Understanding the dynamics of HIV progression in the light of Opportunistic Infections Tuberculosis and Malaria: A Novel Approach

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Abstract

Chronic illnesses to which HIV/AIDS, Malaria and TB is part, have had long term direct impact on the population, social economic status as well as health in general. A lot of commitment by governments, non-governmental organizations, international organizations etc. intended to reduce mortality of these disease. These intentions have not had proportionate return on investment.

This paper explores factors that influence the progression of HIV into AIDS with particular emphasis on opportunistic infections particularly malaria and TB. Although there has been tools and techniques geared towards study of these diseases many of them have been lacking systemic approach or fail to communicate to healthcare providers therefore rendering their efforts ineffective.

The authors argue that the range of infectiousness in the population specifically HIV/AIDS, incidence of new cases and its progression including interventions ideally reduce mortality rate leaving more people living with the disease and requiring more care in the course of the disease. Living with the disease while still on medication awakens latent infections which go on unnoticed but the patient continues with the medication allowing these new infection to gain undue advantage of the immune system. With models to leverage realistic predictions and awareness, simultaneously allowing care delivery can unveil hidden trends in the disease under consideration.

The descriptive model allows systematic inquiry that yields explanations and provides healthcare providers with common decision making platform. The authors further suggest triumvirate model of HIV, malaria and TB that utilizes system dynamics in a resource limited setting.

1. Introduction

Over the years, demand for health care services by the general population has been on the rise. Age, complex modern lifestyle, rising prevalence of diseases etc have contributed directly or indirectly to this demand. Throwing technology into the equation has seen people becoming more and more aware of their health without heavily depending on health care providers for prognosis. Increasingly, health care providers are facing scaling costs and competition over both customers and limited resources. With investments risks growing and legal frameworks getting tougher and resultant distance from social health amenities, the hope of providing best care is gradually becoming a challenge.

HIV/AIDS, a long standing illness invokes opportunistic infection in the course of its progression. These infections have symptoms similar to those of advancing HIV affecting people in the same social setting. The level of infectiousness largely dependent on incidence of new cases, progression of the disease and deaths, while interventions ideally reduce mortality rate. The result of these implies people living with the disease will continue requiring care at a later point in time. In the same note, infected population prevented from advancing to a more serious stage will have fewer health care requirement at a later point in time. These issues raises question about: 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 bring this into focus, it is necessary to track the effects of interventions over time. Simulation and modeling with ICT derives its power of projections for these kind of problems through simulation experiments.

In Africa, Tuberculosis makes the first visible symptoms of HIV infection coming also in advance of others in causing deaths among PLWHIV. Similarly, literature alludes that people living with HIV appear to be more susceptible to malaria infection due to HIV induced immunosuppression. Malaria related deaths and its severity seems to have hit PLWHIV of all ages living in regions with unstable malaria transmission.

The fact that TB and malaria are leading causes of death in people living with HIV makes addressing TB/malaria/HIV synergy critical in any strategy that aims to reach those most in need. The good history of simulation and modeling in numerous decision support is imperious in managerial or policy implementation. The impending structural immunosuppression (systemic weaknesses) invisible over long duration of time attributed to HIV affect decision making and can be uncovered through simulation and modeling. Most linear mathematical models are linear as developed by [1, 2, 3, 4] and are approximations to more realistic nonlinear models for viral and infected cell decay, and thus are applicable only over short periods of time, most likely on the order of day. As much as these linear models have useful in characterizing short-term dynamics of HIV infection therapy, several researchers have attempted to use these models to estimate time to eradication of virus from individuals. llll asserts that to model data over long periods of time and make predictions about long term outcomes, nonlinear mathematical models are necessary. Additionally the unrealistic simplifying assumptions that make it difficult for linear models to accurately describe long-term HIV infection dynamics, factors that could play an important role in dynamic disease outcomes may be ommited in linear models. Researcher have raised questions as whether or not mathematical models have adequately described the decay of compartments relevant to HIV infection dynamics. The authors of [5] for example argues that more complex nonlinear models are needed to accurately describe long-term viral decay.

2 State of Practice in HIV/TB/Malaria treatment

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 [6, 7]. A number of models exists that attempts to help understand the progression of HIV. Mathematical modeling, agent-based modeling as well as system dynamics modeling have been leading in explaining the progression of HIV. These models have gone as far as modeling co-infections but none has adequately addressed trio infections within the same host. This paper will discuss mathematical modeling which has proved relevant in HIV progression. Agent-based modeling is still in the formative stages and its focus is the constituent parts of the whole. It thrives in modeling system that learn, that exhibit memory or path dependence [8]. Modeling of HIV has been focusing on the depletion of $CD4^+$ T cells, the cells commonly known as T cells or T4 cells. [9] argues that the decline in number of $CD4^+$ T cells in peripheral blood and the peripheral blood ratio of $CD4^+$ / $CD8^+$ T cells are both used in clinical settings as indicators of the disease stage. The authors of this paper feels that any model that purports to quantitatively characterize the effects of HIV infection be able to make realistic predictions about the status of the immune system in the presence of HIV infections. Over the Years, Mathematical modeling of the immune system has embarked on its interaction with the HIV. Stochastic and deterministic models have been developed about these. The stochastic models as presented by [10], have been used to account the early events during the time when there are few infected cells and small number of viruses, or in situations where the variability among individuals is of interest. The model of [11] looks at the effects of variability among viral strains. On the other hand, deterministic models such as the ones developed by [12, 9, 13] examine the changes in mean cell numbers and are more applicable to later stages of the process in which population sizes are large. These models typically consider the dynamics of the $CD4^+$ helper and virus population. [14] alludes that linear and nonlinear mathematical models lack the important delay term which is a crucial during the initial stages of how the virus interact with the immune systems. Traditionally, DES models have been applied at tactical operational level. By definition, these models are stochastic in nature and deal with distinct entities, scheduled activities, queues and decision rules and simulated in unequal timesteps when something happens requiring huge amount of numerical data. They are often used to compare scenarios, prediction, or optimization criteria [15].

With the relative strengths and deficiencies in the current health care models therefore successful achievements of better understanding, appropriate model should primarily have the ability to capture delays and feedback resulting in interactions among the factors that clutch immune system together. Secondly, the model should be able to support evaluation and synthesis of the healthcare in a manner that promotes explanation and insight into the problem under investigation in order to communicate amongst the healthcare providers. With the above two conditions then the model should carry out a holistic analysis of the HIV progression with opportunistic infections variability. This inclusion is pertinent in understanding the progression of HIV and achieving a cost-effective measure of treatment views.

3. System Dynamics Modeling

System Dynamics (SD) is a methodology that applies system thinking methods to facilitate the understanding of systems by focusing on relationships that link the parts of the whole [16] that makes up the complex system. The complexity of a system is defined by feedback loops, non-linearity and time delays that often affect the system behavior. Real world systems are complex and so explanation and general insights regarding the behavior of these system can be elucidated by a methodology that supports such. Decision rules and 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 as well as physical and information delays can be incorporated in the model. Additionally, soft behavioral relationships for which adequate statistical data may not be available can be modeled. This makes SD quite adequate in modeling complex systems as explanations that yields from simulations can be used to foster and further understanding and insights. System Dynamics also 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 [17].

4 Factors the influence HIV progression under Opportunistic Infections

Following is a demonstration of the factors that influence progression of HIV and how the relate to those of TB and malaria. The reference model of these factors is based on mathematical bio-sciences literature [9, 18, 19, 20, 21]. Six (6) commonly used variables were identified as those that influence the triumvirate HIV, TB and malaria progression. They are (a) TB infecteds (b) Malaria infecteds (c) HIV infecteds - *people living with HIV - PLWHIV* (d) Immunity Level (e) Toxicity and (f) Treatment. The importance of these variables for consideration into the model elaborated below. According to [22] the collection of cells, tissues and molecules that mediate resistance to infections is called the immune system whose physiologic function is to prevent infections and to eradicate established infections. HIV virus targets these cells through changing their central role of defending the body to causing to acquire immunal deficiency and subjecting the body to other diseases. The HIV virus exhibits a long asymptomatic phase of approximately 10 years on average before the onset of AIDS. During the initial stages, the virus is highly infectious and the phase is demonstrated by high viral load [**?** , Yadavalli2009] During this incubation period [23], called the clinical latency period, the individuals appear to be well and may contribute significantly to the spread of the epidemic community. The clinical markers of HIV such as CD4 cell count provide information about the progression of the disease in infected individuals. It is during this clinical latency period that awakening of latent illness like TB and location dependent illnesses like malaria strike and suppressive therapeutic intervention should be addressed. [24] through experimental studies of the dynamics of HIV replication in the presence of antiretroviral agents reported that HIV has enormous potential of showing resistance to drugs by undergoing several mutations. [25] also reported a high drug resistance and unique combination of mutations of the same when they proposed a stochastic model to test the resistance of protease inhibitors. HIV treatment through *(HAART-highly active antiretroviral therapy)* enables individuals infected with HIV to live longer, but because infection is not eradicated, this individual may infect others causing an increase in the number of HIV infections in the population (HIV incidence). Such an individual may also remain at greater risk of tuberculosis infection and, therefore, can also contribute to the spread of tuberculosis in the population. The same can be said about MDRTB, where duration of infectiousness may be prolonged. An individual co-infected with both HIV and MDRTB may remain infectious for both diseases unless MDRTB treatment is effective. The transmission dynamics of tuberculosis and HIV at the population level (macro level) cannot be disassociated from the behavior of these diseases at the individual level (micro level). However, while the behavior of these two diseases at the individual level has been the subject of much biomedical research for many years and is, therefore, relatively well understood, the behavior of these interacting diseases at the population level is more difficult to understand. The reason is that this behavior is driven by complex interactions between variables related to the epidemiology of the diseases within single individuals, behavior of these and other individuals, health service structures and processes, and the policies put in place to deal with these diseases (Atun et al, 2005b). For example, an aggressive policy to detect individuals with the drug sensitive tuberculosis (DSTB) disease can have counter-productive results if the treatment capacity and resources are not adequate to treat the detected individuals. This will potentially lead to a high rate of DSTB deaths (and potentially more infections with MDRTB if individuals receive interruptions to their treatment). Similarly, an effective treatment system for tuberculosis will not have the desired effect on the spread of tuberculosis if individuals with the disease remain undetected in the population and infect others. If individuals do not receive appropriate treatment for DSTB, they can develop MDRTB and infect others. This can have far reaching consequences in terms of the size of the population with MDRTB and the resources required for their detection and treatment. The long delay between HIV infection and AIDS

means many persons with HIV infection may remain unaware of their HIV status and continue their high risk behavior, until they succumb to an opportunistic infection, such as TB as their immune function deteriorates System.

HIV has shown to increase the risk of malaria infection and accelerate the development of clinical symptoms of malaria, with the greatest impact in immune-suppressed persons. Conversely,malaria has shown to induce HIV-1 replication in vitro and in vivo. A biological explanation for these interactions lies in the cellular-based immune responses to HIV and malaria. Studies have shown that when HIV-infected individuals are attacked by malaria, their body immune system weakens significantly, creating a conducive environment for the HIV virus to replicate (virtually unchallenged), resulting in an increase in the viral load (the amount of HIV virus in the body). As alluded by [26] viral load is correlated with malarial infectiousness, such a process (co-infection with malaria) leads to an increase in the number of new HIV cases in the population. The author further states that morbidity is higher in HIV-infected individuals. Other recent research on HIV-malaria co-infection [27, 28] confirm and extend earlier findings [29, 18, 30, 31] by showing that co-infection leads to an almost one log increase in viral load in chronic stage HIV-infected patients during febrile malaria episodes with HIV infection substantially increasing susceptibility to malaria infection. [26] observes that in regions of low malaria transmission, immunity develops gradually and malaria affects all age groups. Since HIV infection interferes with cellular immune function, HIV may interfere with the development of partial immunity to malaria, particularly amongst children.

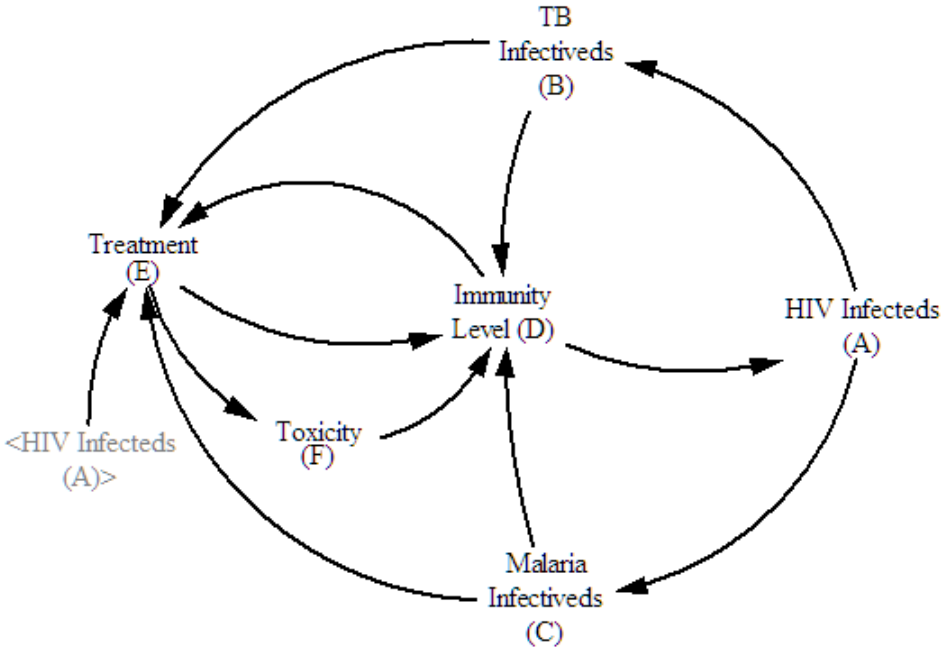

Figure 1: A reference model of the factors that influence HTM

5 Modeling Triumvirate of HIV/TB and Malaria

Numerous data collection techniques can be used to validate a model. In this research, semi-structured interview technique was adopted as it is the most efficient method where the number of experts to be involved is small ranging from 0-20 and the topic under investigation is not multi-disciplinary [32]. Since experts in HIV co-infections are limited then interviews is the most efficient data collection and validation method.

Semi-structured interviews were used as a strategy for data collection. Discussions with HIV co-infections experts were conducted in a setting of $1^1/2$ hrs interviews. Respondents included immunologist, HIV expert, TB experts, researchers in Malaria among others. The interviews questions included sections on immune system, HIV, Tuberculosis, Malaria and Drug toxicity specifically trying to address the problems the respondents face and deal with in the course of their practicing, the

parameters considered for addressing the progression of HIV, TB and Malaria as well as their measurements, not forgetting whether there is inter-drug reaction in the course of treatment of the diseases. The validation process took into consideration threats to model validity. Practitioners agreed on the progression markers of type 0, the natural history marker, defined as a marker of disease severity that reflects underlying pathogenetic mechanisms and predicts clinical outcome independent of treatment. progression for monitoring patients. CD4 T-cell count was cited as the best HIV type 0 marker and HIV 1 plasma RNA level marking the disease severity on the target organ and as well as measure of viral burden respectively [33]. Table 1 is an indicative summary of the discussants view of the level of importance of the variables as experienced and used in practice. The importance level is indicated by + and where the discussant did not consider the variable important is indicated by a -.

Experts job descriptions	HIV infections	TB Fresh infections	TB Re-infections	Malaria infections	Drug Toxicity	HTM	Therapy / Treatment	Immunity Level
Virologists Researchers in HIV at A	-	+	+	+	+	+	-	+
Infectious Disease Experts at B	-	+	+	+	+	+	-	+
System Dynamist at C	-	+	-	-	+	+	+	+
Mathematical Biologist at D	+	-	+	+	-	+	+	+
System Biologist at E	+	+	+	+	+	+	+	-
Experts in HIV prognosis at F	+	+	+	-	+	+	+	+
Immunologist at G	-	+	+	+	+	+	+	+
Clinicians at H	-	+	-	+	-	+	+	+
Epidemiologists at I	+	+	-	+	-	+	+	+
Biostatisticians at J	+	+	-	+	+	+	+	-
Total G	5	9	6	8	7	10	8	8

Table 1: Summary of results from the Experts

The variables presented to the interviewees were HIV infections, Fresh TB infections to HIV patients, TB re-infections, malaria infections, drug toxicity from inter-drug reactions, treatment and therapy as well as immunity level.

The interviewees were got researchers, modelers, practitioners like clinicians, statistician as well HIV experts among others as listed in the table /refsumtable. Out of the seven (7) aforementioned variables presented to the interviewees HIV infections at 50% showed that it is the least influential cause of death to HIV progression as long as the patient feeds and does exercises. TB fresh infections and re-infections together carries the heaviest burden at 150% from 90% and 60% respectively in HIV progression to AIDS. They were of the view that since its is the same disease and that TB infecteds with HIV do not get completely healed should be handled together. The infection of malaria while infected with HIV is quite influential at 80% to cause death to PLWHIV. The interviewees all agreed that the triumvirate of HIV, Malaria, and TB synergy contribute the highest mortality to PLWHIV at 100%. They interviewees comments had therapy and immunity level having the same weight of 80% and attributed these partly to PLWHIV having the same symptoms with those malaria hence occasional treating the wrong infections and these boosting the environment for the other disease not in consideration at the time of treatment thereby compromising the immune level.

6 Descriptive model for HTM

A descriptive model is a qualitative representation of triumvirate of HTM infectivity synergy that will guide quantitative mathematical relationships in future. The model factors validated in the table 1 facilitated the development of feedback descriptive through redefinition of the relationship among the factors as well as determining their measures and values. Table

/refmtable presents the measures for the variables considered and further indicating those that were were obtained from field studies and those that were obtained from HTM literature.

Key to this forgoing research is the toxicity, immunity level and holistic view of HTM synergy not obtained in literature as important variables for HIV progression and which the authors consider most relevant in contributing to development of HIV to AIDS mortality from field studies This research capitalizes on these three factors but key to is the fact the person

Variable	Measure	Units	Obtained from the Filed (Yes/No)
HIV population	CD4 T cell count	cells /μl	No
TB population	CD4 T cell count	cells /μl	No
Malaria population	CD4 T cell Count	cells/ μl	No
Toxicity	Unit less	0-1	Yes
Immunity	CD4 T cell Count	cells/ μl	Yes
Treatment	CD4 T cell Count	cells/ μl	No

Table 2: HTM variable measures for the revised descriptive model

is living with HIV. Figure 2 provides a systemic and descriptive view of the variables that influence decision making in response to symptoms of the HTM. It is derived from iterative response with experts from the field as illustrated in table 1. In system dynamics a descriptive model is a causal loop diagram with arrows indicating direction and polarity (+/-) indicating the kind of influence for each loop [34]. The figure 2 showing revised descriptive model has three (4) balancing loops and one (3) reinforcing loops. A reinforcing feedback loop (Rn) where n is a number from 1,2..n represents growth or declining actions while balancing loop (Bn) is a goal seeking loop that seeks stability or return to control [34]. The loops show the interrelationship between the variables and how they influence each other. The relationship give a picture of the system behavior and the variables involved for each loop structure contribution to the system. Analysis of the behavior of each loop plays a major role in understanding the impacts of changes in one or more variables on system behavior and limits within which efficiency can be achieved for a set of variables An example of such a relationship in the HTM feedback descriptive

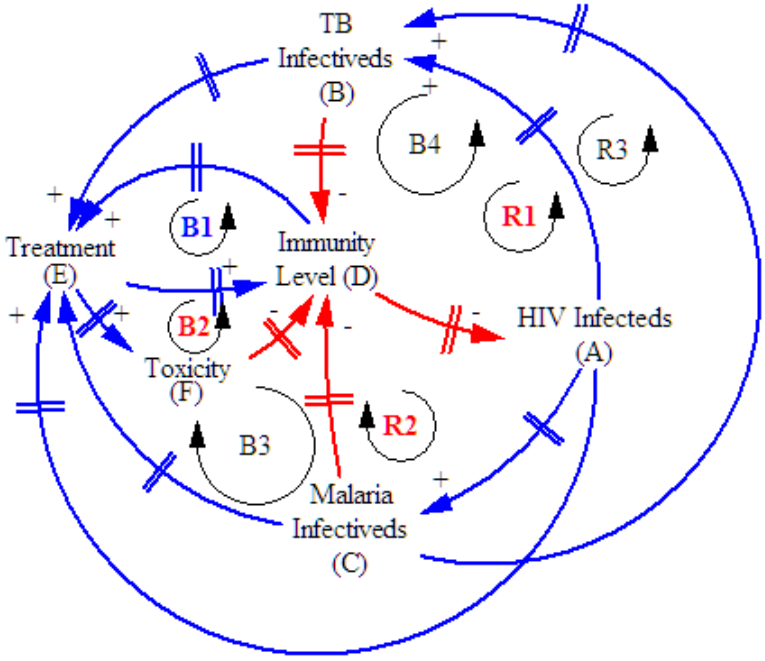

Figure 2: The HTM descriptive feedback model

model is R3 that goes through A-C-B-D-A. It is a reinforcing loop indicating the burden of immune system where the host

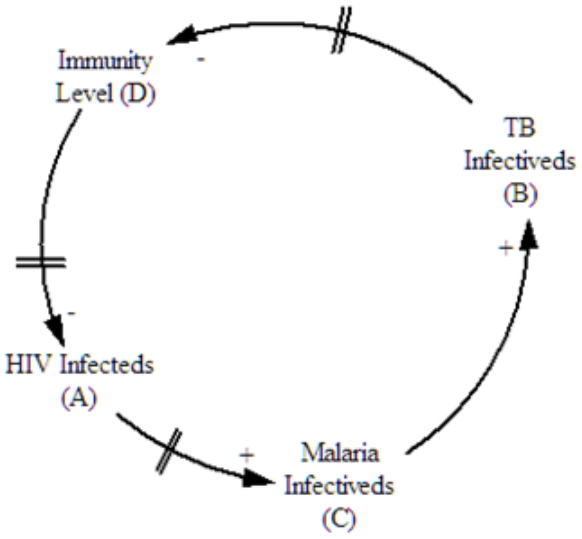

Figure 3: Immune system over burdened with HTM synergy

has three infections i.e. HIV infections (A) will expose the host to low levels of immune deficiency making it easy for malaria pathogens (C) to replicate which in turn subject the host to TB infections (B). This has the overall effect of highly compromising the immunity level (D) of the host compounding more infections by HIV (A). An example of a balancing loop is B4, that is marked by and goes through the variables A-C-B-E-D-A. It is called the therapy loop. With it, an increase

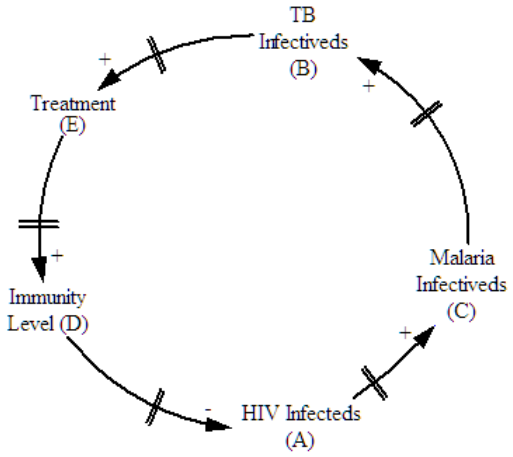

Figure 4: Treatment introduction

in HIV infections (A) lowers the immune response subjecting the host to more malaria (C) and TB infections (B) whose symptoms make the host seek treatment (E). An increase in treatment will boost the immunity level (D) which feeds back to HIV infections (A).

These descriptions demonstrates that there is need to analyze these feedback loop structures in more holistic manner. Observed also in the descriptive model is the double lines in most of the links. This are referred to as delays and depict the fact that effects are felt or observed over time. The reinforcing feedback loops are controlled by the balancing loops to prevent the system from burn out or chaotic behavior of the system.

The causal loop diagram in figure 2 also known as the descriptive model reveals that system dynamics uses loops and time delays as an embodiment of complex systems. They are then used for conceptualizing the system structures as well

as communicating model insights. Inspite of the difficulties in converting qualitative data to quantitative data for decision eliciting, the causal loop diagram aids in this purpose in system dynamics methodology. This has been the key strength of system dynamics - the ability to capture qualitative views and simulate them quantitatively. Analysis of the descriptive model offers a base for identifying propositions that can be derived from it and subsequent testing.

7 Propositions Derived from the Model

With System dynamics descriptive model, mental models about HIV progression with co-infections can be enhanced hence ease decision making strategies as well as development of policies that will counter development of HIV to AIDs. Up until now there is no theory or research that sheds light on how mental models of how HIV breaks down the immune system or how immunosuppression exposes impacts mental models.

This tool can used as a model by practicing health care providers in HIV progression analysis in TB and malaria hit areas as well as researcher of HIV and training and learning situations. The following propositions can be derived from the feedback descriptive model in figure 2

1. Immunity level goes down with advancement of HIV.

   Cells of the immune system are maintained at a particular level. The HIV virus target the CD4 cells which are tasked with innate immunity. The virus also replicates at a very high rate hence attack on these cells is very high. The model shows that with a boost in host immunity level lowers HIV virus population in the host. Since the virus can not be eliminated from the host whatsoever, we expect sine wave in the course of HIV progression to later stages

2. The more the HIV virus in the host, the more the host is prone to malaria infections.

   HIV virus suppresses the host immune system and therefore cannot fight against previous infection thence increase in malaria pathogens. With malaria infections, CD4 cells are kept at high levels and therefore on HIV introduction, target cells are already activated. In this case we expect an overshoot of the viral load

3. The more the HIV virus in the host, the more the host is subjected to active TB infections.

   TB infections are kept at low levels by the body's immune system. When the HIV virus suppresses the immune system, it is no longer able to fight pathogens thereby re-awakening those pathogens. In its fight to kill the pathogens, more CD4 cells are produced which are targets of the HIV virus. When this cells get infected, it leads to their bursting which results to more viral load. The same case happens to malaria infection

4. Increase in treatment leads to increase in toxicity.

   Hyperactive anti-retroviral therapy is usually encouraged at some stage of HIV infection to PLWHIV. Continued intake of these drugs do not have proportionate uptake by the system. Occasionally HIV virus becomes resistant to the HAART thereby leading to toxicity.

5. Increase in toxicity compromises host immunity

   Toxicity destabilizes host organs responsible for production of cells necessary for the immune system. Researchers found that certain people taking antibiotics had reduced levels of cytokines which are hormone messengers of the immune system.

6. Increased infections of malaria and TB leads to demand for more treatment

   Once infected by any disease, it common for the host to seek medical attention. According to the model increase in infections of malaria and tuberculosis leads to more treatment

8 Summary and Further Research Directions

The contribution of this paper has been threefold as follows. Firstly, a literature survey that helped identify the gap that exists in HIV progression in the midst of opportunistic infections particularly malaria and TB and the feedback interaction that exist with the host immune system. Secondly, a proposed novel approach to understanding the dynamics HTM and finally validating the key variables for HTM and the emerging feedback loops

The the immediate future work will be development of a system dynamics model that will be used to determine the strengths of the relationships and thus the relative importance of each key variable discussed in this paper. We have further proposed how the gap with existing in therapy for HTM synergy would be addressed.

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