown in the Equation (5.4). The component $TH1\_Proli\_Strength$ is the number of TH1 cells that arise from a single TH1 per day.

$$replicating\_self = Actd\_TH1\_Cells * TH1\_Proli\_Strength \quad (5.4)$$

TH1 population growth is affected as shown by the Equation (5.5) which

represent infection rate of TH1 as dependent on viral load and virus infectivity.

$$TH1\_Infection = virus\_dying * HIV\_infectivity - absorbing\_arv* TH1\_per\_ARV * Infd\_TH1\_Cells \tag{5.5}$$

APC play a significant role in the immune system. The Equation (5.6) present the computation of activated APC. The inflow to activated APC is shown by Equation (5.7) which is largely as a result of TB, HIV and Malaria.

$$Actd\_APC(t) = Actd\_APC(t - dt) + (activating_APC - APC\_Infection\_Rate) * dt \tag{5.6}$$

$$activating\_APC = APC\_activation\_per\_MTB * MTB\_multiplying + APC\_activation\_per\_virus * virus_multiplying\_in_APC + activated\_APC\_per\_IFNg\_secretion * IFNg\_Secretion \tag{5.7}$$

The outflow to the equation is presented by the relationship in Equation (5.8) that represent the infectivity of APC. APC is largely comprised of macrophages and this houses the TB as the cells are highly aerobic until the TB matures.

$$APC\_Infection\_Rate = Infectivity\_by\_MTB * TB\_parasites\_dying \tag{5.8}$$

CTL cells are important to the immune system for they are for they are responsible for destroying free pathogens from viruses to all forms of parasites including malaria merozoites. They do so by secreting cytokines that destroy the pathogens. In this model they are represented by the Equation (5.9)

$$CTL\_Cells(t) = CTL\_Cells(t - dt) + (producing\_CTL - CTL\_Death) * dt \tag{5.9}$$

The inflow to Equation (5.9) is CTL production which is represented by the relationship in Equation (5.10). The production of CTL is a continuous process with the cells produced by naive T helper cells

$$producing\_CTL = IL2\_Cytokine * IL2\_productivity + activating\_TH1 * CTL\_per\_activated\_TH1 \tag{5.10}$$

The outflow for the above stock is shown in Equation (5.11) that represent the natural death rate of CTL

$$CTL\_Death = CTL\_Cells / CTL\_Time\_to\_Live \tag{5.11}$$

TH1 concerted effort to fight pathogens is also seen in it secreting IFNg cytokines. This is represented by the Equation (5.12)

$$IFNg(t) = IFNg(t - dt) + (IFNg\_Secretion - IFNg\_Clearance - IFNg\_TReg\_Control) * dt \tag{5.12}$$

The inflow to stock in Equation (5.12) is represented in Equation (5.13). This is a funtion of activated TH1 and NK cells that implies that absense of activated TH1 or NK cells result to no secretion of IFNg and their presence means a proportionate secretion of IFNg which is a cytokine that is used to fight pathogens. The concentration of the same in the system also means activation of more APC to present pathogens to TH1 as well as engulfing the pathogens APC can.

$$IFNg\_Secretion = if(Actd\_TH1\_Cells <= 0 or NK_Cells <= 0) then 0 \; else(Actd\_TH1\_Cells * Activated\_TH1\_Secr\_Fraction + NK\_Cells * IFNg\_and\_NK\_Secretion\_Fraction)/ IFNg\_Time\_to\_Secrete \tag{5.13}$$

The outflow of the Equation (5.12) is the relation shown in Equations (5.14) and (5.15). In Equation (5.14), IFNg is dependent on the probability of contanct between MTB and IFNg divided by IFNg time to clear while in equation (5.15), it is dependent on regulartory T helper cells after some delay.

$$IFNg\_Clearance = IFNg * Probability\_of\_Contact\_Between\_MTB\_and\_IFNg/ IFNg\_Time\_to\_clear \tag{5.14}$$

$$IFNg\_TReg\_Control = DELAY(Treg * Treg\_Control\_Frac/TReg\_IFNg\_Control\_Time, 1) \tag{5.15}$$

Immunoglobin G (IgG) used for marking pathogens and inhibiting them from attaching to immune cells is another fighting mechanism of the immune system. IgG is secreted by TH2 and is shown below by the Equation (5.16).

$$IgG(t) = IgG(t - dt) + (Producing\_IGg - clearing\_IGg) * dt \tag{5.16}$$

The inflow to the Equation (5.16) is represented by Equation (5.17) that is a function of TH2 population and its productivity.

$$Producing\_IGg = TH2 * TH2\_Productivity \tag{5.17}$$

The outflow to the equation (5.16) is represented by Equation (5.18) that is computed based on clearance of regulartory T helper cells

$$clearing\_IGg = Treg/IgG\_Time\_to\_Clear * IGg\_Clearance\_Rate \tag{5.18}$$

Interleukins(IL) are chemokines that facilitates in communication between cells of the immune system. One such IL is IL10 that facilitate communication between Treg and TH1 with the message that TH1 should control

its replication. When there is no danger, Treg reduces secretion of IL10 subsequently reducing concentration of IL10. With reduction in IL10 concentration, TH1 reduces self replication. IL10 is also secreted by TH2 that is antagonistic effort to control TH1 replication.

$$IL10\_Cytokine(t) = IL10\_Cytokine(t - dt) + (TH2\_secreting\_IL10 + Treg\_Secreting\_IL10) * dt \tag{5.19}$$

The inflow to the Equation (5.19) is the relationships Equations (5.20) and (5.21) that represent activities of Treg and TH2 secretion of IL10 as ouflow and inflow respectively

$$TH2\_secreting\_IL10 = TH2 * IL10\_secretion\_rate\_by\_TH2 \tag{5.20}$$

$$Treg\_Secreting\_IL10 = Treg * IL10\_secretion\_rate\_by\_Treg \tag{5.21}$$

Another communication effort is that between APC and naive TH through APC secretion of IL12 with the message that naive TH cell polarizes fast to TH1 in a bid to conquer the enemy (pathogens). This is represented by the Equation (5.22)

$$IL12\_Cytokine(t) = IL12\_Cytokine(t - dt) + (secreting\_IL12 - IL12\_clearing) * dt \tag{5.22}$$

The inflow to Equation (5.22) and the ouflow is represented by Equation (5.24) that show effort of Treg to indirectly control over polarization of TH1 through reduction of IL12 meaning low concentration of IL12 with naive TH reads reduced polarization of TH1

$$secreting\_IL12 = Actd\_APC * IL12\_secretion \tag{5.23}$$

$$IL12\_clearing = Treg * IL12\_clearance\_frac\_of\_Treg \tag{5.24}$$

Another important communication chemokine is IL4 that is secreted by NK cells signalling more replication of TH1 cells. NK cells destroys infected immune cells like the TH1 and macrophages and RBC. More pathogens in the body mean destruction of more TH1 and macrophages and RBC. Therefore production of IL4 is an effort of NK to influence more production of TH1 as a backup of the already destroyed lot. This relationship is shown by Equation (5.25) and inflows Equation (5.26) and outflow Equation (5.27) respectively

$$\begin{aligned} IL4(t) =& IL4(t-dt) + (NK\_cells\_Secreting\_IL4 + \\ & secreting\_IL4 - IL4\_clearance) * dt \end{aligned} \tag{5.25}$$

$$\begin{aligned} NK\_cells\_Secreting\_IL4 &= NK_Ccells * IL4\_Secretion\_by\_NK\_cells \\ secreting\_IL4 &= TH2 * IL4\_Secretion\_by\_TH \end{aligned} \tag{5.26}$$

$$IL4\_clearance = Treg * IL4\_per\_Treg\_cells \tag{5.27}$$

IL6 cytokine is secreted by APC as represented in the Equation (5.28) with the resposibility of reinforced activation of APC and is balanced by Treg and indicated in Equations (5.29) and (5.30) respectively

$$\begin{aligned} IL6\_Cytokine(t) =& IL6\_Cytokine(t-dt) + (secreting\_IL6 - \\ & IL6\_Clearance) * dt \end{aligned} \tag{5.28}$$

$$secreting\_IL6 = Actd\_APC * il6\_secretion \tag{5.29}$$

$$\begin{aligned} IL6\_Clearance =& if(IL6\_Cytokine <= 0) \text{ then } 0 \text{ else } Treg * \\ & Treg_Clearance\_Frac / IL6\_Clearance\_time \end{aligned} \tag{5.30}$$

IL6 contribution in the immune system is to stimulate naive T cell to polarize to TH1 and TH2. Polarization of TH1 is presented by Equation (5.31) with

inflow and outflow represented by Equations (5.32) and (5.33)

$$Resting\_TH1_Cells(t) = Resting\_TH1\_Cells(t - dt) + (Polarization\_to\_TH1 - activating_TH1) * dt \tag{5.31}$$

$$Polarization\_to\_TH1 = Contact\_ratio\_between\_IL12\_and\_TH1 + IL6\_Cytokine * IL6\_polarization\_rate - IL4 * IL4\_polarization\_rate \tag{5.32}$$

$$activating\_TH1 = RBC\_Infection * TH1\_cells\_per\_RBC\_infection + virus\_multiplying\_in\_APC * TH1\_cells\_per\_APC + TH1\_cells\_per\_virus * virus\_multiplying\_in\_TH - IL10\_activation\_fraction * IL10\_Cytokine - IL4 * TH1\_per\_IL4 \tag{5.33}$$

Equation (5.33) represent the activation of TH1 as a result of attack of RBC by merozoites. Activation of TH1 also result in increased virus population as not all TH1 are genuine TH1 as some have already gone through sero conversion to produce viruses. A run of the system shows clearly demonstration this as can be seen in the Figure 5.3. On activation TH1 rise suddently in order to avert in invasion of merozoites but then the patient is already infected with HIV and very fast, the virus take charge and invades the TH1. From day 2.3 to day 30.1, the TH1 start responding due to collective activity of NK and TH1 cells. The Model predicts this well as indicated in Figure 5.2 graph labelled 5 that immediatelly the TH1 is presented with pathogens by APC, it starts replicating exponentially. Command into action is initiated by TH1 and so the model predicts well that all the body cells respond to the attack. Accordingly and in line with Equation (5.6) on Page 107 the model predicts well that APC remains on high alert and this is presented in Figure 5.2 by graph line 4. The immune system responds to invasion of merozoites by secreting cytokines IFng and IgG by TH1 and TH2 respectively and the subsequent excitation of NK cells. NK cells kill the infected TH1 and the

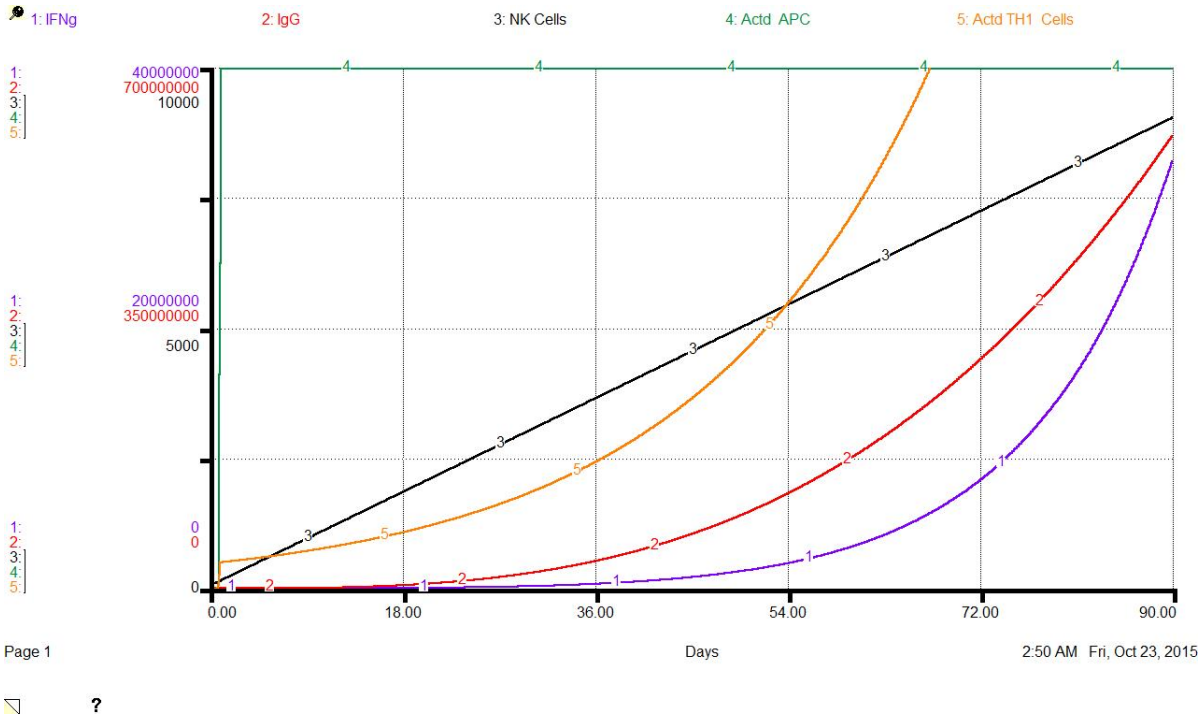


FIGURE 5.2: Immune System response to pathogens

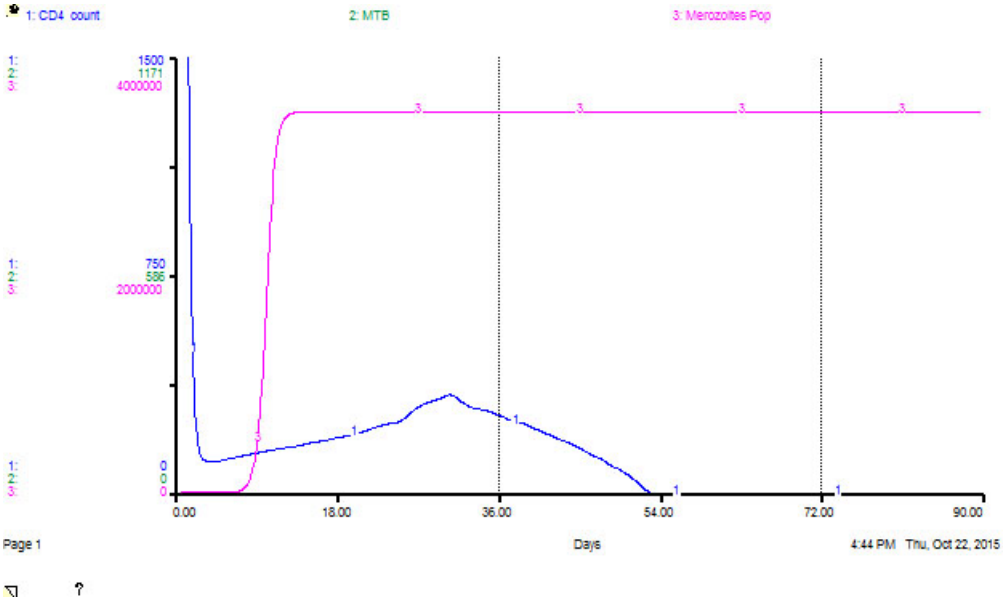


FIGURE 5.3: Impacts of Merozoites on CD4 Count

RBC that are invaded by virus and merozoites respectively. NK is responding according to the equation (5.26)

In summary this effects are presented in figure 5.4

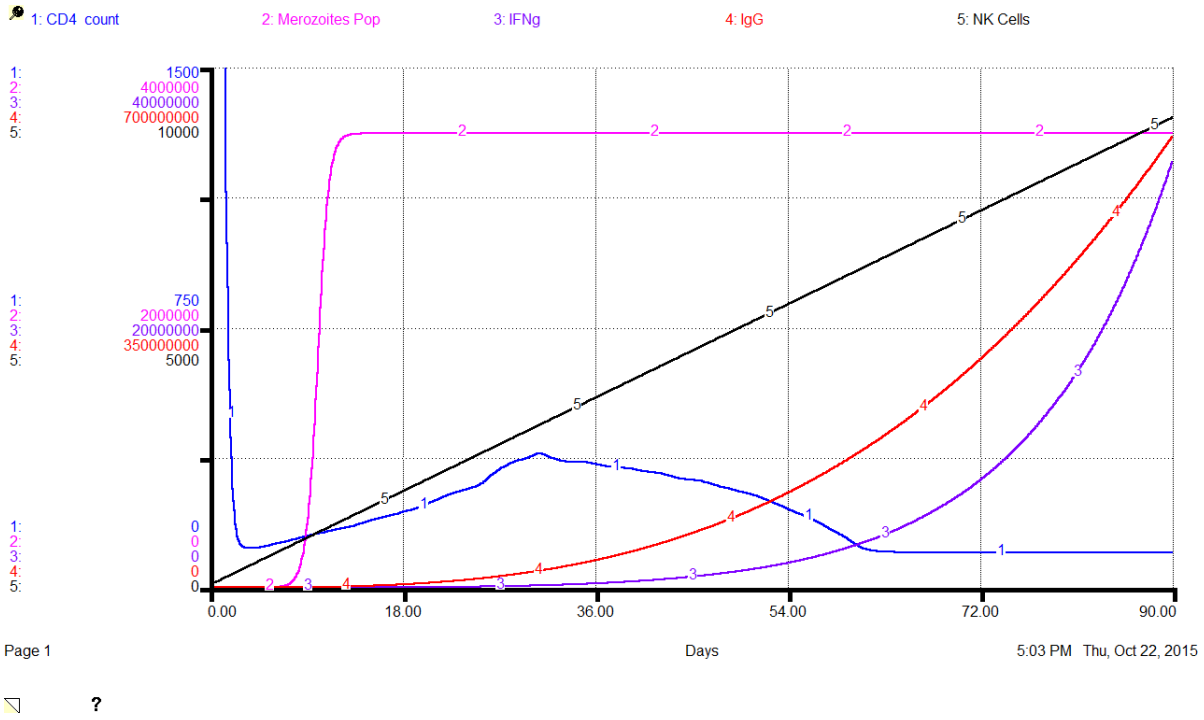


FIGURE 5.4: Impacts of Merozoites on CD4 Count and response by NK Cells

b.) **HIV Subsystem Sector.**

The HIV sector has one stock presented in the model as free_virus_pop or the viral load as presented in Figure 5.5. This is in like with other mathematical modelling methods particularly because the virus hardly exist freely since most of the times it is dependent on the host for its survival. In this case the host is the CD4 cells that is manifested by both APC and TH1 cells. The virus remain within the host for a long duration of time and only becomes free when the host is activated especially in response to other pathogens. As above the pathogens under consideration are those of malaria - the merozoites and tubercle baccillus - those of TB. This stock is presented in the Equation (5.34)

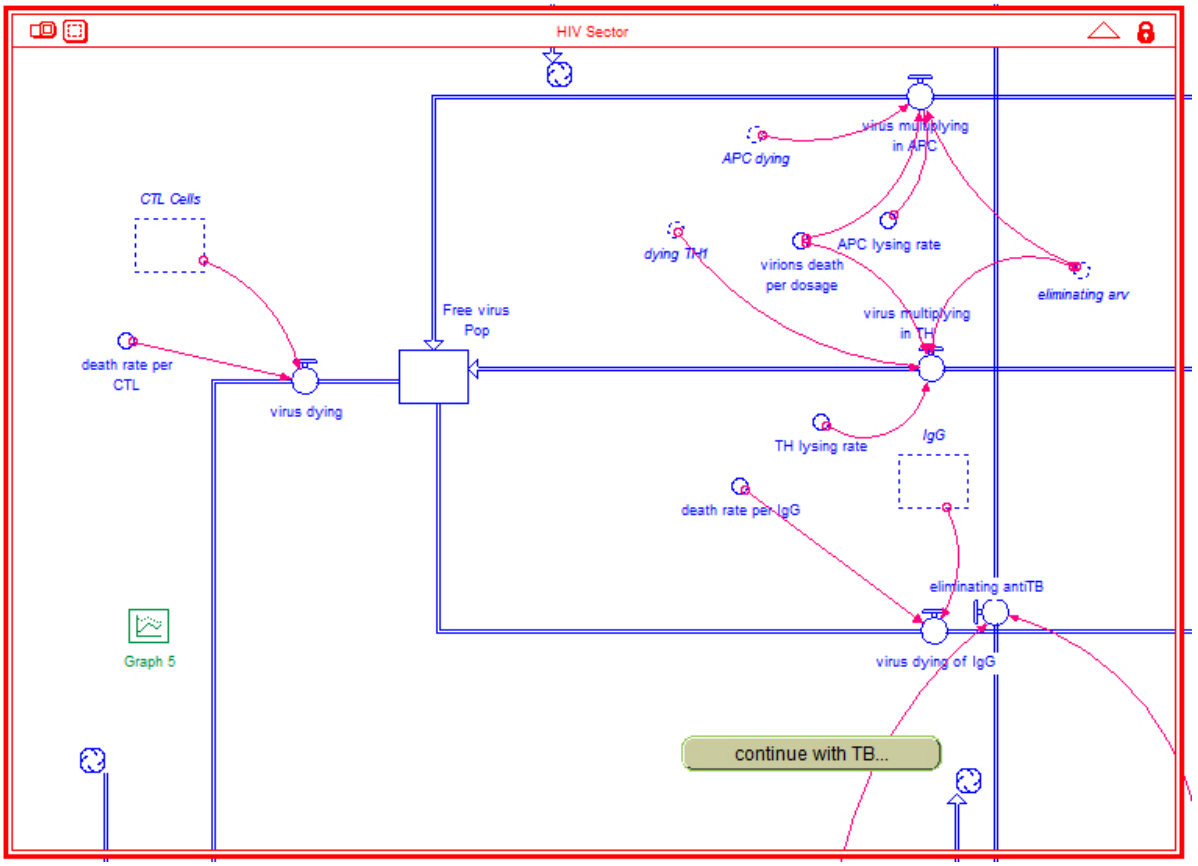


FIGURE 5.5: HIV Stock and Flow Diagram

$$\begin{aligned} Free\_virus\_Pop(t) = & Free\_virus\_Pop(t - dt) + (virus\_multiplying \\ & \_in\_APC + virus\_multiplying\_in_TH - \\ & virus\_dying\_of\_IgG - virus\_dying) * dt \end{aligned} \tag{5.34}$$

The inflow to the free Free_virus_Pop stock is represented by the two Equations (5.35) and (5.36). Equation (5.35) shows the contribution of APC whereas Equation (5.36) shows the contribution of TH1. The virus can remain in these two set of cells for a long duration of time as long as the immune system is not purtubed by pathogens.

$$\begin{aligned} virus_multiplying\_in\_APC = & APC\_dying * APC\_lysing\_rate - \\ & eliminating_arv * virions\_death\_per\_dosage \end{aligned} \tag{5.35}$$

Equation (5.35) shows how virus multiply within APC and the virus becomes free through the dying of APC and the same applies to equation (5.36) for

the virus multiplying in TH1

$$virus_multiplying\_in_TH1 = dying\_TH1 * TH\_lysing\_rate - virions\_death\_per\_dosage * eliminating\_arv \tag{5.36}$$

A run of the model demonstrate this (equation (5.34)) in figure 5.6 through graph marked by line 3. It is apparent from the Figure 5.6 that once APC de-

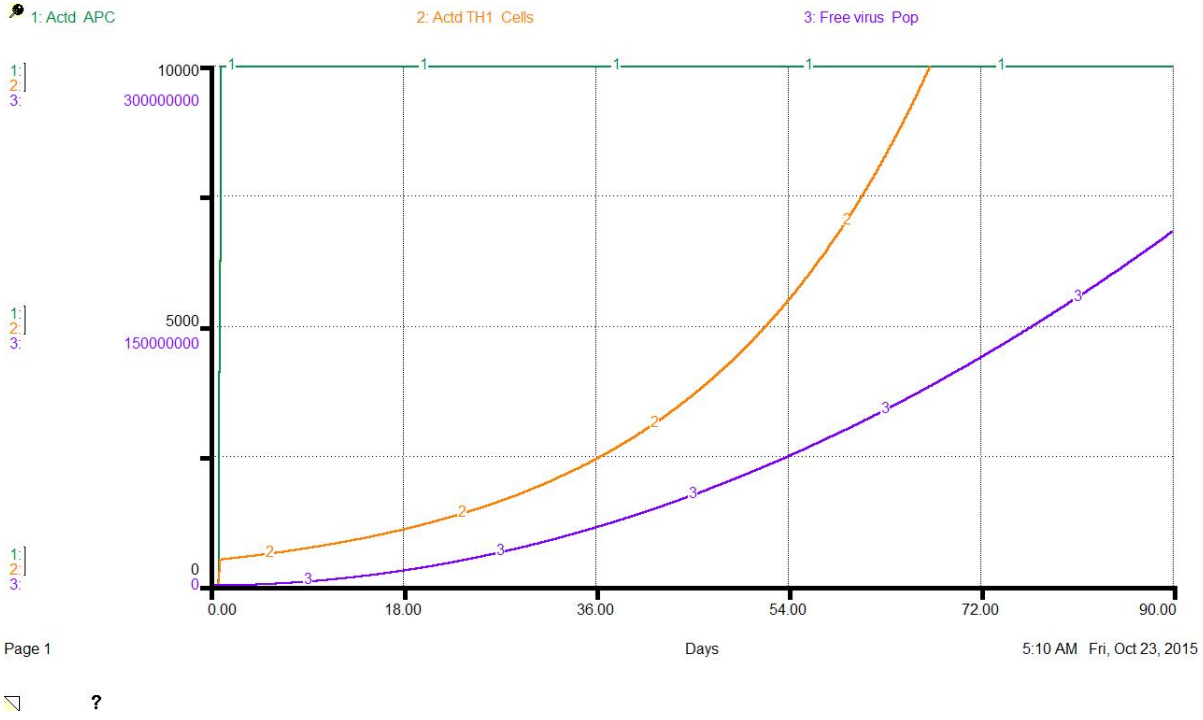


FIGURE 5.6: Relationship between HIV virus, APC and TH1 cells

tect pathogens in form of virus, they remain activated. This is as a result self replication as indicated in Equation (5.29) where IL6 continuously invokes the process consequently maintaining the population of APC at maximum high. Meanwhile the population of TH1 continues growing exponentially. This should not be mistaken as a healthy situation as literature shows that if TH1 can be maintained at rest state, viral load will be reduced. The model predicts this well since from Figure 5.6 graph presented by line 3 indicates that as long as graph line 2 continues to grow exponentially so will graph line 3 which represents free virus.

c.) **TB System Sector**

This model TB sector is presented one stock as shown in Equation (5.37)representing the MTB population with one inflow and two outflows. The stock and flow diagram for TB is presented in Figure 5.7.

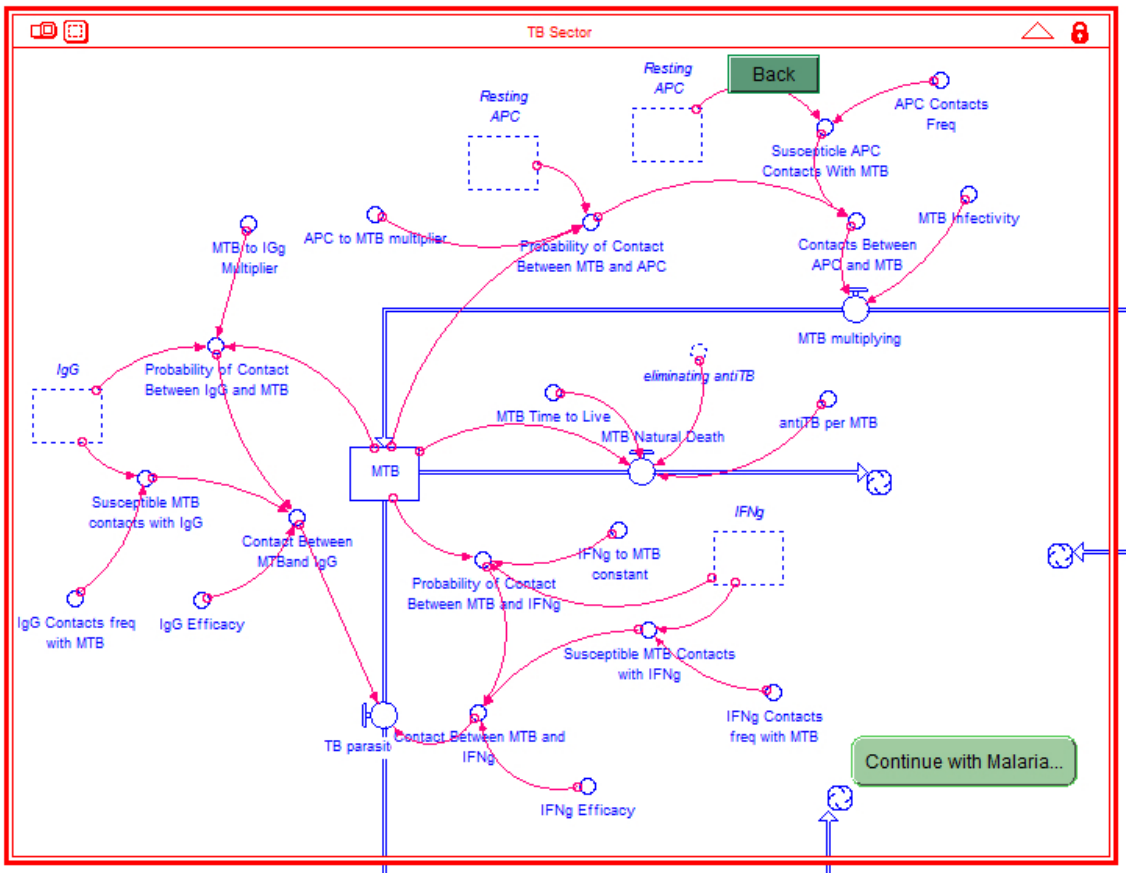


FIGURE 5.7: TB Stock and Flow Diagram

$$MTB(t) = MTB(t - dt) + (MTB\_multiplying - MTB\_Natural\_Death - TB\_parasites\_dying) * dt \tag{5.37}$$

The inflow to MTB is represented by Equation (5.38) that represent computation of how MTB multiplies with APC as the very cells that MTB inhabits. MTB infectivity is rate at which MTB infects APC

$$MTB\_multiplying = Contacts\_Between\_APC\_and\_MTB * MTB\_Infectivity \tag{5.38}$$

$$MTB\_Natural\_Death = (MTB/MTB\_Time\_to\_Live)/init(MTB) + antiTB\_per\_MTB * eliminating\_antiTB \tag{5.39}$$

$$TB\_parasites\_dying = (Contact\_Between\_MTB\_and\_IFNg + Contact\_Between\_MTBand\_IgG)/ init(Contact\_Between\_MTBand\_IgG) \tag{5.40}$$

The immune system upon infection by MTB reacts in two ways as represented in Equations (5.39) and (5.40). Equation (5.39) presents the natural death of MTB which in this model was added to it the response due to antiTB drugs. The second Equation (5.40) represent response of the immune system to MTB pathogens

The figure 5.8 shows the immune system response to TB pathogens without external influence through medication.

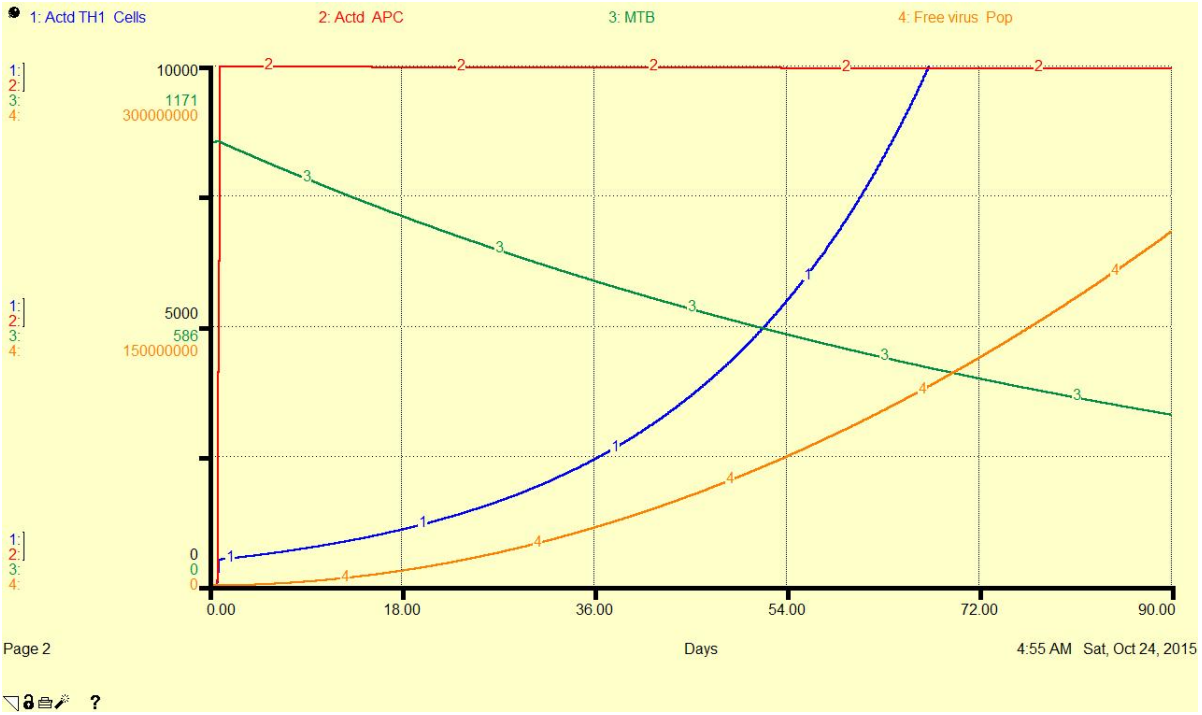


FIGURE 5.8: Relationship between HIV virus, APC and TH1 cells

It is apparent that immediately upon APC infection, the target cells of TB get activated and remain so as the immune system responds to the pathogens.

Consequently, TH1 cells gradually get activated (Figure 5.8 graph line 1) in order that they may initiate elimination of MTB. With activation of TH1, viral load also starts increasing as can be seen in the Figure 5.8 graph line 4. This correctly agrees with research carried out by (Snchez 2010, Sharma et al. 2005, Roeger et al. 2009).

d.) **Malaria System Sector**

This sector was modelled using five (5) stock represented as immature sporozoites, merozoites population, RBC population, Infected RBC population and Susceptible HPC population. The stock and flow diagram for malaria is presented by Figure 5.9. In line with literature, mosquito parasites are injected in the body by infected mosquito as immature sporozoites that invades hepatocytic (HPC) cells. The sporozoites multiply and mature in the liver and get released in the blood stream where they infect the red blood cells. This is represented in equation (5.41)

$$\begin{aligned} Susceptible\_HPC(t) =& Susceptible\_HPC(t-dt) + \\ & (-immature\_parasites\_multiplying) * dt \end{aligned} \tag{5.41}$$

Outflow to this stock is presented in the equation (5.42) showing the parasites released into the blood stream.

$$\begin{aligned} immature\_parasites\_multiplying =& Contacts\_between\_Sporozoites\_and\_HPC * \\ & HPC_to_Parasites\_converter \end{aligned} \tag{5.42}$$

Upon release in the blood stream, the mature merozoites look for, attach and infects the red blood cells consuming, multiplying and budding repeatendly and then back into the blood stream for more RBC. This is represented by the Equation (5.43)

$$RBC\_Pop(t) = RBC\_Pop(t-dt) + (RBC\_Multiplication - RBC\_Infection) * dt \tag{5.43}$$

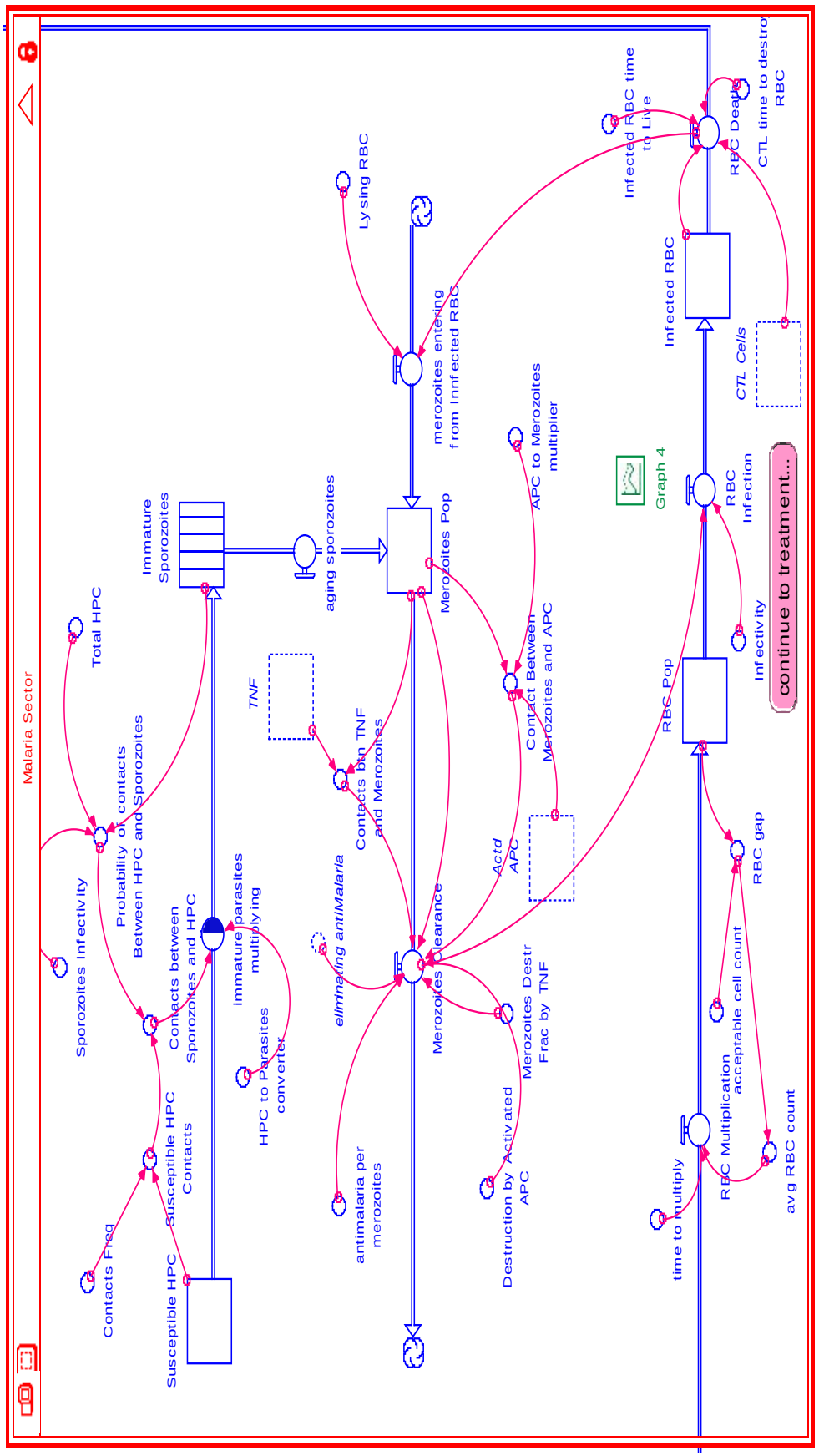


FIGURE 5.9: Malaria Stock and Flow Diagram

The inflow into this stock is the multiplication rate of RBC represented by Equation (5.44). The outflow to this is the infection of RBC by the merozoites presented in Equation (5.45). This outflow forms the stock of the infected RBC represented by Equation (5.46)

$$RBC\_Multiplication = avg\_RBC\_count/time\_to\_multiply \tag{5.44}$$

$$RBC\_Infection = Infectivity * Merozoites\_Clearance \tag{5.45}$$

$$Infected\_RBC(t) = Infected\_RBC(t - dt) + (RBC\_Infection - RBC\_Death) * dt \tag{5.46}$$

The inflow to infected_RBC stock is represented in Equation (5.47) that defines the infectivity of the red blood cells and the outflow as the death of the Red blood cells represented by Equation (5.48)

$$RBC\_Infection = Infectivity * Merozoites\_Clearance \tag{5.47}$$

$$\begin{aligned} RBC\_Death =& delay(CTL\_Cells/CTL\_time\_to\_destroy\_RBC + \\ & Infected\_RBC/Infected\_RBC\_time\_to\_Live, 15) \end{aligned} \tag{5.48}$$

e.) **Treatment Subsystem Sector**

The treatment sector is modeled with seven stocks defined by Equations (5.49), (5.52), (5.55), (5.58), (5.61) among others and presented in Figure 5.10

$$\begin{aligned} ARV\_Drug\_in\_Bloodstream(t) =& ARV\_Drug\_in\_Bloodstream(t - dt) + \\ & (absorbing\_arv - eliminating\_arv) * dt \end{aligned} \tag{5.49}$$

The Equation (5.49) demonstrates the dynamics of ARV drugs in the bloodstream representing how the drug is absorbed based on its inflow represented

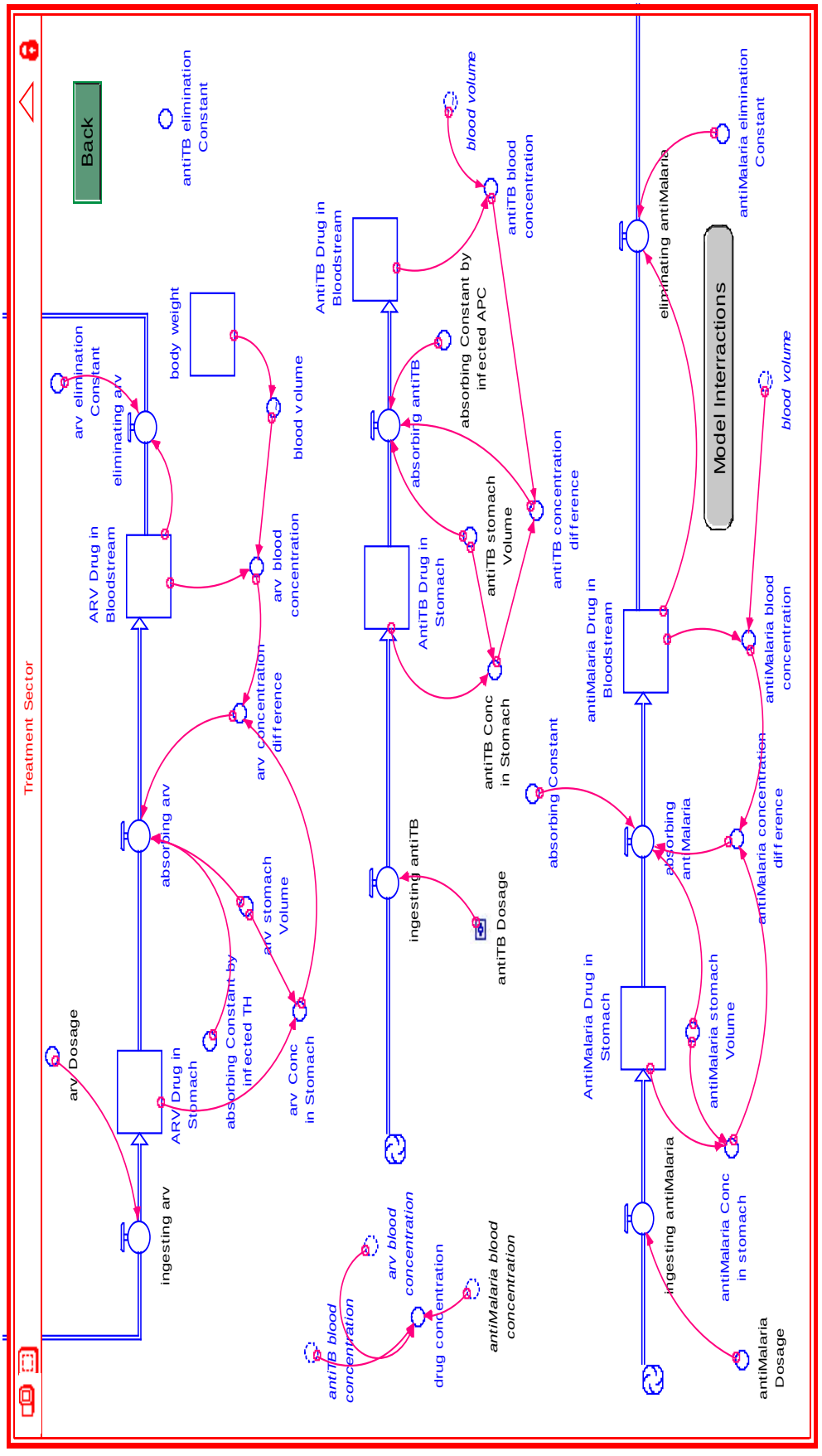


FIGURE 5.10: Treatment Stock and Flow Diagram

in Equation (5.50) and outflow represented by Equation (5.51) that shows the elimination of the drug.

$$absorbing\_arv = arv\_concentration\_difference * arv\_stomach\_Volume * absorbing\_Constant\_by\_infected\_TH \tag{5.50}$$

$$eliminating\_arv = ARV\_Drug\_in\_Bloodstream * arv\_elimination\_Constant \tag{5.51}$$

On the other hand Equation, (5.52) shows the relationship of malaria drugs intake, its dynamic in the stomach Equation (5.55), absorption represented by the inflow Equation (5.53) and elimination represented by the equation (5.54).

$$antiMalaria\_Drug\_in\_Bloodstream(t) = antiMalaria\_Drug\_in\_Bloodstream(t - dt) + (absorbing\_antiMalaria - eliminating\_antiMalaria) * dt \tag{5.52}$$

$$absorbing\_antiMalaria = antiMalaria\_concentration\_difference * antiMalaria\_stomach\_Volume * absorbing\_Constant \tag{5.53}$$

$$eliminating\_antiMalaria = antiMalaria\_Drug\_in\_Bloodstream * antiMalaria\_elimination\_Constant \tag{5.54}$$

$$AntiMalaria\_Drug\_in\_Stomach(t) = AntiMalaria\_Drug\_in\_Stomach(t - dt) + (ingesting\_antiMalaria - absorbing\_antiMalaria) * dt \tag{5.55}$$

$$ingesting\_antiMalaria = PULSE(10, antiMalaria\_Dosage, 3) \tag{5.56}$$

Still on malaria, equation (5.56) represent the uptake of malaria drugs after every eight (8) hours as prescribed by the physicians

$$\begin{aligned} absorbing\_antiMalaria =& antiMalaria\_concentration\_difference* \\ & antiMalaria\_stomach\_Volume * absorbing\_Constant \end{aligned} \tag{5.57}$$

Likewise the Equation (5.58) models the anti-tb-drugs in the bloodstream with the stock inflow presented by Equation (5.59) presenting the absorption the drugs by the host as well as the outflow represented by the Equation (5.60) showing the elimination of the drugs by the host.

$$\begin{aligned} AntiTB\_Drug\_in\_Bloodstream(t) =& AntiTB\_Drug\_in\_Bloodstream(t - dt) + \\ & (absorbing\_antiTB - eliminating\_antiTB) \\ & * dt \end{aligned} \tag{5.58}$$

$$\begin{aligned} absorbing\_antiTB =& antiTB\_concentration\_difference* \\ & antiTB\_stomach\_Volume* \\ & absorbing\_Constant\_by\_infected\_APC \end{aligned} \tag{5.59}$$

$$\begin{aligned} eliminating\_antiTB =& AntiTB\_Drug\_in\_Bloodstream* \\ & antiTB\_elimination\_Constant \end{aligned} \tag{5.60}$$

The equation (5.61) models the uptake of the anti-tb drugs and this represent the drug in the stock. The Equations (5.62) and (5.63) represents the ingestation of the drug and absorbing of the same while in the stomach.

$$\begin{aligned} AntiTB\_Drug\_in\_Stomach(t) =& AntiTB\_Drug\_in\_Stomach(t - dt) + \\ & (ingesting\_antiTB - absorbing\_antiTB) \\ & * dt \end{aligned} \tag{5.61}$$

$$ingesting\_antiTB = PULSE(200, antiTB\_Dosage, 3) \tag{5.62}$$

$$\begin{aligned} absorbing\_antiTB = & antiTB\_concentration\_difference* \\ & antiTB\_stomach\_Volume* \\ & absorbing\_Constant\_by\_infected\_APC \end{aligned} \tag{5.63}$$

Modelling of treatment was done as an integrated component where the drugs for malaria, TB and HIV were assumed to be taken all together as show in Figure 5.11.

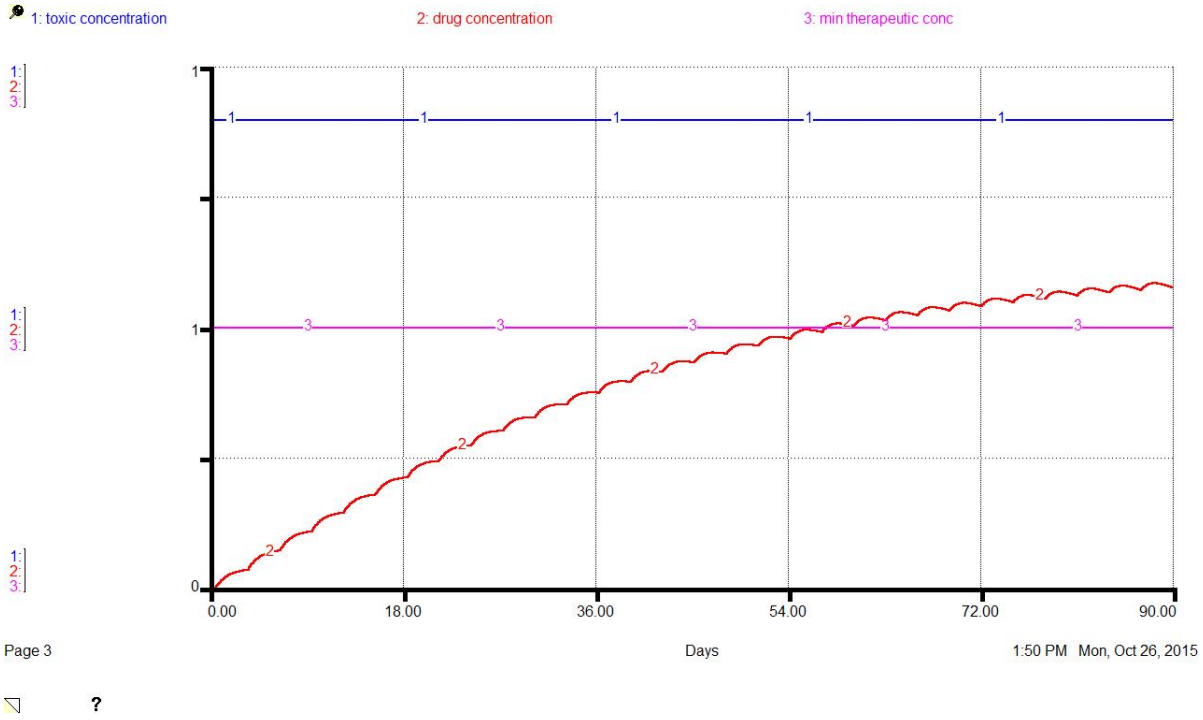


FIGURE 5.11: Relationship of toxic, drug and therapeutic concentration of Drug dosage

The toxic concentration shown in the Figure 5.11 as graph line 1 indicates the anticipated level that can cause damage to internal organs while minimum therapeutic concentration refers to drug levels in the stomach that are too little to impact on the pathogens. Therefore the stomach drug concetration that can cuase effect to the patient and improve the immune system counter effect on pathogens is shown by line graph 2 in Figure 5.11

A run of the model when the host is attacked by cofactors without treatment is presented in Figure 5.12. By looking closely, the figure shows that malaria attacks replicate very fast within the host more than how the RBC can

replicate and faster than the way the host immune system can respond to these attacks. This response by malaria parasite is represeted by graph line 3. As the model run presents, the malaria parasites replicates very fast in the inffected RBC cells particularly when they bursts. This vivid in the first two days of malaria attack. The immune system commander, TH1, responds by commanding the killing all the infected RBC by CTLs. As can be seen by graph 1 of CTL, it shows at the time of the attack by the parasites, the CTLs are high in proportion to the infected RBC. And as the infected RBC goes up after the second day, the CTLs goes down. The reason for this is they are no longer replicating as the replicating commander, TH1, having been activated has been attacked by the free HIV virus. The same happens to the activated APC, graph, that are targeted by TB pathogens and free virus. The resulting scenario is that of high viral load, rising RBC, rising levels of infected TH1, low levels both TH1 and CTLs.

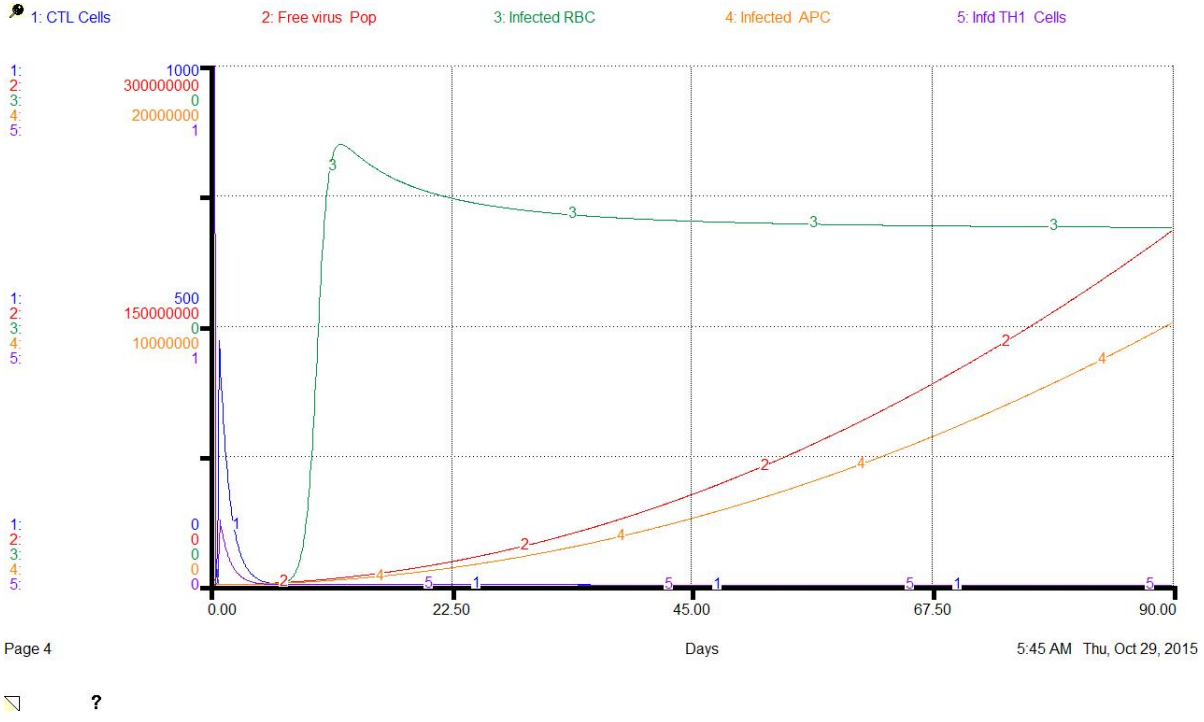


FIGURE 5.12: Relationship of TB, Malaria, and HIV with not Treatment

However when proper medication is administered, merozoites are cleared from the body within days as presented by graph 3 of Figure 5.13 that shows the sudden drop of merozoites population. TH1 and CTLs takes time

to replicate, and specifically TH1 which is always under attack by the HIV virus since the it never get eliminated completely from the host body. This behaviour is shown by graph 1 and 5 that shows CTLs and infected TH1 respectively. The entire documentation of the stock, flows and converters is

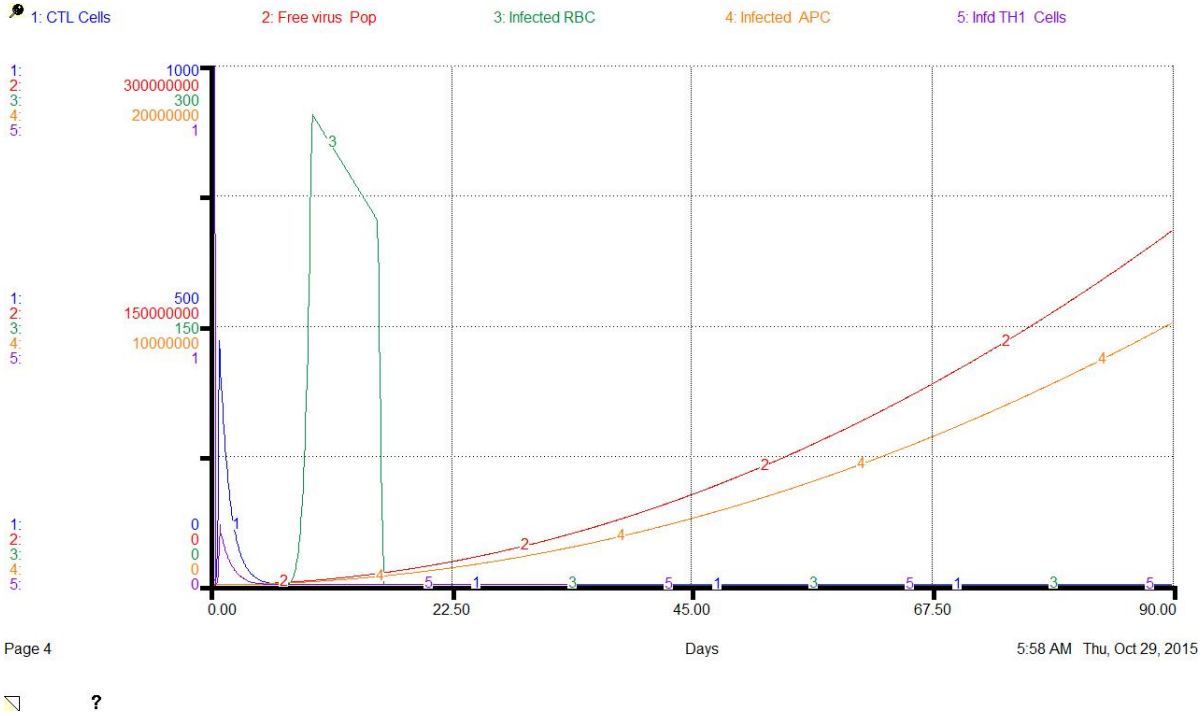


FIGURE 5.13: Relationship of TB, Malaria, and HIV with Treatment

shown in Appendix B on Page 177. Section 5.4 outlines the decision, input, output and computed variables and their relationships used in the stock and flow diagram.

5.4.4 Reference to Other Important Model Structures

This section highlights some of the model structure from literature that have been used as a reference to HTM System Model development. Of particular importance is the mathematical model of (Anderson & May 1981). As earlier reviewed, the model uses SIR, SIRS and SIER as its key variables. While this served as the starting point to developing the HTM model, the variables were seen as very few to depict the system HTM model. The HTM model by Mwangi et al. (2015*a*) was a new true representation of the dynamics of the immune system under HIV,

malaria and TB attacks. Likewise the models by Bonabeau (1999), Dimitri (2009) which were largely agent based models elicited knowledge sufficient enough to discover the decision variables though, as pointed out in literature in Chapter 2, agent based modelling is a new area which is attracting researchers in order to develop models that are usable.

5.4.5 HTM System Model Base Case Behaviour

This section represents the base case runs of the model and preliminary validation runs which were done to show the stability of the model as well as check whether the model does what is expected to do (Maani & Cavana 2000). The model base run is presented in Figure 5.14. There are five graphs labelled 1-5 presenting activated APC, activated TH1, MTB, free virus population and merozoites population. As can be seen, APC rises very fast and remain high through out the 90 days of the model run. This is because, when the immune system is attacked by disease causing pathogens, the APC are the cells responsible for capturing the pathogens and presenting them to the TH1 cells through the IL6 immune effector. Resting TH1 responds by getting activated by IL6 levels and remains so until all the pathogens are eliminated from the body. This is reflected by graph 2 and is also highlighted in (NIAID 2007). HIV virus affects activated TH1 cells and not resting TH cell. In this model, when TH1 are activated, the free virus population is seen to be rising as result of budding and busting process within TH1. Similarly merozoites population, graph 4, is seen to move up very fast and then start going down. This can be explained by the fact that the malaria causing agent affect and resides in RBC. Since not of the TH1 nor APC are associated with destruction of infected RBC, and free merozoites population, their levels remains as high, as long as there are there are still RBC to be infected. If the patient does not secure treatment in the first 15 days, this situation can lead to anaemic condition (Brieger 2011, Onifade et al. 2007, Sullivan 2003). When the APC get activated, the conducive living condition for the merozoites get compromised, since they depend on oxygen with the APC cells (NIAID 2007). This combined activities of activating

APC and TH1 cells causes the high levels of virus population and MTB population. Graph 5 shows the behaviour of the TB etiological causal agent, MTB. In this cause, the MTB consume and replicate with the resting APC. Soon after the APC are activated, the living condition for MTB becomes unfavourable and they get released into the plasma. Since there are not more APC to attack due to the immune reactivation by the presence of malaria and HIV virus, the MTB seem to be going down. When the host does not seek treatment within the first 90 days, these may lead to immune collapse (Mwangi et al. 2015*b*,*a*)

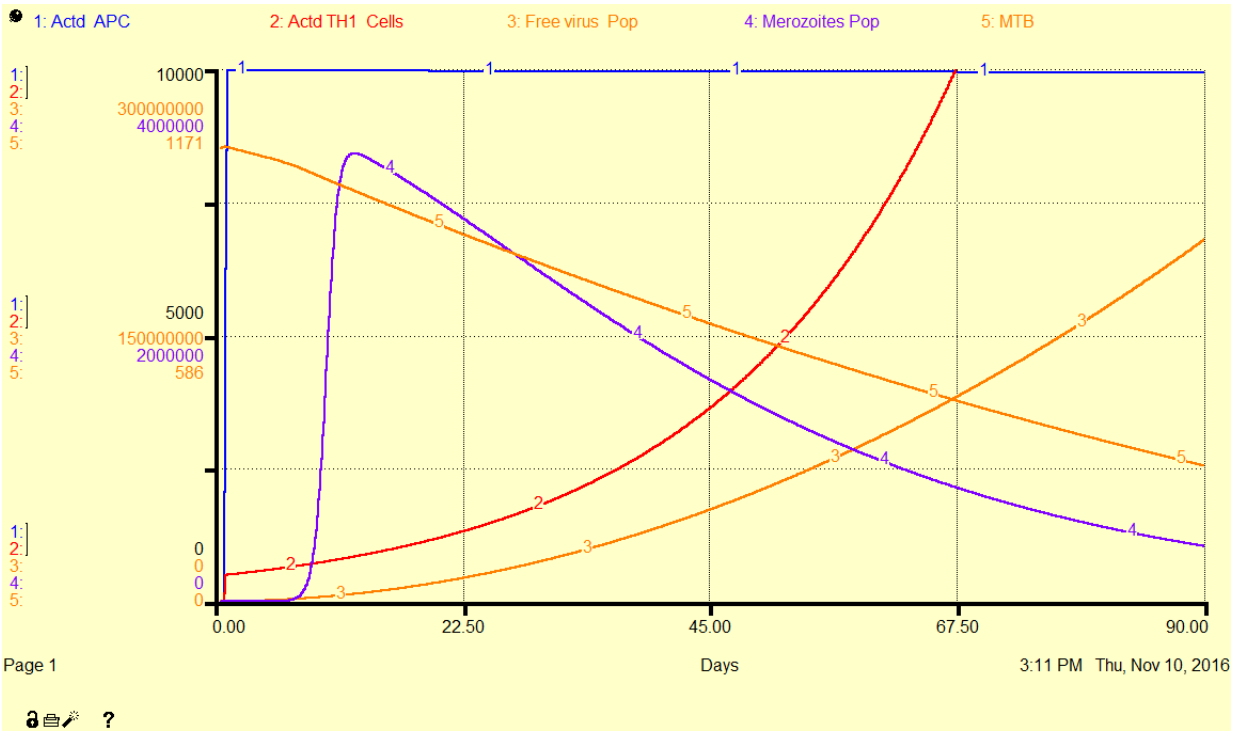


FIGURE 5.14: Model Base Run

5.4.6 Graphical User Interface

Stella software's components for interface interface design came in handy for creating the Graphical user interface of HTM system. The model was developed incorporating screens that could be used by policy makers of the HIV/AIDS, TB and Malaria. This section explore the various screens and output of the model. Once the model starts, the user is presented with screeen in Figure 5.15. This window present the user with a friendly interface to the model users This interface

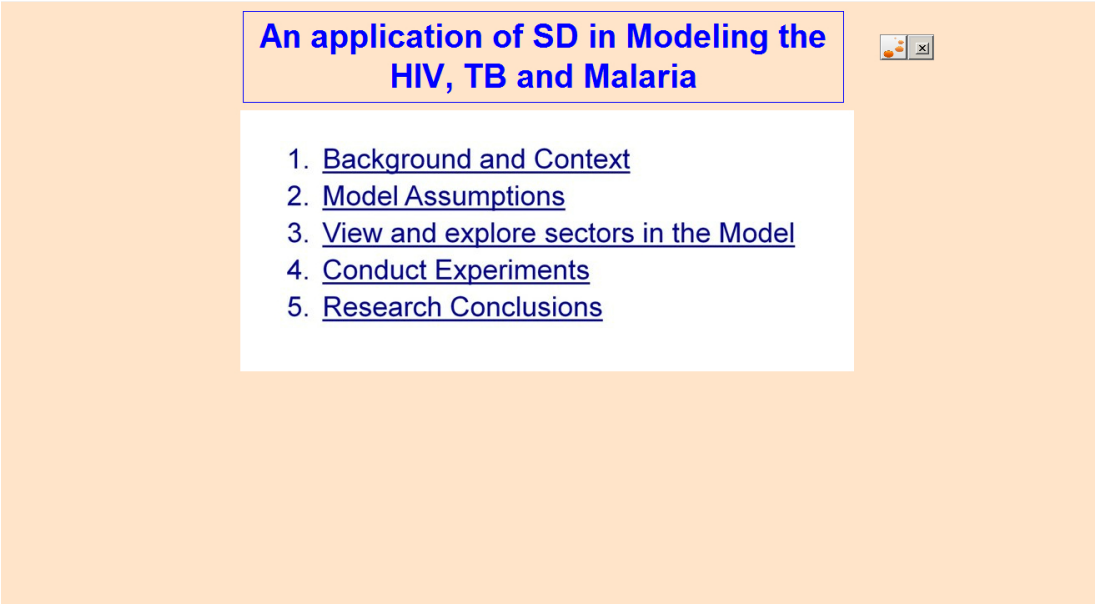


FIGURE 5.15: Main Interface

has Five links to the model. The first link gives the background and context of the HTM system as presented in Figure 5.16 Option Two highlight the model as-

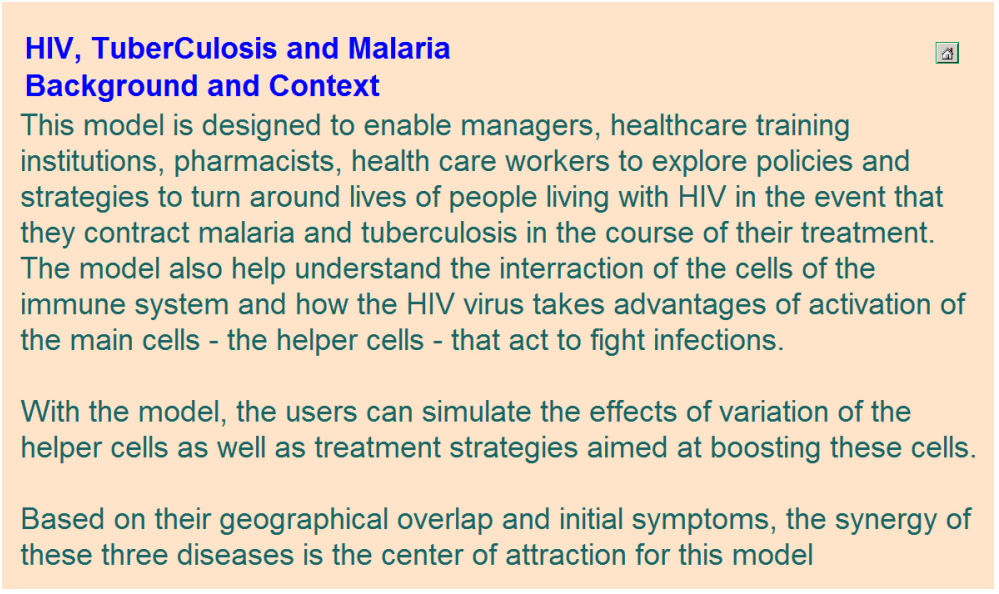


FIGURE 5.16: HTM System Context

sumptions while option three represent the technical part of the model presenting HTM story. When selected, it unveils the sectors of the system with each sector presenting its own story. The figure is represented by Diagram 5.17 The screen on 5.17 presents the main sectors of the system. Each sector itself is a button which when clicked/selected opens the model map e.g. Figure ?? representing stocks,

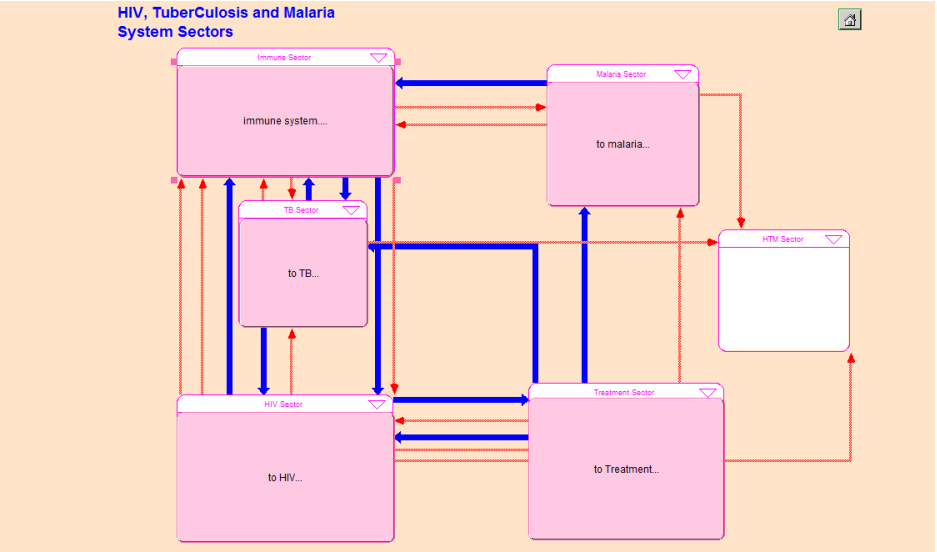


FIGURE 5.17: HTM System High Level View

flows and converters. Through each of the buttons the relationship of the variables is unveiled and formulation thereby.

5.4.7 Model verification and Validation

As alluded by Maani & Cavana (2000) that before it can be used, a model should gain the confidence of the management in usefulness and soundness. Confidence of the model accumulates gradually as the model passes more test and is more comparable to the reality (Forrester 1961, Richardson & Pugh 1981, Sterman 2000). Validation enables the modeler to determine the correctness and accuracy of the model. Coyle (1996) outlined the following test which should be used to validate a model in System Dynamics

a.) **Verification tests** are concerned with verifying the structure and with the parameters used in the model representing the real system.

b.) **Validation tests** entails demonstration that the model behaviour is similar to that of the real system.

c.) **Legitimating tests** are applied to determine that the model is developed based on the laws of the system structure and any other generally accepted rules

5.4.7.1 Verification of the Causal Loop Diagram

Causal Loop Diagrams as earlier stated in chapter 2 plays a major role in identifying the main variables as well as drawing behaviour over time charts and illustrating the relationship amongst variables. In this case of HTM system, variables were from the literature and field studies. During the FGDs, the participants were made to critically focus on the dynamic structure of the HTM system as presented in Appendix A on data collection and validation tool. This served to show the leverage points in the HTM system facilitating in development of the HTM system and subsequent simulation that were key for the extensive detail that the system required.

The following tests were undertaken in the verification process:

a.) Test for clarity: the extent to which the model clearly captures and communicates issues associated with HIV/AIDS

b.) Test the existence of the variables that are shown in the diagram

c.) Test whether the relationship between variables in the model have been clearly represented

5.4.7.2 Behavioural Verification

Figure 2.6 presented the domain expert's view of the results of immune activation. Immune activation was the center of this research particularly the TH1 cells, which are central to pathogen resistance and clearance. In consistent with the 2.6 are the graphs presented in Figures: 5.2, 5.3, 5.4 that discusses the behaviour of the immune system under attack by TB, malaria and HIV pathogens. The target

audience of the verification tool were the problem owners specifically researchers in malaria, tuberculosis and malaria as well as students of immunology as show in table 5.8

TABLE 5.8: HTM System Verification Participants

	Position	**Role in the Organization**
1	Lab Officer	Test blood samples for the presence of viral load, malaria parasites as well TB parasites
2	Seniour Medical Officer	Responsible for the procument, storage and distribution of blood samples and other medical equipments
3	Immunologist Trainer	Instructing/teaching immunology student which is a core unit to medical, microbiogist, pharmacist students
4	HIV, TB Physician	Coordinate, test, diagonise and prescribe HIV and TB patients
5	Malaria Research Scientist	Conduct field studies and report on regions under focus on malaria incidences
6	Pharmacist Practitioner	Administration and prescription of drug

Chapter 6

Discussion of Findings, Achievements and Limitations

6.1 Introduction

Chapter 5 presented the Within-Host HTM treatment policy model. This chapter will focus on findings and discussions of this research. A personal critical opinion and reflection on research process is presented. The chapter highlights the benefits that can be derived using System Dynamics qualitative approach to HIV progression in the light of TB and Malaria.

6.2 Discussion of Findings

The findings of the study are discussed under the following themes: Understanding issues sorrounding HIV progression, the role of Tubercle bacilli, the role of RBC, the role of Merozoites, drug Interractions, review of the dynamic hypothesis and effectiveness of the dynamics synthesis methodology.

6.2.1 Understanding issues sorrounding HIV and the Immune system

The immune system is made such that it is self sustaining NIAID (2007). This is clearly shown in figure 4.5. This means that when it is attacked, the cells of the immune systems popularly known as the effectors whose work is to inform other cells that act as the 'generals' tasked with organizing and coordinating the immune system in terms of the current attack and the future handling of this enemy. The effector cells belong to a large category of cells called Antigen Presenting Cells. These cells include the machrophages and the dendritic cells. These cells digests the antibodies and secretes cytokines-communicating signals- that excites the 'generals' into action. These cytokines - interlekin IL6 or IL12 - stimulates the Naive T Cell into polarization to TH2 and TH1 respectively. TH1 are the one we are referring here as the 'generals' as they are the ones that co-ordinate the activities of the immune system. These activities are invocation of NK cells, Regulator cells, Cytotoxic T cells (CTLs) among others, all of which are necessary for the purposes of maintaining or stopping the fight with the enemy. These cells are generated every second and die every other time to maintain an equilibrium. When there is no attack, they are said to be resting and when presented with antigens they become activated (Mwangi et al. 2015*b*). When activated through attack, these TH1 cells multiply very fast in tunes of millions.

The HIV virus target the 'generals' of the immune system. However, the virus remains dormant within the TH1 cells even after it has successfully converted the TH1 into a factory of its' own production. This remains as such until the immune system is attacked and causes the TH1 cells to start replicating to avert the enemy. The virus weakens the immune system by replicating very fast and in big numbers. This is depicted in the model in Figure 5.6 showing the relative replication of the virus and that of the TH1 and by extension CD4.

The immune system cells like the TH2 secretes antibodies whose work is to mark enemies for killing by the NK cells or by the CTLs. The TH2 cells also antagonise the activities of the TH1 cells by secreting interlukin IL10 whose work is to

neutralize production of TH1.

6.2.2 The role of Tubercle bacilli

As noted in Section 5.4.3 that HIV can remain dormant for along period of time, having attacked and converted the DNA of TH1 cells to its own, attack by infection like TB will cause the TH1 cells to replicate quite fast. But this time it is not copies of TH1 that are made, rather those of the virus. Tubercle Bacillus target cells are the macrophages and as mentioned in Section 5.4.3 these are the Antigen Presenting Cells, the systems ability to deal with the bacteria is completely hampered. This is demonstrated by the Model in **??** where on attack by the bacteria, the viral load continously reaches exponential levels. This is partly because the cells of the immune system specifically the TH1 tries to compete with TB bacteria rate of replication but instead it is the virus that results. Shortly after, the TH1 become spent of and dies out. Also the macrophages now being attacked by the TB bacteria cannot present the virus antigen to the TH1 cells.

6.2.3 The role of Merozoites

There are many forms of malaria; **P. falciparum**, which is found worldwide in tropical and subtropical areas, **P. vivax**, which is found mostly in Asia, Latin America, and in some parts of Africa, **P. vivax** (as well as P. ovale) has dormant liver stages ("hypnozoites") that can activate and invade the blood ("relapse") several months or years after the infecting mosquito bite, **P. ovale** is found mostly in Africa (especially West Africa) and the islands of the western Pacific, **P. malariae**, found worldwide, is the only human malaria parasite species that has a quartan cycle (three-day cycle) and P. knowlesi found throughout Southeast Asia as a natural pathogen of long-tailed and pig-tailed macaques WHO (2009). This study considered *P. falciparum* because it is the most common in Africa and provide the highest overlap with TB and HIV. When the host get a mosquito bite, the

mosquito transmits parasites in to the host body. These parasites are called sporozoites and are not mature at the time of transmission. They mature and multiply by the help of liver cells - hepatocytic cells. They mature to merozoites. Merozoites replicates assexually and infecting the red blood cell. In about 7 to 10 days the human host can have trillions of circulating infected erythrocytes. The release of daughter merozoites from a population of erythrocytes correlates to the symptoms of fever, sweats, rigors and chills called malaria as seen in the model extract Figure 6.1 graph labelled line 3.

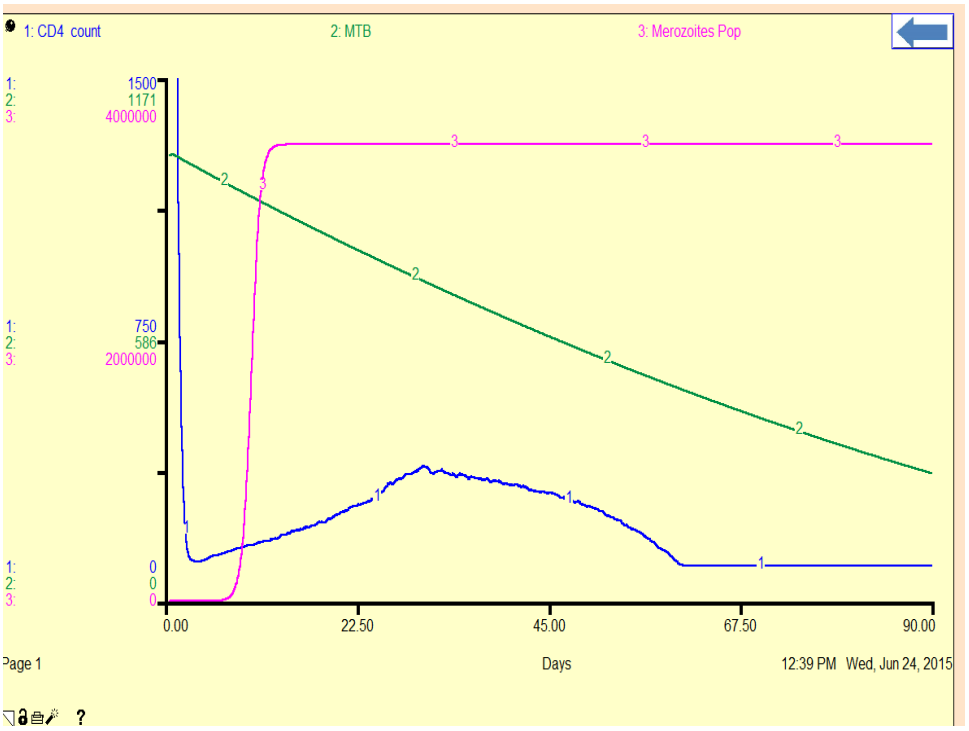


FIGURE 6.1: Relationship of Malaria, TB and CD4

6.2.4 Need for Treatment therapy

In general the immune system is capable of sustaining itself NIAID (2007), Copley et al. (2008). However the strategy of invading parasites and microbes is to replicate and overpower the immune system Mwangi et al. (2015*b*), NIAID (2007) power of replication. The base run of the model, without intervention agree with this views as shown in Figure 6.1. Drugs that we take, on falling sick, are based on chemokines that the immune system generates inorder to fight the diseases.

In this case when we boost the immune system by administering therapy, CD4+ cells are activated (TH1 and macrophages) and significant drop of the parasites as Figure 5.13 presents

6.2.5 Understanding the HIV, TB and Malaria treatment strategies

This thesis demonstrates how qualitative System Dynamics Methodology can be used to provide a better understanding of Health Systems thus facilitating better development and design of computer-based health information system. System Dynamics is used to capture and analyze the complex interractions between behavioural, technical and policy issues which provides a broad integrated view of the HTM system which facilitates communication and caters for the different views of the stakeholders. The synthesis of the various theoretical concepts through use of causal loop diagrams facilicates the understanding of the HTM which enables agreement on different policies and priorities.

Causal Loop Diagrams facilitates communication among stakeholders by linking up the non-technical user view and the technical view of the designers and programmers of the information systems thereby capturing the requisite information requirements for a healthcare systems.

This thesis has established an understanding of the HIV, Malaria and Tuberculosis interractions from feedback point of view. The developed SD model provides an opportunity for discussion and enhanced understanding of HIV progression. The thesis extends the scope of existing models by incorporating the dynamics involved in the activation of helper cells during attacks by other infectious or parasitic diseases. The progression of HIV is modelled to capture existing delays that impact the helper cells in the event of attacks.

The status of HIV and its interraction with the immune systems, the role of merozoites, the role of tubercle bacilli, the treatment strategies and flow of information has been presented in Section 6.2.

6.2.6 Proposed Intervention Strategies

Leverage points are actions or interventions that can have lasting impacts on the system interms of reversing a trend or breaking a vicious cycle Maani & Cavana (2000). Leverage points can have a lasting effects on the system as opposed to dealing with symptoms of the problem. A quick-fix solution can have unintended consequences that exacerbate the problem. Dealing with problem symptoms will diminish for a short while and then return to its previous level, or become even worse over time. This section highlights the key leverage points which could substantially improve quality of life for people living with HIV.

a.) **Regular Testing**

The nature of the immune system is such that when infected, the TH1 cells - the army - takes control and begin to replicate in order to counter the infection NIAID (2007). Normally when testing is done, the idea is to know the CD4 count followed by subsequent diagnosis and transcribing the right medicine according to WHO guidelines WHO (2006, 2007, 2009). According to findings by Mwangi et al. (2015*b*) and WHO (2009) it is apparent that HIV, Malaria and TB have an overlap in their geographical distribution and the initial symptoms. There are frequent attacks by these dieseases implying failure by HCW doing the tests will result to poor medication and aggravation of the HIV. The results of the model show heavy viral load on attacks by any one of TB and Malaria infections as indicated in the Figure 6.2. Figure 6.2 shows the immediate activation of TH1 as well as APC upon infection.

b.) **Prevention of Malaria and Tuberculosis**

When an individual gets infected with Malaria or Tuberculosis, the TH1 cells replicate very fast inorder to avert the challenge. While this is important to the immune system and body protection from diseases in general, it is worse for PLWHIV since these are the very cells that are target of the HIV virus. Unfortunatelly the medicines on offer at the moment fail to address this issue. The incubation period for Malaria is 12-15 days. By the time

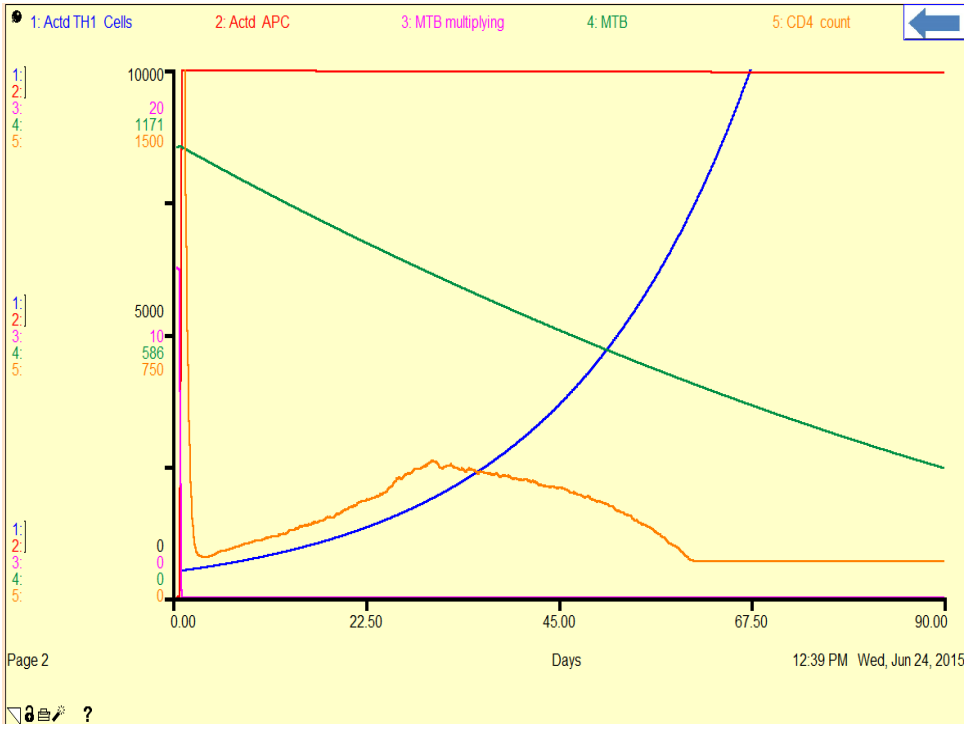


FIGURE 6.2: Activation of CD4 as a result of Malaria and TB infections

it is detected and prevented, it is already too late and the HIV virus has had enough share of the activated TH1 cells. The study therefore calls upon medical practitioners for tests that can detect malaria for PLWHIV early enough. On the other hand TB Bacilli remains in APC long enough unless it has reached threshold levels to cause TB. Once TB matures to a disease, the bacilli continue replicating within the APC until they are no more. It is therefore important to come up with drugs that take shorter periods to eradicate and detect these diseases. With the model it can show the progress of TB and Malaria with a view to stop the continued activation of TH1.

c.) **Handling Toxicity**

Toxicity according to Szekely (2010) is the the degree to which a substance can harm humans or animals. It is difficult at the moment to detect toxic levels and more so to a case where a patient is parmanetly on one line or cocktail of drugs as is the case with PLWHIV. With the model it will be direct to manage toxic levels and the patients response to drugs as indicate in Figure 6.3

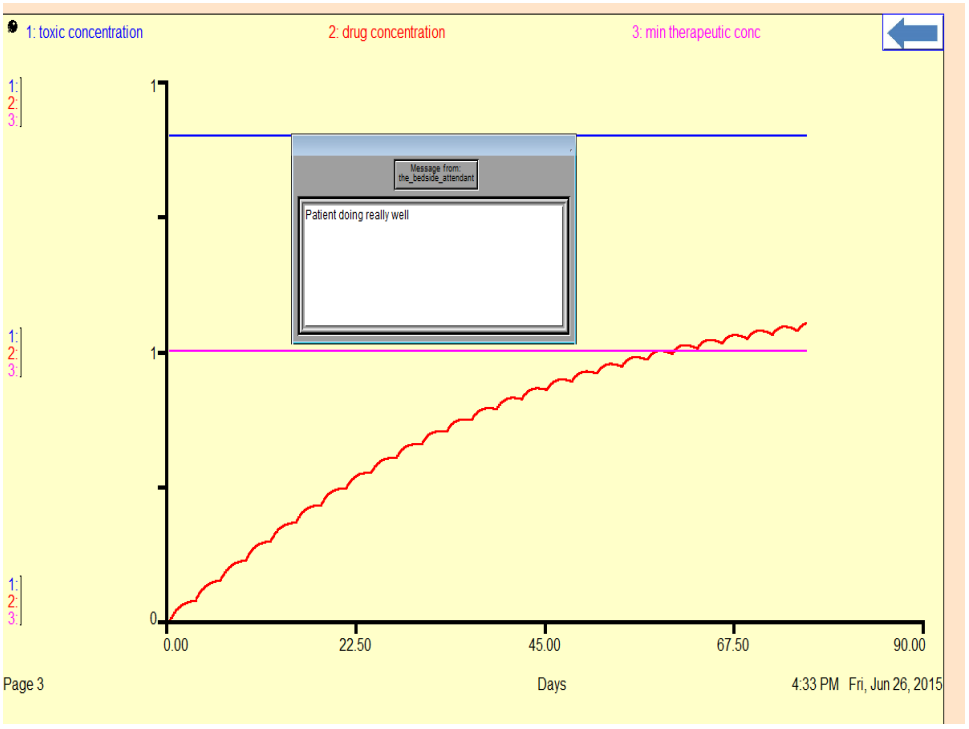


FIGURE 6.3: Treatment monitoring for toxicity

d.) **Combined Drug development for Malaria and Tuberculosis**

The state of practice is that when infected with one of HIV, Malaria and Tuberculosis there are specific drugs for each one of them. The study showed significant activation of TH1 cells as in Figure 6.2. This means that HIV virus will have prey once the immune system is attacked by other diseases. Since at the time of the attack the patient is on ARVs, consumption of other drugs will only raise the toxic level of these drugs and this compromise the proper function of victim organs. The study therefore proposes innovations for combined drugs for disease combination HIV, TB and Malaria.

e.) **Special Test tool**

The state of practice for testing against HIV, TB and Malaria have been independent for quite a while. There is a need to develop a test tool that captures combined illness of HIV, TB and Malaria as throughout the study we have shown that these three disease share geographical distribution as well as initial symptoms.

f.) **Innovative ICT Solutions**

While advances in Information and Communition Technology has improved care delivery, it has been limited in the areas of coverage, service delivery and data management. One important area that is missing is monitoring patients whether self or by the HCW and where it is existing, it is only few in the society that can afford and are concentrated in urban settings. This model serves as example of a tool that is understandable and one that the patient can use to monitor their CD4 levels. That said, the patient can with a little more education, assist HCW in improving his/her status. eHealth technologies to which this model is part, empower patients to take more responsibility for their own health and quality of life, and that would lead to better cost-efficiency in the health sector. The use of the HTM model will allow mutually beneficial collaboration and involvement of PLWHIV and HCW in the monitoring of CD4 levels.

6.2.7 Development of HTM Information System

This thesis demonstrates the benefits of using qualitative System Dynamics to understand systems with very complex interractions thus facilitating the development of an information system that meet the stakeholders requirements. While the use of health information system through web-based technologies can increase the quality of healthcare service delivery through provision of reliable information and effective communication thus enabling improverished communities to access healthcare services, previous experience has showed that healthcare software developed for the requirements of industrialized countries do not fit developing countries healthcare facilities' requirement, often requiring major-reenginering. The conceptual diagram (Figure 2.5) shows the key processes and flow of information while the cause loop diagrams (Figure 4.4, 4.5, 4.6) provide the broad integrated view of the system for the stakeholders to prioritize and set policies. These views provide deeper understanding of the system with which different information systems that need to be developed for the improvement of quality of life for people living with HIV can then be generated. It is through such understanding that effective

healthcare information system can be developed for communities in developing countries

6.2.8 HTM treatment improvement model

The model equations (Appendix B) derived and discussed in Chapter 5 from the conceptual diagram (Figure 2.5) and Dynamic Hypothesis (Figure 2.7) form a defined description of the key variables in terms of feedback loops, time delays and non-linearity that are believed to control the processes in the model. The model can be used in the following ways:

a.) Improved understanding and planning.
The complex relationship of the cells of the immune system and that of infectious infections be it bacteria, virus or other parasites is analyzed through the variables in the model. The time delays and feedback relationship amonst these organisms help to better understand them.

b.) Learning and Training.
The presentation of the holistic view of the cells of the immune system and its behaviour when under attack provide a learning environment especially with the story telling ability of the software.

c.) Strategic Planning and Management of HIV.
The thesis presents a model to enable healthcare workers understand the present state of PLWHIV, its fast progression when other infections are considered - malaria and TB - and how they can be mitigated for future planning. Various policy designs can be used to provide proper use and management of healthcare resources. The model can be used for strategic planning and management since it provides tools that test the different scenarios and enables decision makers to investigate effects of possible change in policy.

d.) Tool for operational Management.
The model captures requisite information requirements as well as the key

cells of HIV Progression when malaria and TB are involved which provide support for process improvement and operational management which are useful in the design of information systems for better operational effeciency.

6.2.9 Review of the Dynamic hypothesis

The Figure 6.1 on Page 137 affirms that an increase in malaria-causing-parasites in the host causes an increased immune activity through TH1 activation, an increase in TH1 means improved immunity which causes a decrease in virus activity for a short duration of time as indicated on the graph from 2^{nd} day to 25^{th} day. This is followed by a decline from 26^{th} onwards as a result of the virus now attacking the activated TH1 cells. Most notably is the fact that TH1 will success accord resistance to the virus through CTLs cells and consequently get infected by the HIV virus which multiply within the cells that results in the depletion of the TH1 if no treatment is given. This is depicted by the balancing loop B4 in Figure 2.7 on Page 56. An increase in therapy increases the immunity level thereby lowering infections of HIV in TH1. An increase in TH1 means ability of the body to fight malaria parasites hence reducing need for treatments as alluded by loop R3 in Figure 2.7 as confirmed by Table 5.6. Table 5.4 affirms that a compromised immune system due to infections of HIV will cause an increased TB activities resulting in further failures which reinforces need for increased therapy. An increased therapy will subject the host to increased toxic levels further which further weakens the immmune system and this results to conducive envionment for HIV replication as indicated in loop R6 of figure 2.7. Hence an effective treatment of TB and Malaria will lead to decreased activation of TH1 cells resulting dampened HIV replication hence increasing the quality of life of PLWHIV as indicated in Table 5.6. These results confirm the dynamics, feedback loops, time delays presented in the dynamic hypothesis presented in Figure 2.7.

6.2.10 Effectiveness of the Dynamic Synthesis Methodology

This thesis shows that Dynamic Synthesis Methodology is suited for complex problems such as those presented by the HTM system. DSM which combines the System Dynamics and case study methods was used to study and understand the inhost behaviour of HTM system. The causal loop as well as stock and flow diagrams defines DSM providing a template for understanding the system further.

Causal loop diagrams provide for understanding of the nature of the HTM system as well as eliciting knowledge from experts about the key factors that are key players into the cause and progression of the same as indicated in Figures 4.1, 4.2, 4.3, 4.4 and 4.5. In addition, it enables researchers in the area of TB, Malaria and HIV to understand and comprehend the HTM system, share observations and experiences. The variables presented in the causal loop diagrams are especially useful in data poor environments therefore facilitating decision makers into identifying the key data that is needed yet cannot be collected from field studies.

6.3 Achievements

This section provides the achievement of this research by establishing whether the objectives were met and how they were met as well as the results of each objective.

a.) The first objective was to identify and define factors (variables) that influence the progression of HIV/AIDS infected persons with TB and malaria to provide variables for the model. This was achieved in chapter 2 from the critical review of literature that demonstrated the investigation of state of the art and practice by:

   (a) Studies on HTM symptoms, pathogenesis and immune system counter effects on the pathogens.

   (b) Investigations on methods used to study HTM.

(c) Applications of simulation modelling in Healthcare and disease progressions.

b.) The second objective was to design a system structure model of Trio-infections of HIV/AIDS, TB and malaria. This was achieved in chapter 4, through a detailed study that identified empirical data and descriptive information on the activities and challenges associated with HTM pathogenesis which is expansively discussed. The results and classification of variables are further presented in the same including the corresponding causal loop diagrams

c.) The other objective was to implement the SD simulation model. This was achieved in chapter 5. The data collected using FGD and literature was used to populate the model. This model was used to explore and understand the HTM pathogenesis including the impact these diseases to the immune system as well as the communication amongst the immune cells using cytokines and chemokines to kill pathogens. Insights from the model are discussed in the same chapter and proposed intervention strategies presented in Section 6.2.6 Page 139.

d.) Another objective was testing and validating the simulation model as a tool to support enhanced understanding of the HIV/AIDS disease progression and co-factors in malaria and TB. Section 5.4.7 presents the validation of results of the causal loop diagram. Model verification and validation is explained further in the same Section. Critical and empirical evaluation of the effectiveness of DSM as a general problem solving methodology is done in Chapters 4 and 5 providing a HTM tool for use in HTM issues understanding. Section 6.2 discusses the findings from the application of DSM, including Section 6.2.10 that demonstrates the effectiveness of DSM.

6.4 Limitations of the Study

This research applied SD modelling to understanding HIV progression when the immune system is unders siege of TB and malaria representing the issues associated with pathogenesis of all the three diseases. In the course of model development however, various limitations were experienced during the research.

One of the key limitations of the developed HTM model is its inability to accurately predict CD4, APC and Merozoites counts due to the unreliability of the data used to populate the model. Unreliability of the data may have resulted from the following:

a.) Data for some of the variables was not readily avaialable particularly TH1, rate of TH1 replication, number of naive TH cells, the budding rate of HIV, number of HIV virus that resuls from infected TH1, number of TB causing pathogens that results from budding of a single APC, as well as number of merozoites that rests from a single RBC budding.

b.) Different values of variables from various sources like KAIS and WHO

c.) Some data was entered using graphical relationships.

In a view to diminish the confines resulting due to no or absence of data, previous data was used in the model. With reference to wellness, data from Kenya AIDS Indicator Survey and World Health Organization was considered more accurate compared to that of government as it was assumed that it is less biased and assumptions in Section 5.3.3 were applied in incidences where data was unavailable

Modelling of the immune system was seen as most challenging as the immune effectors like cytokines and chemokines were replicated in the diseases under consideration. As such graphical inputs supported by expert opinion were used for most of the cases.

Six respondents participated in the FGD during the verification of the causal loop diagram. These were experts drawn from research in HIV, TB and malaria either

teaching and conducting research or doing research alone. It was intended to have a workshops involving all the parties but this was not possible since the researcher are very busy and travel alot.

Inspite of the above limitations, the model analysis provides a basic guideline for understanding and eliciting knowledge about HIV pathogenesis under other infections.

Chapter 7

Conclusions, Contributions and Recommendations

7.1 Introduction

This chapter gives the conclusions and contributions derived from this study as well as recommendation for practice, policy makers and further research. We will also highlight advantages of using the HTM tool derived from this work.

7.2 Conclusions

HIV/AIDS is so widespread disease and millions of people are affected every other year. Apparently, upon infection, the HIV virus resides in resting TH1 and APC cells for a long duration of time. APC are the first cells that interracts with pathogens as alluded by NIAID (2007), Atun et al. (2011), Bennett et al. (2013), and processes these pathogens and present them to TH1 cells and during this process they get activated. This activation as presented in Figure 2.6 graph 2, and causes the acivated TH1 to replicate. This replication results in more HIV virus since resting TH1 is already HIV virus infected. This results in more virus in indicated in graph 4 of Figure 2.6. This results are were obtained through

the focus group discussion and are in tandem with the findings of this study as presented in Figures 5.2, 5.3, and 5.8.

Similarly APC causes the resurgence of TH2 and subsequent increase of TH1 cells as presented in Figure 4.1 by the reinforcing loop marked by the following cells: APC, Naive T cell Polarization Rate, TH2 Polarization Rate, TH2 Production Rate, TH2 Population, IL10 Production rate, IL10 Concentration, TH1 Production rate, TH1 Concentration, IFNg Production rate, and IFNg Concentration. This is now evident since the methodology used, System Dynamics, is not limited to the number of variables as posed by other methodologies like Monte carlo and discrete event simulations.

Consumption of regimens for HIV, TB and Malaria leads to toxicity. This was capture through Figure 4.5. While prevention against diseases is critical to the health of a patient, consumption of medicine like HAART, as is the recommended regiments for HIV hyperactivity as a result of HIV reactivation **??**, together with the consumption of TB regiments and those of Malaria will lead to high drug concentration in the blood and that result to poor immune response as presented in Figure 2.6 and in tadem with these research findings Figure 5.2.

Due to the rate of spread of TB and the inability to elimate Malaria which are very common in developing and poor countries WHO (2009, 2007, 2006), there has been resurgence of HIV and medical professionals must implement new strategies for diagnosis, management, treatment and containment of these immune reactivation. Simulation and Modelling tools taking advantage of the emerging power of computers, sandwitched in medical professionalism, will effectively render success in cutting edge technological experiments in the expansive range of health services Mwangi et al. (2015*a*), Anderson & May (1981), Perelson (2004)

7.3 Contributions

This research work focused on understanding the progress of HIV under TB and Malaria infections. The research has demonstrated the benefits of using System Thinking for qualitative and quantative aspects in eliciting understanding of healthcare systems. Causal loop diagrams represented by Figures 4.1 - 4.5 showed the key processes and flow of information for the HTM System. They represented how the immune system conduct itself under siege including how it communicate amongst itself and how it arms itself inorder to conquer attacks.

In summary the contributions from these research are:
A conceptual diagram (Figure 2.5) shows the key processes and flow of information with the cause loop diagrams (Figures 4.4, 4.5, 4.6) providing the broad integrated view of the system by the stakeholders to prioritize when setting HTM related policies. These views provide deeper understanding of the system with which different information systems that need to be developed for the improvement of quality of life for people living with HIV can then be generated. It is through such understanding that effective healthcare information system can be developed for communities in developing countries

Another major contribution was the showing the relationship between TH1 and TH2. This research showed that there is a relationship between TH1 and TH2 particularly in the module related to malaria discussed in Section 5.3.

Tool for operational Management. The model captures requisite information requirements as well as the key cells of HIV Progression when malaria and TB are involved which provide support for process improvement and operational management which are useful in the design of information systems for better operational effeciency.

An effective treatment of TB and Malaria will result in decreased immune activation that will lead to dampening HIV replication hence improving the quality of

life for PLWHIV as indicated in Table 5.6. These findings confirms the dynamics, feedback loops, time delays presented in the dynamic hypothesis presented in Figure 2.7 about impacts of malaria and TB on PLWHIV.

The **model** can be used as a tool for improved understanding and planning, learning and training, strategic planning and management of HIV, Cofactors as well as physiology of the immune system in general.

This research contributed to the body of knowledge through the published papers (Mwangi et al. 2015*b*,*a*).

7.4 Recommendations

7.4.1 Recommendations for Practice

The HTM model will be of great use to researchers in the field of immunology, HIV/AIDS, Tuberculosis as well as malaria, healthcare students and policy makers in the following ways:

a.) The causal loop diagram were highly appreciated from the start by the practitioners. Some of the experts especially those from teaching and research quarters were very excited by the strengths of CLD in teaching immunology. It is with this view that the researcher views that the system will be of invaluable use to understanding the HTM system.

b.) The developed model presents the key processes of the HTM system which may be used by researchers including lecturers, policy makers and care givers of HIV, TB and Malaria for process improvement, operational management and design of relevant information systems for better service delivery.

c.) The developed model will assist the policy makers understand the current status HIV patient and improve the way such patient can be handled at any stage.

d.) The developed model is presumed to enable stakeholders from researchers, students to policy makers share their ideas on how other diseases may cripple PLWHIV especially by the use of integrated CLDs

e.) The model being the result of Dynamic Synthesis Methodology provide with detailed description of HTM system which contribute greatly to theory building and testing.

7.4.2 Recommdendations for Policy

Based on the result and findings from the study and proposed intervention this thesis proposes the following recommendation to government and national pocicy makers towards the improvement of care delivery to people living with HIV:

a.) It is apparent from the model that HIV on its own does not kill. Therefore its is other ailments that activate the immune system that lead to HIV taking advantage of the situation and multiplying with the host immune army cells - the TH1 and APC. It is this assertion that we recommend that the Government strengthen the healthcare system in congested area that are prone to TB and Malaria. It should also fully commit to making sure every household is supplied with Mosquito treated nets regardless of the region. Other than that, the Government should commit to provision of equipment interms of medicine, labs and power to all health facilities to assure that patients are taken good care of.

b.) There is an urgent need for more input in the study multi-infections. More research need to be carried out amongst people living with HIV to analyse other ailments especially diseases that attack the APC and that activate TH1. Diseases like Pneumonia, cancer, STDs among other should be investigated further since they are common diseases amongst PLWHIV. This research was done at cell level. Modelling at population level could shed more light at this level.

c.) There is an ardent need for the Government to improve strategies to reach out its people to improve their literacy levels about HIV inorder that people know their status and the relationship between their living style in the event that they contaminate HIV.

d.) Healthcare providers, Government and donors should focus their attention now to ailments related to crippled immune system as opposed to HIV as the model has proved beyond reasonable doubt that PLWHIV can live quite longer were it not for other TB and Malaria

e.) Use of Information and Communication Technologies should be emphasized by the government to track and monitor PLWHIV for all round treatment as well as use of tested model to understand the treatment regimes employed to counter ailments.

7.4.3 Recommendations for Further Research

a.) The conceptual model, a representation of the qualitative and the simulation model, the quantitative were developed based on data from WHO and KAIS drawn from various African countries as well as South East Asia. The developed HTM model focuses on the dynamics involved in the immune system under HIV, TB and malaria as cell level. The model can be extended in scope to incorporate population level. In addition the model looked at HIV, TB and malaria. This view can be extended to other chronic diseases like various forms of cancer and other diseases in general either at cell or population level. Apparently the model concentrated on resource constrained settings but can be extended to resource rich setting to concentrate on lifestyle diseases.

b.) The treatment sector can be extended to look various treatment regimes particularly drug resistant TB and various other forms of malaria. This would help researchers and managers by providing decision support and policy implementation in the maintenance of effecive efficacy levels reuqired in HIV management.

c.) Resource allocation. In developing countries like Kenya, that is resource constrained, there is need to design tools that can be used by policy makers to design better policies as far as management of resources suchs HIV drugs, testing, followup, transport, setup of healthcare facilities.

d.) Health care models. There is need to model the dynamics involved in progression of chronic diseases in order to stimulate understanding of these ailments as well as strength exploration of the same.

7.5 Advantages of using HTM Tool

System Dynamics has been applied widely in healthcare systems in the developed world. Healthcare systems are seen as feedback systems and strives for solutions that are sympathetic with their ogranisational and social environment. Feedback systems appreciate that problem stem from events, and solutions are not implemented in a vacuum. Instead problem and solutions coexist and are interdependent. Therefore SD as a methodology that is based on feedback systems, is an effective approach that can be used to understand other complex systems other than the physiology of the immune system, HIV, malaria and TB that has been considered in the thesis or extension of the same. SD methodology is candindate methodology that can be used to study complexities of healthcare system in developed and developing countries as well as elucidating knowledge of chronic diseases that are slowly but consistently maiming people's lives.

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Appendix A

Data Collection and Validation Tool

A Tool for Validation of the Relationships between Variables for the Trio-Infection of HIV, Malaria and Tuberculosis (Trio-HMT)

Introduction:

The Trio-HMT Dynamic Hypothesis Model has been designed by Mr. Henry Mwangi, a PhD student at the University of Nairobi as part of his ongoing Research on HIV progression in the light of opportunistic infections of Tuberculosis and Malaria using System Dynamics approach with the aim of capturing the "causal and effect" that influences rapid progression of HIV to AIDs for PLWHIV once the immunity becomes highly compromised (i.e. when the CD4 count becomes quite low or less than 300). This will help and deduce leverage points guide in development of simulation model for Tri-HMT. Kindly devote 20 minutes of your time to answer the questions related to this Topic.

Objective:

The objective of this exercise is to get an expert opinion on the Trio-HMT descriptive model's relationships and interrelationships

Target Audience

1. Virologist Researchers in Human Immunodeficiency Virus
2. Infectious Diseases Experts
3. System Dynamics Experts
4. Mathematical Biologist
5. System Biologists
6. Experts in HIV progression
7. Immunologists

Guiding Principles

1) Relationship between variables A and B are indicated using an arrow as follows (A ⟶ B or A ⟶ B)
2) A Positive arrow (A ⟶[+] B) means that Variable A is directly related to Variable B. If A increases, the effect on B is an increase in the same magnitude of what it would otherwise have been, and if A decreases, B decreases with a magnitude of what it would otherwise have been.

3) A Negative arrow (A ⟶ B) means that Variable A is inversely related to Variable B. If A increases, the effect on B is a decrease in a magniture of what it would otherwise have been, and if A decreases, B increases with a magnitude of what it would otherwise have been.
4) A Delay (A ⟶‖ B) denoted by double lines marks on some arrow indicates that the relationship between variable A on B is visible over time
5) A Feedback loop represented by complete cyclic arrows indicates that a given change kicks off a set of changes that cascade through other factors so as to either amplify (“reinforce” represeted by Ri where i=1,2..n) or push back against (“damp”, “balance” represented by Bi where i=1,2..n) the original change
6) A Dynamic Hypothesis (or Descriptive Model) is a causal loop diagram that captures the problematic behaviour of a system by providing an explanation of the dynamics that characterize the problematic situation expressed interms of feedbacks and delays in the structure of a system. The CLD in the figure below illustrates the Key Variables of Tri-HMT that impacts the rapid progression of HIV to AIDs from which the hypothesis of the study is generated.

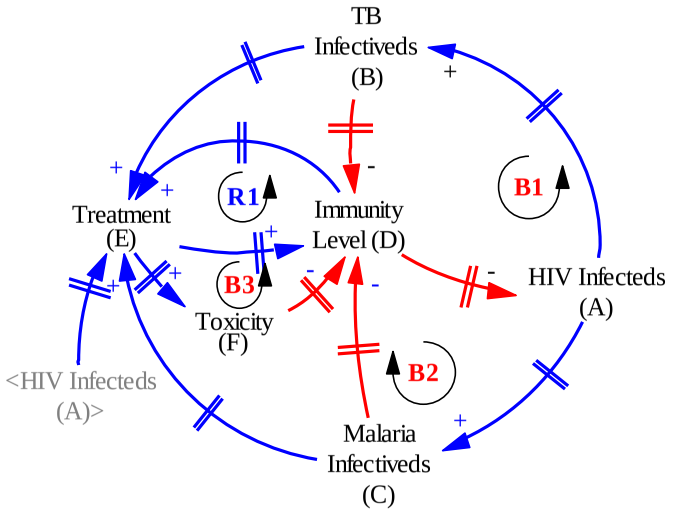
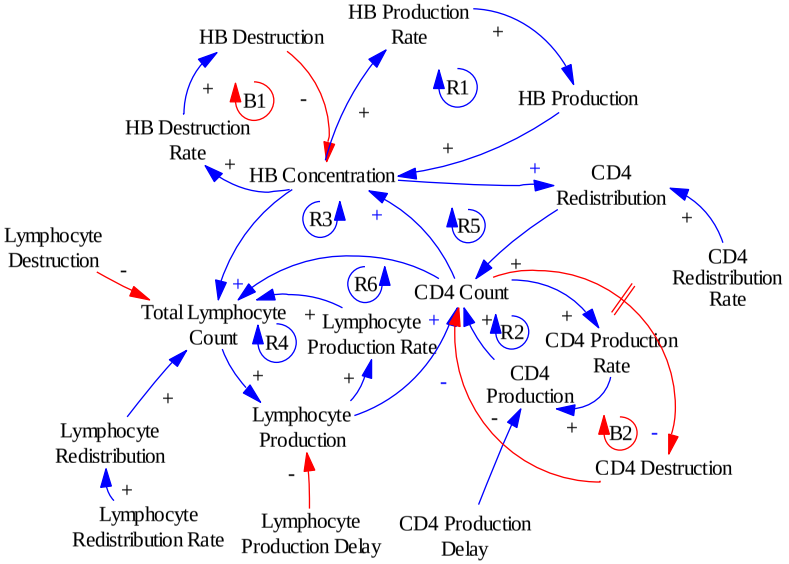
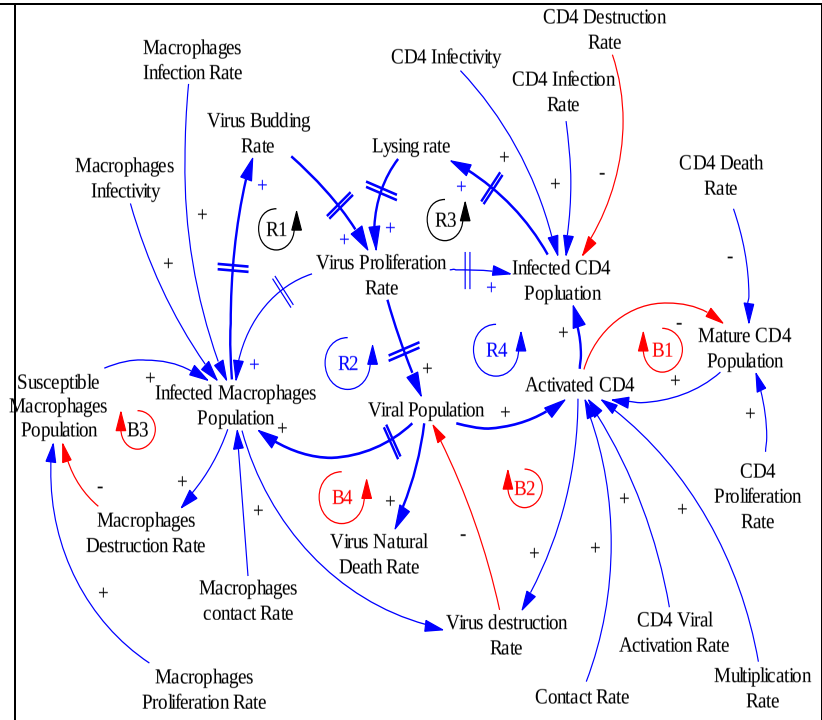


Figure 1: A descriptive model showing the most important variables that affect Trio-HMT

No.	Causal Link	Qualitative Verbal statement of the hypothesis generated
1	**Immune Section**	
		The Reinforcing Loop R1 refers to Hemoglobin generation (HB) production; An increase in HB concentration will cause an increase in HB production rate. An increase in production rate of HB will cause an increased production of HB which is directly proportional to HB concentration. The Loop Balancing B1 refers to regulation of HB. An increase in HB will increase the HB death rate/destruction rate. An increase in HB destruction rate will increase HB destruction which is inversely proportional to HB concentration. Reinforcing Loop R2 called CD4 production means that; increased CD4 count is directly proportional to CD4 production and CD4 production is also directly proportional to CD4 count Balancing Loop B2 referred to as CD4 regulation means that increased CD4 count is inversely proportional to CD4 destruction. Reinforcing Loop R3 means that HB Concentration is direction proportional to Total Lymphocyte Count (TLC) which is directly proportional to Lymphocyte production which is directly proportional to CD4 count which is directly proportional to HB concentration Reinforcing Loop R4 is the production loop for TLC. Increased TLC is directly proportional to LC production rate which is also directly

	proportional to LC production Reinforcing Loop R5 refers to the Redistribution loop. Increased HB concentration enhances CD4 production which is directly proportional to CD4 count. CD4 Redistribution is directly affected by CD4 Redistribution rate Reinforcing Loop R6 refers to Increased TLC being directly proportional to TC production which is directly related to CD4 count Lymphocyte Destruction/death is inversely proportional to TLC Lymphocyte Redistribution rate in directly proportional to Lymphocyte Redistribution which is directly proportional to TLC **Question:** From your experience are the said relationships as claimed exist in the professional practice?	
2	**HIV Section**	



The Reinforcing Loop R1 is referred to as Budding due to Macrophages. It means that as more macrophages become infected with the virus, more virus buds with the macrophages and over time buds to increase virus proliferation rate.

Infected Macrophages are direct proportionally affected by macrophages infection rate and infectivity.

Reinforcing Loop R2 is called Virus production by Macrophages. It shows that More virus population leads to infection of Macrophages which over time buds and affects virus proliferation rate which has a direct relationship with Viral population

The Balancing Loop B3 called Macrophages infection loop. It means that as more Macrophages become infected, More Macrophages becomes destructed by the virus or by the Activated CD4 cells which is inversely proportional to the entire population of the Macrophages.

Susceptible Macrophages are directly proportional related to Macrophages production rate.

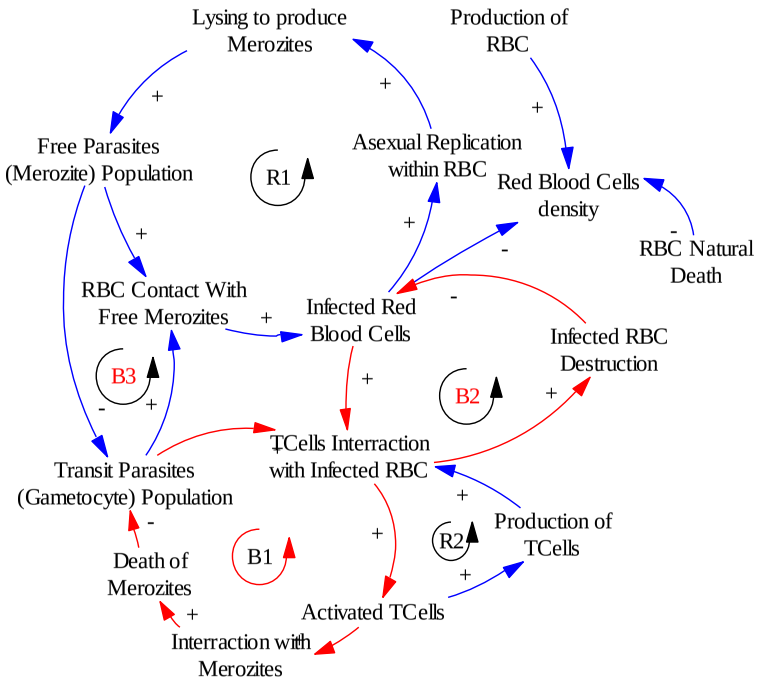
Infected Macrophages population is directly proportional affected by Macrophages contact rate with the free virus.

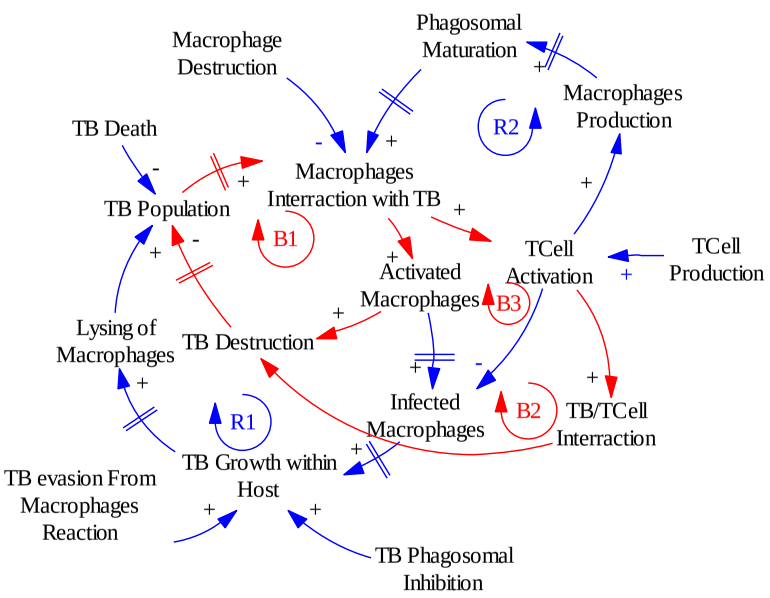
Balancing Loop B4 called Virus Regulation by Infected Macrophages refers to the fact that as more Macrophages become into contact with the Virus, More viruses are destroyed and this reduction is inversely proportional to virus population

Virus population is directly proportional to virus natural death rate.

Reinforcing Loop R3 called Proliferation of Viruses due to CD4 cells infection. Means that as more CD4 becomes infected, viral DNA reproduces with the CD4 cell and over time lyses to increase the virus

	proliferation rate. Reinforcing Loop R4 is called Virus production by Infected CD4. It shows that More virus population leads to interaction with activated CD4 cells. This results in either death of virus or infection of CD4 cells, whose infection over time causes lysing of the virus leading to increased proliferation of the virus Infected CD4 is directly proportional to CD4 infectivity and Infection rate and inversely related to CD4 destruction rate **Question:** From your experience are the said relationships as claimed exist in the professional practice?	
		3 **Malaria Section**

		Infected Red Blood Cells are directly proportional to Red Blood Cells density and Red Blood Cells density is directly proportional to RBC natural death as well as their production The Reinforcing structure R1 among Lysing to produce merozites, free parasite production, Red Blood Cells (RBC) contact with merozites, infected RBC and asexual replication with RBC may lead to an exponential growth or decay i.e. may not be controllable and may lead to anemic condition The Reinforcing Loop R2 involving interrelationship of TCells interaction with Activated TCells and these with production of TCells will lead to exponential growth of TCells production which may be uncontrollable or infinite The Balancing Feedback structure can be explained as follows 1) B1: This is goal seeking meaning the Merozites interaction, their death, and interaction with TCells may result in a steady state where the merozites will be eliminated from the body. 2) B2: This is also goal seeking and may result in a steady state when all infected red blood cells are eliminated by Activated TCells 3) B3: This balancing loop means that merozites interrelationship with RBC cells may reach a steady state when all Red Blood Cells are eliminated and therefore no more cells to feed the parasites. **Question:** From your experience are the said relationships as claimed exist in the professional practice?
4	**Tuberculosis Section**	



The Reinforcing Feedback structure can be explained as follows

1) R1: Tubercle Bacilli, the bacterium responsible for the causation of TB gradually grows within the host and as it continues to develop and lysing and subsequently destroy the macrophages, it may reach uncontrollable levels or steady state where all the macrophages finished.
2) R2: This structure signifies production of Macrophages and their maturation. This means that the process continues to be amplified as long as there are infected macrophages.

The Balancing Feedback structure can be explained as follows:

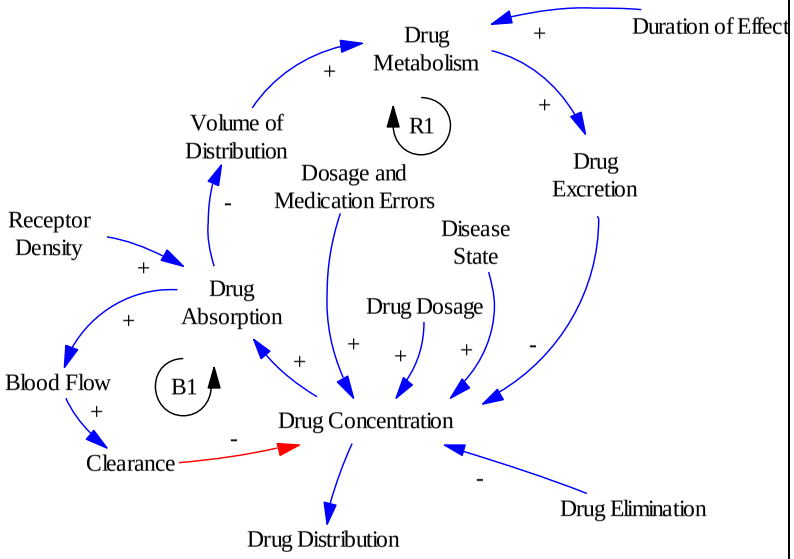
1) B1: This structure involves production and destruction of TB as well as infected macrophages by the macrophages on one hand and natural death on the other hand hence will reach a steady state at some point
2) B2: This goal searching feedback loop relates Free TB cells destruction by the Activated TCells and will reach a steady point at some point
3) B3: Also a goal searching Feedback loop involving the elimination of infected macrophages by the activated TCells

Other than the above Feedback loops, there is a direct proportional relationship involving an increase in TB Growth within host and TB evasion from Macrophages reaction as well as TB Phagosomal inhibition

Macrophages Interaction with Macrophage is a direct proportional relationship.

TB Population and TB death are directly proportional related and the same with TCells production and Activation.

Question: From your experience are the said relationships as claimed exist in the professional practice?

5	**Toxicity Module**	
		The Reinforcing Feedback structure (R1) is that involving amplification of Drug intake, metabolism and excretion which in this case is showing exponential growth leading to toxication or decay leading to complete removal from the body. There is also direct proportional relationship with drug concentration increase and that of drug dosage, dosage medication errors as well as disease state which is relation to physiological factors like age as well as drug elimination and drug distribution. The Balancing Feedback Structure B1 is a goal seeking where drug are cleared from the body and will reach a steady state at some point. **Question:** From your experience are the said relationships as claimed exist in the professional practice?

Evaluation of the Trio-HMT Descriptive Model

1) Are all the variables in the descriptive Model relevant in the Trio-HMT?

◉ Strongly Agree ○ Agree ○ Neutral ○ Disagree ○ Strongly disagree

2) In your own opinion which of the variables are key to Trio-HMT? (Please tick () as many as possible)

a) TB Infecteds ☒
b) Malaria Infecteds ☒
c) HIV Infecteds ☐
d) Treatment ☐

e) Toxicity ☐

3) Are there significant variables that you think are missing in the Trio-HMT? (Please state as many variables as possible)

a) _____

b) _____

c) _____

d) _____

e) _____

f) _____

4) Please rank the following variables in order of importance for Trio-HMT including variables in question FOUR if any

a. TB Infecteds ☐

b. Malaria Infecteds ☒

c. HIV Infecteds ☒

d. Treatment ☐

e. Toxicity ☐

f. _____ ☐

g. _____ ☐

h. _____ ☐

i. _____ ☐

j. _____ ☐

k. _____ ☐

5) Do the claims as explained in the descriptive model in figure 1 exist in your professional practices?

6) The Feedback loops B1, B2, R1, and R2 identified in the descriptive model are considered to be important loops that drive Trio-HMT. Do you have a different perspective?

7) Does the descriptive model as whole represent realistic interrelationship in the Trio-HMT process? Please explain.

8) Please give any comments on any piece of work that have not been addressed.

Appendix B

Model Equations

HIV Sector

Free_virus__Pop(t) = Free_virus__Pop(t - dt) + (virus_multiplying__in_APC + virus_multiplying__in_TH - virus_dying_of_IgG - virus_dying) * dt
INIT Free_virus__Pop = 1
UNITS: virions

INFLOWS:

- virus_multiplying__in_APC = APC_dying*APC_lysing_rate-eliminating_arv*virions_death__per_dosage
  UNITS: virions/day
- virus_multiplying__in_TH = dying_TH1*TH_lysing_rate-virions_death__per_dosage*eliminating_arv
  UNITS: virions/day

OUTFLOWS:

- virus_dying_of_IgG = IgG*death_rate_per_IgG
  UNITS: virions/day
- virus_dying = CTL_Cells*death_rate_per__CTL
  UNITS: virions/day

eliminating_antiTB = AntiTB_Drug_in__Bloodstream*antiTB_elimination__Constant
UNITS: mg/day
OUTFLOW FROM: AntiTB_Drug_in__Bloodstream (IN SECTOR: Treatment Sector)

APC_lysing_rate = 1000
UNITS: Virions/cells

death_rate_per_IgG = 0.0001
UNITS: virions/mg/day

death_rate_per__CTL = 0.005
UNITS: virions/cells/day

TH_lysing_rate = 100
UNITS: Virions/cells

virions_death__per_dosage = 0.001
UNITS: virions/mg

HTM Sector

CD4__count(t) = CD4__count(t - dt) + (treatment + self_replication - normal_dying - reducing_due_to__RBC_inf - reducing_due_to__actd_TH1 - reducing_due_to__MTB_inf) * dt
INIT CD4__count = Resting_APC+Resting__TH1_Cells+Actd_TH1__Cells+Actd__APC
UNITS: Cells

INFLOWS:

- treatment = status/time_to_reco
  UNITS: Cells/day
- self_replication = smth1(poisson(immune_Gap*cd4_replic/INIT(cd4_replic),123),1)
  UNITS: Cells/day

OUTFLOWS:

- normal_dying = CD4__count*dying_rate
  UNITS: Cells/day
- reducing_due_to__RBC_inf = RBC__Infection*CD4_per_RBC
  UNITS: Cells/day

reducing_due_to__actd_TH1 = replica_per__actvn*virus_multiplying__in_TH
UNITS: Cells/day

reducing_due_to__MTB_inf = MTB_multiplying*MTB_per_CD4
UNITS: Cells/day

average_med = SMTH1(POISSON(medication,123),time_to_reco)

cd4_gap = desired_cd4_level-CD4__count

desired_cd4_level = 350

desired_immune_level = 500

dying_rate = 2

immune_Gap = smth1(desired_immune_level-CD4__count,1)

medication = arv_Dosage + antiMalaria__Dosage + antiTB_Dosage

status = average_med+cd4_gap

time_to_reco = 1

CD4_per_RBC = GRAPH(TIME)
(0.00, 0.00), (6.00, 2.00), (12.0, 3.00), (18.0, 5.00), (24.0, 9.50), (30.0, 16.5), (36.0, 27.0), (42.0, 60.5), (48.0, 88.0), (54.0, 95.5), (60.0, 99.0)
UNITS: cells/cells

cd4_replic = GRAPH(TIME)
(0.00, 1.00), (6.00, 3.00), (12.0, 9.00), (18.0, 19.5), (24.0, 39.5), (30.0, 100), (36.0, 81.0), (42.0, 61.0), (48.0, 41.5), (54.0, 19.5), (60.0, 0.00)

MTB_per_CD4 = GRAPH(TIME)
(0.00, 1.00), (6.00, 2.00), (12.0, 4.50), (18.0, 10.0), (24.0, 18.5), (30.0, 31.5), (36.0, 56.5), (42.0, 72.0), (48.0, 83.0), (54.0, 91.5), (60.0, 97.0)
UNITS: cells/Parasites

replica_per__actvn = GRAPH(TIME)
(0.00, 0.5), (6.00, 0.5), (12.0, 1.00), (18.0, 2.00), (24.0, 4.00), (30.0, 6.50), (36.0, 9.50), (42.0, 14.5), (48.0, 25.5), (54.0, 50.5), (60.0, 94.5)
UNITS: cells/Virions

Immune Sector

Actd_TH1__Cells(t) = Actd_TH1__Cells(t - dt) + (activating_TH1 + replicating_self - TH1_Infection) * dt
INIT Actd_TH1__Cells = 0
UNITS: Cells

INFLOWS:

activating_TH1 =
RBC__Infection*TH1_cells_per_RBC_infection+virus_multiplying__in_APC*TH1_cells_per_APC+TH1_cells_per_virus*virus_multiplying__in_TH-IL10_activation_fraction*IL10__Cytokine-IL4*TH1_per_IL4
UNITS: Cells/day

replicating_self = Actd_TH1__Cells*TH1_Proli_Strength
UNITS: Cells/day

OUTFLOWS:

TH1_Infection = virus_dying*HIV_infectivity-absorbing_arv*TH1_per_ARV*Infd_TH1__Cells
UNITS: Cells/day

Actd__APC(t) = Actd__APC(t - dt) + (activating_APC - APC_Infection_Rate) * dt
INIT Actd__APC = 0
UNITS: Cells

INFLOWS:
- activating_APC = APC_activation__per_MTB*MTB_multiplying+APC_activation__per_virus*virus_multiplying__in_APC +activated_APC_per_IFNg_secretion*IFNg_Secretion
  UNITS: Cells/day

OUTFLOWS:
- APC_Infection_Rate = Infectivity_by_MTB*TB_parasites_dying
  UNITS: Cells/day

CTL_Cells(t) = CTL_Cells(t - dt) + (producing_CTL - CTL_Death) * dt
INIT CTL_Cells = 10
UNITS: Cells

INFLOWS:
- producing_CTL = IL2__Cytokine*IL2_productivity+activating_TH1*CTL_per_activated_TH1
  UNITS: Cells/day

OUTFLOWS:
- CTL_Death = CTL_Cells/CTL_Time_to_Live
  UNITS: Cells/day

IFNg(t) = IFNg(t - dt) + (IFNg_Secretion - IFNg_Clearance - IFNg_TReg_Control) * dt
INIT IFNg = 0
UNITS: mg

INFLOWS:
- IFNg_Secretion = if(Actd_TH1__Cells <=0 or NK_Cells<=0) then 0 else (Actd_TH1__Cells*Activated_TH1__Secr_Fraction+NK_Cells*IFNg_and_NK_Secretion_Fraction)/IFNg_Time_to__Secrete
  UNITS: mg/day

OUTFLOWS:
- IFNg_Clearance = IFNg*Probability_of_Contact_Between_MTB_and_IFNg/IFNg_Time_to_clear
  UNITS: mg/day
- IFNg_TReg_Control = DELAY(Treg*Treg_Control_Frac/TReg_IFNg__Control_Time,1)
  UNITS: mg/day

IgG(t) = IgG(t - dt) + (Producing_IGg - clearing_IGg) * dt
INIT IgG = 10
UNITS: mg

INFLOWS:
- Producing_IGg = TH2*TH2_Productivity
  UNITS: mg/day

OUTFLOWS:
- clearing_IGg = Treg/IgG_Time_to_Clear*IGg_Clearance__Rate
  UNITS: mg/day

IL10__Cytokine(t) = IL10__Cytokine(t - dt) + (TH2_secreting_IL10 + Treg_Secreting_IL10) * dt
INIT IL10__Cytokine = 10
UNITS: mg

INFLOWS:
- TH2_secreting_IL10 = TH2*IL10_secretion_rate_by_TH2
  UNITS: mg/day
- Treg_Secreting_IL10 = Treg*IL10_secretion_rate_by__Treg
  UNITS: mg/day

IL12_Cytokine(t) = IL12_Cytokine(t - dt) + (secreting_IL12 - IL12_clearing) * dt
INIT IL12_Cytokine = 10
UNITS: mg
INFLOWS:
secreting_IL12 = Actd__APC*IL12_secretion
UNITS: mg/day
OUTFLOWS:
IL12_clearing = Treg*IL12_clearance_frac_of_Treg
UNITS: mg/day

IL2__Cytokine(t) = IL2__Cytokine(t - dt) + (secreting_IL2) * dt
INIT IL2__Cytokine = 10
UNITS: mg
INFLOWS:
secreting_IL2 = Actd_TH1__Cells*Actd_TH1_Secretions+actd_APC_IL12__production_rate*Actd__APC
UNITS: mg/day

IL4(t) = IL4(t - dt) + (NK_cells_Secreting_IL4 + secreting_IL4 - IL4_clearance) * dt
INIT IL4 = 10
UNITS: mg
INFLOWS:
NK_cells_Secreting_IL4 = NK_Cells*IL4_Secretion_by_NK_cells
UNITS: mg/day
secreting_IL4 = TH2*IL4_Secretion_by_TH2
UNITS: mg/day
OUTFLOWS:
IL4_clearance = Treg*IL4_per_Treg_cells
UNITS: mg/day

IL6_Cytokine(t) = IL6_Cytokine(t - dt) + (secreting_IL6 - IL6_Clearance) * dt
INIT IL6_Cytokine = 10
UNITS: mg
INFLOWS:
secreting_IL6 = Actd__APC*il6_secretion
UNITS: mg/day
OUTFLOWS:
IL6_Clearance = if(IL6_Cytokine<=0) then 0 else Treg*Treg_Clearance__Frac/IL6_Clearance__time
UNITS: mg/day

Infd_TH1__Cells(t) = Infd_TH1__Cells(t - dt) + (TH1_Infection - dying_TH1 - apoptosis_of_TH1) * dt
INIT Infd_TH1__Cells = 1
UNITS: Cells
INFLOWS:
TH1_Infection = virus_dying*HIV_infectivity-absorbing_arv*TH1_per_ARV*Infd_TH1__Cells
UNITS: Cells/day
OUTFLOWS:
dying_TH1 = CTL_Cells/CTL_Time_to_Destroy
UNITS: Cells/day

apoptosis_of_TH1 = Infd_TH1__Cells/TH1_Time_to_Live
UNITS: Cells/day

Infected__APC(t) = Infected__APC(t - dt) + (APC_Infection_Rate + viral_Impact - APC_dying) * dt
INIT Infected__APC = 0
UNITS: Cells
DOCUMENT: Infected Antigen Presenting Cells whose units are {cells per mL}

INFLOWS:

APC_Infection_Rate = Infectivity_by_MTB*TB_parasites_dying
UNITS: Cells/day

viral_Impact = Infectivity_by_HIV*virus_multiplying__in_APC
UNITS: Cells/day

OUTFLOWS:

APC_dying = NK_Secreting_TNF*death_due_to_TNF
UNITS: Cells/day
DOCUMENT: APC Destruction is the rate at which Antigen Presenting Cells are Destroyed and Units are cells per mL per day

NK_Cells(t) = NK_Cells(t - dt) + (NK_Multiplication) * dt
INIT NK_Cells = 100
UNITS: Cells

INFLOWS:

NK_Multiplication =

GRAPH(IL2__Cytokine*IL12_rate_of_replicating_NK_cells+NK_Cells*NK_self_multiplication_rate)
(0.00, 1.50), (10.0, 2.00), (20.0, 5.00), (30.0, 10.0), (40.0, 19.0), (50.0, 27.0), (60.0, 42.5), (70.0, 69.0), (80.0, 88.5), (90.0, 97.0), (100, 99.5)
UNITS: Cells/day

Resting_APC(t) = Resting_APC(t - dt) + (- activating_APC) * dt
INIT Resting_APC = 10000
UNITS: Cells

OUTFLOWS:

activating_APC =
APC_activation__per_MTB*MTB_multiplying+APC_activation__per_virus*virus_multiplying__in_APC
+activated_APC_per_IFNg_secretion*IFNg_Secretion
UNITS: Cells/day

Resting__TH1_Cells(t) = Resting__TH1_Cells(t - dt) + (Polarization_to_TH1 - activating_TH1) * dt
INIT Resting__TH1_Cells = 100000
UNITS: Cells

INFLOWS:

Polarization_to_TH1 =
Contact_ratio_between_IL12_and_TH1+IL6_Cytokine*IL6_polarization_rate-IL4*IL4_polarization__rat
e
UNITS: Cells/day

OUTFLOWS:

activating_TH1 =
RBC__Infection*TH1_cells_per_RBC_infection+virus_multiplying__in_APC*TH1_cells_per_APC+TH1
_cells_per_virus*virus_multiplying__in_TH-IL10_activation_fraction*IL10__Cytokine-IL4*TH1_per_IL4
UNITS: Cells/day

TH(t) = TH(t - dt) + (- Polarization_to_TH1 - producing_CTL - Polarization_of_Treg - Polarization_of_TH2) * dt
INIT TH = 1000
UNITS: Cells

OUTFLOWS:
- Polarization_to_TH1 = Contact_ratio_between_IL12_and_TH1+IL6_Cytokine*IL6_polarization_rate-IL4*IL4_polarization__rate
  UNITS: Cells/day
- producing_CTL = IL2__Cytokine*IL2_productivity+activating_TH1*CTL_per_activated_TH1
  UNITS: Cells/day
- Polarization_of_Treg = IFNg*cells_per_IFNg
  UNITS: Cells/day
- Polarization_of_TH2 = Contact_Between_IL4_&_TH2+Contact_Fraction_between_IL2_and_TH2+IL6_Cytokine*IL6_to_TH2_polarization__rate
  UNITS: Cells/day

TH2(t) = TH2(t - dt) + (Polarization_of_TH2 + IL2_activating_TH2_Replication - TH2_Removal) * dt
INIT TH2 = 0
UNITS: Cells

INFLOWS:
- Polarization_of_TH2 = Contact_Between_IL4_&_TH2+Contact_Fraction_between_IL2_and_TH2+IL6_Cytokine*IL6_to_TH2_polarization__rate
  UNITS: Cells/day
- IL2_activating_TH2_Replication = IL2__Cytokine*IL2_generating_replica
  UNITS: Cells/day

OUTFLOWS:
- TH2_Removal = if(TH2<=0) then 0 else Treg/TH2_Time_to_Live
  UNITS: Cells/day

TNF(t) = TNF(t - dt) + (NK_Secreting_TNF + Actd_TH1_secreting_TNF) * dt
INIT TNF = 10
UNITS: mg

INFLOWS:
- NK_Secreting_TNF = NK_Cells*TNF_secretion_by_NK_cells
  UNITS: mg/day
- Actd_TH1_secreting_TNF = Actd_TH1__Cells*TNF_secretion_by_Actd_TH1
  UNITS: mg/day

Treg(t) = Treg(t - dt) + (Polarization_of_Treg) * dt
INIT Treg = 200
UNITS: Cells

INFLOWS:
- Polarization_of_Treg = IFNg*cells_per_IFNg
  UNITS: Cells/day

actd_APC_IL12__production_rate = 10
UNITS: mg/cells/day

- Actd_TH1_Secretions = 1
  UNITS: mg/cells/day
- APC_activation__per_MTB = .8
  UNITS: cells/Parasites
- APC_activation__per_virus = 0.5
  UNITS: cells/Virions
- cells_per_IL12 = 1
  UNITS: Cells/mg/day
- Contact_Between_IL4_&_TH2 =
  Expected_IL4_and__TH2_Cont*IL4_and_TH2__Ratio*IL4_to_TH2_conversion_Multiplier
  UNITS: Cells/day
- Contact_ratio_between_IL12_and_TH1 = cells_per_IL12*IL12_Cytokine
  UNITS: Cells/day
- CTL_per_activated_TH1 = 1
  UNITS: Unitless
- CTL_Time_to_Destroy = 1
  UNITS: day
- CTL_Time_to_Live = 1
  UNITS: day
- death_due_to_TNF = 0.5
  UNITS: cells/mg
- Expected_IL4_and__TH2_Cont = IL4*IL4_Contact_Freq_with_TH2
  UNITS: Cells/day
- HIV_infectivity = 0.85
  UNITS: cells/Virions
- IFNg_Time_to_clear = 1
  UNITS: day
- IFNg_Time_to__Secrete = 1
  UNITS: day
- IGg_Clearance__Rate = 0.005
  UNITS: mg/cells
- IgG_Time_to_Clear = 1
  UNITS: day
- IL10_secretion_rate_by_TH2 = 0.05
  UNITS: mg/cells/day
- IL10_secretion_rate_by__Treg = 0.003
  UNITS: mg/cells/day
- IL12_clearance_frac_of_Treg = 1
  UNITS: mg/cells/day
- IL12_rate_of_replicating_NK_cells = 10
  UNITS: Cells/mg/day
- IL2_generating_replica = 1
  UNITS: Cells/mg/day
- IL4_and_TH2__Ratio = if(IL4=0 and TH2=0) then 0 else TH2/IL4
  UNITS: cells/mg
- IL4_Contact_Freq_with_TH2 = 2
  UNITS: Cells/mg/day

- IL4_per_Treg_cells = 1
  UNITS: mg/cells/day
- IL4_polarization__rate = 100
  UNITS: Cells/mg/day
- IL4_Secretion_by_NK_cells = 1
  UNITS: mg/cells/day
- IL4_Secretion_by_TH2 = 0.075
  UNITS: mg/cells/day
- IL4_to_TH2_conversion_Multiplier = 1
  UNITS: mg/cells
- IL6_Clearance__time = 1
  UNITS: day
- IL6_polarization_rate = 10
  UNITS: Cells/mg/day
- il6_secretion = 1
  UNITS: mg/cells/day
- Infectivity_by_HIV = 0.05
  UNITS: cells/Virions
- Infectivity_by_MTB = 0.0625
  UNITS: cells/Parasites
- NK_self_multiplication_rate = 2
  UNITS: Cells/day
- TH1_cells_per_APC = 1
  UNITS: cells/Virions
- TH1_cells_per_RBC_infection = 1
  UNITS: Unitless
- TH1_cells_per_virus = 1
  UNITS: cells/Virions
- TH1_per_ARV = 0.02
  UNITS: cells/mg
- TH1_per_IL4 = 1
  UNITS: Cells/mg/day
- TH1_Proli_Strength = 0.045
  UNITS: Cells/Cells/day
- TH1_Time_to_Live = 3
  UNITS: day
- TH2_Productivity = 0.05
  UNITS: mg/cells/day
- TH2_Time_to_Live = 1
  UNITS: day
- TNF_secretion_by_Actd_TH1 = 1
  UNITS: mg/cells/day
- TNF_secretion_by_NK_cells = 1
  UNITS: mg/cells/day
- TReg_IFNg__Control_Time = 1
  UNITS: day

activated_APC_per_IFNg_secretion = GRAPH(IFNg)

(0.00, 1.00), (10.0, 1.50), (20.0, 4.00), (30.0, 7.50), (40.0, 13.5), (50.0, 20.5), (60.0, 28.5), (70.0, 39.5), (80.0, 49.5), (90.0, 69.5), (100, 95.0)
UNITS: cells/mg

Activated_TH1__Secr_Fraction = GRAPH(TIME)

(0.00, 0.00), (10.0, 1.00), (20.0, 2.00), (30.0, 5.00), (40.0, 8.50), (50.0, 13.5), (60.0, 21.5), (70.0, 31.5), (80.0, 46.0), (90.0, 69.5), (100, 99.5)
UNITS: mg/cells

cells_per_IFNg = GRAPH(TIME)

(0.00, 1.50), (6.00, 1.50), (12.0, 3.50), (18.0, 6.00), (24.0, 10.0), (30.0, 15.5), (36.0, 25.0), (42.0, 38.5), (48.0, 53.5), (54.0, 71.0), (60.0, 97.5)
UNITS: Cells/mg/day

Contact_Fraction_between_IL2_and_TH2 = GRAPH(IL2__Cytokine)

(0.00, 0.00), (10.0, 1.50), (20.0, 4.00), (30.0, 6.50), (40.0, 10.0), (50.0, 13.5), (60.0, 21.5), (70.0, 35.0), (80.0, 49.0), (90.0, 70.0), (100, 99.5)
UNITS: Cells/day

IFNg_and_NK_Secretion_Fraction = GRAPH(TIME)

(0.00, 0.00), (10.0, 1.00), (20.0, 2.50), (30.0, 4.50), (40.0, 8.50), (50.0, 13.0), (60.0, 20.0), (70.0, 29.5), (80.0, 43.5), (90.0, 63.0), (100, 99.5)
UNITS: mg/cells

IL10_activation_fraction = GRAPH(TIME)

(0.00, 1.50), (10.0, 10.5), (20.0, 20.0), (30.0, 29.5), (40.0, 40.5), (50.0, 49.5), (60.0, 60.0), (70.0, 70.0), (80.0, 80.5), (90.0, 90.0), (100, 99.5)
UNITS: Cells/mg/day

IL12_secretion = GRAPH(TIME)

(0.00, 1.00), (10.0, 2.00), (20.0, 3.50), (30.0, 6.00), (40.0, 10.0), (50.0, 15.0), (60.0, 21.0), (70.0, 30.5), (80.0, 42.5), (90.0, 62.0), (100, 98.0)
UNITS: mg/cells/day

IL2_productivity = GRAPH(TIME)

(0.00, 2.50), (12.0, 3.00), (24.0, 5.00), (36.0, 7.50), (48.0, 12.0), (60.0, 19.5), (72.0, 27.0), (84.0, 38.5), (96.0, 53.0), (108, 73.0), (120, 97.5)
UNITS: Cells/mg/day

IL6_to_TH2_polarization__rate = GRAPH(TIME)

(0.00, 1.00), (12.0, 10.0), (24.0, 20.5), (36.0, 29.5), (48.0, 39.5), (60.0, 49.5), (72.0, 59.0), (84.0, 69.5), (96.0, 79.5), (108, 90.5), (120, 99.5)
UNITS: Cells/mg/day

Treg_Clearance__Frac = GRAPH(TIME)

(0.00, 0.00), (10.0, 1.50), (20.0, 3.50), (30.0, 6.00), (40.0, 11.0), (50.0, 19.5), (60.0, 32.0), (70.0, 62.5), (80.0, 78.0), (90.0, 86.5), (100, 91.0)
UNITS: mg/cells

Treg_Control_Frac = GRAPH(TIME)

(0.00, 0.00), (10.0, 1.50), (20.0, 5.50), (30.0, 12.0), (40.0, 24.5), (50.0, 40.0), (60.0, 67.5), (70.0, 82.5), (80.0, 89.5), (90.0, 92.5), (100, 93.0)
UNITS: mg/cells

Malaria Sector

Immature__Sporozoites(t) = Immature__Sporozoites(t - dt) + (immature_parasites_multiplying - aging_sporozoites) * dt
INIT Immature__Sporozoites = 1000
TRANSIT TIME = 5
INFLOW LIMIT = INF
CAPACITY = INF
UNITS: Parasites

INFLOWS:
- immature_parasites_multiplying(i) = immature_parasites_multiplying(o) * CONVERSION MULTIPLIER
  CONVERSION MULTIPLIER = 10
  UNITS: Cells/day

OUTFLOWS:
- aging_sporozoites = CONVEYOR OUTFLOW
  UNITS: parasites/day

Infected_RBC(t) = Infected_RBC(t - dt) + (RBC__Infection - RBC_Death) * dt
INIT Infected_RBC = 0
UNITS: Cells

INFLOWS:
- RBC__Infection = Infectivity*Merozoites_Clearance
  UNITS: Cells/day

OUTFLOWS:
- RBC_Death = delay(CTL_Cells/CTL_time_to_destroy__RBC+Infected_RBC/Infected_RBC_time__to_Live,15)
  UNITS: Cells/day

Merozoites_Pop(t) = Merozoites_Pop(t - dt) + (aging_sporozoites + merozoites_entering_from_Innfected_RBC - Merozoites_Clearance) * dt
INIT Merozoites_Pop = 0
UNITS: Parasites

INFLOWS:
- aging_sporozoites = CONVEYOR OUTFLOW
  UNITS: parasites/day
- merozoites_entering_from_Innfected_RBC = RBC_Death*Lysing_RBC
  UNITS: parasites/day

OUTFLOWS:
- Merozoites_Clearance = Contacts_btn_TNF___and_Merozoites*Merozoites_Destr__Frac_by_TNF+Contact_Between__Merozoites_and_APC*Destruction_by_Activated_APC+eliminating_antiMalaria*antimalaria_per_merozoites*Merozoites_Pop
  UNITS: parasites/day

RBC_Pop(t) = RBC_Pop(t - dt) + (RBC_Multiplication - RBC__Infection) * dt
INIT RBC_Pop = 300
UNITS: Cells

INFLOWS:
- RBC_Multiplication = avg_RBC_count/time_to_multiply
  UNITS: Cells/day

OUTFLOWS:

RBC__Infection = Infectivity*Merozoites_Clearance
UNITS: Cells/day

Susceptible_HPC(t) = Susceptible_HPC(t - dt) + (- immature_parasites_multiplying) * dt
INIT Susceptible_HPC = Total_HPC
UNITS: Cells
OUTFLOWS:
immature_parasites_multiplying(o) = Contacts_between__Sporozoites_and_HPC*HPC_to_Parasites__converter
UNITS: Cells/day

acceptable_cell_count = 1500
UNITS: Cells

antimalaria_per_merozoites = 0.01
UNITS: Parasites/mg

APC_to_Merozoites_multiplier = 1
UNITS: Cells/day

avg_RBC_count = smth1(RBC_gap,123)
UNITS: Cells

Contacts_between__Sporozoites_and_HPC = Susceptible_HPC__Contacts*Probability_of_contacts_Between_HPC_and_Sporozoites
UNITS: parasites/day

Contacts_btn_TNF___and_Merozoites = Merozoites_Pop/TNF
UNITS: Parasites/mg

Contacts_Freq = 0.25
UNITS: Parasites/Cells/day

Contact_Between__Merozoites_and_APC = if(Actd__APC<=0) then 0 else Merozoites_Pop/Actd__APC*APC_to_Merozoites_multiplier
UNITS: parasites/day

CTL_time_to_destroy__RBC = 1
UNITS: day

Destruction_by_Activated_APC = 0.025
UNITS: Unitless

HPC_to_Parasites__converter = 0.75
UNITS: cells/Parasites

Infected_RBC_time__to_Live = 0.001
UNITS: day

Infectivity = 0.05
UNITS: cells/Parasites

Lysing_RBC = 1
UNITS: Parasites/cells

Merozoites_Destr__Frac_by_TNF = 0.01
UNITS: mg/day

Probability_of_contacts_Between_HPC_and_Sporozoites = Immature__Sporozoites/Total_HPC*Sporozoites_Infectivity
UNITS: Unitless

RBC_gap = acceptable_cell_count-RBC_Pop
UNITS: Cells

- Sporozoites_Infectivity = 1
  UNITS: cells/Parasites
- Susceptible_HPC__Contacts = Susceptible_HPC*Contacts_Freq
  UNITS: parasites/day
- time_to_multiply = 86400
  UNITS: day
- Total_HPC = 350000
  UNITS: Cells

TB Sector

- MTB(t) = MTB(t - dt) + (MTB_multiplying - MTB_Natural_Death - TB_parasites_dying) * dt
  INIT MTB = 1000
  UNITS: Parasites
  INFLOWS:
  - MTB_multiplying = Contacts_Between__APC_and_MTB*MTB_Infectivity
    UNITS: parasites/day

  OUTFLOWS:
  - MTB_Natural_Death = (MTB/MTB_Time_to_Live)/init(MTB)+antiTB_per_MTB*eliminating_antiTB
    UNITS: parasites/day
  - TB_parasites_dying = (Contact_Between_MTB_and_IFNg+Contact_Between__MTBand_IgG)/init(Contact_Between__MTB and_IgG)
    UNITS: parasites/day
- antiTB_per_MTB = .693/16
- APC_Contacts__Freq = 0.01
- APC_to_MTB_multiplier = 1
- Contacts_Between__APC_and_MTB = Probability_of_Contact__Between_MTB_and_APC*Suscepticle_APC_Contacts_With_MTB
- Contact_Between_MTB_and_IFNg = Probability_of_Contact_Between_MTB_and_IFNg*Susceptible_MTB_Contacts_with_IFNg*IFNg_Efficacy
  UNITS: parasites/day
- Contact_Between__MTBand_IgG = Probability_of_Contact_Between_IgG_and_MTB*Susceptible_MTB__contacts_with_IgG*IgG_Efficacy
  UNITS: parasites/day
- IFNg_Contacts__freq_with_MTB = 0.8
  UNITS: parasites/mg/day
- IFNg_Efficacy = 0.075
  UNITS: Unitless
- IFNg_to_MTB__constant = 1
  UNITS: mg/parasites
- IgG_Contacts_freq_with_MTB = 0.25
  UNITS: parasites/mg/day
- IgG_Efficacy = 0.025
  UNITS: Unitless
- MTB_Infectivity = 0.0125
- MTB_Time_to_Live = 15
  UNITS: day

- MTB_to_IGg_Multiplier = 1
  UNITS: mg/parasites
- Probability_of_Contact_Between_IgG_and_MTB = if(IgG=0 or MTB=0) then 0 else MTB/IgG*MTB_to_IGg_Multiplier
  UNITS: Unitless
- Probability_of_Contact_Between_MTB_and_IFNg = if(IFNg=0 or MTB=0) then 0 else MTB/IFNg*IFNg_to_MTB__constant
  UNITS: Unitless
- Probability_of_Contact__Between_MTB_and_APC = if(MTB=0) then 0 else Resting_APC/MTB*APC_to_MTB_multiplier
- Susceptible_MTB_Contacts_with_IFNg = IFNg*IFNg_Contacts__freq_with_MTB
  UNITS: parasites/day
- Susceptible_MTB__contacts_with_IgG = IgG*IgG_Contacts_freq_with_MTB
  UNITS: parasites/day
- Suscepticle_APC_Contacts_With_MTB = Resting_APC*APC_Contacts__Freq

Treatment Sector

- antiMalaria_Drug_in__Bloodstream(t) = antiMalaria_Drug_in__Bloodstream(t - dt) + (absorbing__antiMalaria - eliminating_antiMalaria) * dt
  INIT antiMalaria_Drug_in__Bloodstream = 0
  UNITS: mg
  INFLOWS:
  - absorbing__antiMalaria = antiMalaria_concentration_difference*antiMalaria_stomach__Volume*absorbing_Constant
    UNITS: mg/day

  OUTFLOWS:
  - eliminating_antiMalaria = antiMalaria_Drug_in__Bloodstream*antiMalaria_elimination__Constant
    UNITS: mg/day
- AntiMalaria_Drug_in__Stomach(t) = AntiMalaria_Drug_in__Stomach(t - dt) + (ingesting_antiMalaria - absorbing__antiMalaria) * dt
  INIT AntiMalaria_Drug_in__Stomach = 0
  UNITS: mg
  INFLOWS:
  - ingesting_antiMalaria = PULSE(10,antiMalaria__Dosage,3)
    UNITS: mg/day

  OUTFLOWS:
  - absorbing__antiMalaria = antiMalaria_concentration_difference*antiMalaria_stomach__Volume*absorbing_Constant
    UNITS: mg/day
- AntiTB_Drug_in__Bloodstream(t) = AntiTB_Drug_in__Bloodstream(t - dt) + (absorbing_antiTB - eliminating_antiTB) * dt
  INIT AntiTB_Drug_in__Bloodstream = 0
  UNITS: mg
  INFLOWS:

absorbing_antiTB =
antiTB_concentration_difference*antiTB_stomach__Volume*absorbing_Constant_by__infected_APC
UNITS: mg/day

OUTFLOWS:
eliminating_antiTB (IN SECTOR: HIV Sector)

AntiTB_Drug_in__Stomach(t) = AntiTB_Drug_in__Stomach(t - dt) + (ingesting_antiTB - absorbing_antiTB) * dt
INIT AntiTB_Drug_in__Stomach = 0
UNITS: mg

INFLOWS:
ingesting_antiTB = PULSE(200,antiTB_Dosage,3)
UNITS: mg/day
OUTFLOWS:
absorbing_antiTB =
antiTB_concentration_difference*antiTB_stomach__Volume*absorbing_Constant_by__infected_APC
UNITS: mg/day

ARV_Drug_in__Bloodstream(t) = ARV_Drug_in__Bloodstream(t - dt) + (absorbing_arv - eliminating_arv) * dt
INIT ARV_Drug_in__Bloodstream = 0
UNITS: mg

INFLOWS:
absorbing_arv =
arv_concentration_difference*arv_stomach__Volume*absorbing_Constant_by__infected_TH
UNITS: mg/day
OUTFLOWS:
eliminating_arv = ARV_Drug_in__Bloodstream*arv_elimination__Constant
UNITS: mg/day

ARV_Drug_in__Stomach(t) = ARV_Drug_in__Stomach(t - dt) + (ingesting_arv - absorbing_arv) * dt
INIT ARV_Drug_in__Stomach = 0
UNITS: mg
INFLOWS:
ingesting_arv = PULSE(200,arv_Dosage,3)
UNITS: mg/day
OUTFLOWS:
absorbing_arv =
arv_concentration_difference*arv_stomach__Volume*absorbing_Constant_by__infected_TH
UNITS: mg/day

body_weight(t) = body_weight(t - dt)
INIT body_weight = 150

absorbing_Constant = 0.75
UNITS: 1/day

absorbing_Constant_by__infected_APC = .693/16
UNITS: 1/day

absorbing_Constant_by__infected_TH = 0.75
UNITS: 1/day

antiMalaria_blood__concentration = antiMalaria_Drug_in__Bloodstream/blood_volume
UNITS: Unitless

antiMalaria_concentration_difference = antiMalaria_Conc_in_stomach-antiMalaria_blood__concentration
UNITS: Unitless

antiMalaria_Conc_in_stomach = AntiMalaria_Drug_in__Stomach/antiMalaria_stomach__Volume
UNITS: Unitless

antiMalaria_elimination__Constant = .693/16
UNITS: 1/day

antiMalaria_stomach__Volume = 500
UNITS: mg

antiMalaria__Dosage = 0
UNITS: mg/day

antiTB_blood__concentration = AntiTB_Drug_in__Bloodstream/blood_volume
UNITS: Unitless

antiTB_concentration_difference = antiTB_Conc_in_Stomach-antiTB_blood__concentration
UNITS: Unitless

antiTB_Conc_in_Stomach = AntiTB_Drug_in__Stomach/antiTB_stomach__Volume
UNITS: Unitless

antiTB_Dosage = 0
UNITS: mg/day

antiTB_elimination__Constant = .693/16
UNITS: 1/day

antiTB_stomach__Volume = 500
UNITS: mg

arv_blood__concentration = ARV_Drug_in__Bloodstream/blood_volume
UNITS: Unitless

arv_concentration_difference = arv_Conc_in_Stomach-arv_blood__concentration
UNITS: Unitless

arv_Conc_in_Stomach = ARV_Drug_in__Stomach/arv_stomach__Volume
UNITS: Unitless

arv_Dosage = 0
UNITS: mg/day

arv_elimination__Constant = .693/16
UNITS: 1/day

arv_stomach__Volume = 500
UNITS: mg

drug_concentration =
arv_blood__concentration+antiTB_blood__concentration+antiMalaria_blood__concentration
UNITS: mg

blood_volume = GRAPH(body_weight)
(100, 4500), (110, 4595), (120, 4695), (130, 4795), (140, 4895), (150, 5005), (160, 5105), (170, 5205), (180, 5305), (190, 5405), (200, 5500)
UNITS: mg

Not in a sector

old_cd4_count(t) = old_cd4_count(t - dt)
INIT old_cd4_count = Actd__APC+Actd_TH1__Cells+Resting_APC+Resting__TH1_Cells

- min_therapeutic_conc = 0.5
  DOCUMENT: This is the minimum level of concentration you need to achieve for the patient to experience positive effects from the drug.
- the_bedside_attendant = drug_concentration-min_therapeutic_conc
  DOCUMENT: This converter is used to generate messages to the doctor, based on how well the patient is doing...
- toxic_concentration = .9
  DOCUMENT: If the patient achieves a concentration of this level (in the blood stream), it is fatal.
- your_superiors = if drug_concentration>toxic_concentration then 1 else 0
  DOCUMENT: This converter is used to generate messages to the doctor, based on how well the patient is doing...

Appendix C

Ethical Clearance

NATIONAL COMMISSION FOR SCIENCE, TECHNOLOGY AND INNOVATION

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When replying please quote

Our Ref: **NCST/RCD/12A/013/137**

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P.O. Box 30623-00100
NAIROBI-KENYA

Date:

9th October, 2013

Henry Mwangi
University of Nairobi
P.O.Box 30197-00100
Nairobi.

RE: RESEARCH AUTHORIZATION

Following your application dated ***15th August, 2013*** for authority to carry out research on ***"Modeling of Triad Infection of HIV/AIDS, Tuberculosis and Malaria: A System Dynamics Approach,"*** I am pleased to inform you that you have been authorized to undertake research in **Nairobi County** for a period ending **31st December, 2014.**

You are advised to report to **the County Commissioner and the County Director of Education, Nairobi County** before embarking on the research project.

On completion of the research, you are expected to submit **two hard copies and one soft copy in pdf** of the research report/thesis to our office.

DR. M. K. RUGUTT, PhD, HSC.
DEPUTY COMMISSION SECRETARY
NATIONAL COMMISSION FOR SCIENCE, TECHNOLOGY & INNOVATION

Copy to:

The County Commissioner
The County Director of Education
Nairobi County.

KENYA MEDICAL RESEARCH INSTITUTE

Centre for Respiratory Diseases Research, P.O. Box 47855 - 00100, NAIROBI - Kenya
Tel. 254 (020) 2724264/5, Fax: (020) 2729308 Email:crdr@todays.co.ke. Website: www.kemri.org

KNH/UON/-ERC 16TH December, 2013

Dear Sir/Madam,

RE: MODELLING OF TRIAD INFECTION OF HIV/AIDS,TB AND MALARIA:

A SYSTEM DYNAMIC APPROACH (P530/10/2013

We note that Mr. Henry Mwangi has been ethically approved from KNH/UON and KEMRI (CRDR) is willing to give him access to individuals for his studies.

Thank you.

Dr. Evans Amukoye

Director, CRDR

In Search of Better Health

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Ref: KNH-ERC/A/75 Link:www.uonbi.ac.ke/activities/KNHUoN

28th March 2014

Mr. Henry N. Mwangi
School of computing and Informatics
University of Nairobi

Dear Mr. Mwangi

Research Proposal: Modeling of Triad Infection of HIV/AIDS, Tuberculosis and Malaria: HIV/AIDS, Tuberculosis and Malaria: A system Dynamics Approach (P530/10/2013)

This is to inform you that the KNH/UoN-Ethics & Research Committee (KNH/UoN-ERC) has reviewed and **approved** your above proposal. The approval periods are 28th March 2014 to 27th March 2015.

This approval is subject to compliance with the following requirements:

a) Only approved documents (informed consents, study instruments, advertising materials etc) will be used.
b) All changes (amendments, deviations, violations etc) are submitted for review and approval by KNH/UoN ERC before implementation.
c) Death and life threatening problems and severe adverse events (SAEs) or unexpected adverse events whether related or unrelated to the study must be reported to the KNH/UoN ERC within 72 hours of notification.
d) Any changes, anticipated or otherwise that may increase the risks or affect safety or welfare of study participants and others or affect the integrity of the research must be reported to KNH/UoN ERC within 72 hours.
e) Submission of a request for renewal of approval at least 60 days prior to expiry of the approval period. (*Attach a comprehensive progress report to support the renewal*).
f) Clearance for export of biological specimens must be obtained from KNH/UoN-Ethics & Research Committee for each batch of shipment.
g) Submission of an *executive summary* report within 90 days upon completion of the study
This information will form part of the data base that will be consulted in future when processing related research studies so as to minimize chances of study duplication and/or plagiarism.

For more details consult the KNH/UoN ERC website **www.uonbi.ac.ke/activities/KNHUoN.**

Protect to Discover

Yours sincerely

PROF. M. L. CHINDIA
SECRETARY, KNH/UON-ERC

c.c. The Chairperson, KNH/UoN-ERC
The Deputy Director CS, KNH
The Principal, College of Health Sciences, UoN
The Assistant Director, Health Information, KNH
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