AN EXTENDED MATHEMATICAL MODEL FOR SIV TO HIV FROM CHIMPANZEES TO HUMAN

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AN EXTENDED MATHEMATICAL MODEL FOR SIV TO HIV FROM CHIMPANZEES TO HUMAN

by

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LIST OF VARIABLES

A_h	AIDS human
I_1	Asymptomatic human
A_c	Chimpanzees with AIDS-like symptoms
I_c	Infected chimpanzees
I_h	Infected human
P	Pre-AIDS human
S_c	Susceptible chimpanzees
S_h	Susceptible human
I_2	Symptomatic human

LIST OF PARAMETERS

κ_1	Asymptomatic human immigrants
β_1	Contact rate of susceptible human with infected / asymptomatic humans
β_2	Contact rate of susceptible human with infected chimpanzees / symptomatic humans
β_3	Contact rate of susceptible human with infected chimpanzees
β_4	Contact rate of susceptible chimpanzees with infected chimpanzees
μ_0	Disease induced death of human
φ	Disease induced death for chimpanzees
ε_h	Fraction of susceptible newborn (human)
ε_c	Fraction of susceptible newborn (chimpanzees)
ε	Human rate of developing symptoms of infection
κ_3	Infected chimpanzees immigrants
μ_c	Natural death rate for chimpanzees
μ_h	Natural death rate for human
c_1	Number of sexual partners of susceptible human with infected / asymptomatic humans
c_2	Number of sexual partners of susceptible human with symptomatic human / number of infected chimpanzees

c_3	Number of infectious chimpanzees
c_4	Number of sexual partners of susceptible chimpanzees with infected chimpanzees
α	Rate of developing AIDS symptoms
σ	Rate of developing AIDS-like symptoms
b_1	Rate of giving birth by infectious classes of human
b_2	Rate of giving birth by infectious classes of chimpanzees
δ	Rate of movement from infected class to pre-AIDS class
π_c	Recruitment rate of chimpanzees
π_h	Recruitment rate of human
τ	Removal rate of human
κ_2	Symptomatic human immigrants

SUATU MODEL LANJUTAN UNTUK SIV TO HIV DARIPADA CIMPANZI KEPADA MANUSIA

ABSTRAK

Tujuan kajian ialah mengkaji dinamik penyebaran SIV/HIV pada manusia, bersama kehadiran cimpanzi yang mempunyai Simian Immunodeficiency Virus (SIV) dan mencadangkan beberapa strategi kawalan di sub-Sahara Afrika. SIV dipercayai oleh sekumpulan saintis sebagai punca kepada kemunculan HIV yang menjadikan penyakit ini menular di sub-Sahara Africa di mana sebahagian besar cimpanzi ditemui. Satu model asas yang terdiri dari populasi manusia dan cimpanzi telah dibentuk dan titik keseimbangan ditentukan. Didapati bahawa titik keseimbangan yang bebas-penyakit adalah stabil dari aspek asimptotikalnya apabila bilangan pembiakan asas didapati kurang berpadu dan tidak stabil. Model ini dikembangkan lagi dengan membuat pertimbangan ke atas kesan-kesan strategi-strategi kawalan. Analisis sensitiviti telah dijalankan untuk memperolehi parameter sensitif yang paling banyak membantu penularan penyakit. Keputusan menunjukkan bahawa kadar hubungan manusia yang sensitif kepada penyakit dengan manusia yang sudah dijangkiti dan kadar hubungan cimpanzi yang sensitif dengan cimpanzi yang dijangkiti adalah parameter-parameter yang paling sensitif. Beberapa parameter kawalan (penggunaan kondom, rawatan dan penakaian) telah dipertimbangkan untuk mengawal penularan penyakit. Begitu juga dengan model asas yang dikembangkan untuk memberi pertimbangan ke atas kesan transmisi menegak (ibu kepada anak) ke atas kedua-dua populasi tentang penyebaran virus. Ciri-ciri asas model telah dikaji dan bilangan pembiakan asas telah dianalisis menggunakan

kaedah pengoperasi generasi berikutnya. Analisis sensitiviti parameter model telah dijalankan; Prinsip maksimum Pontryagins telah diaplikasi dengan beberapa parameter kawalan ujian-HIV, rawatan dan penakaian untuk mengurangkan kelas-kelas jangkitan manusia dan cimpanzi dengan dana intervensi yang minimal. Tambahan pula, model asas telah dikembangkan untuk mempertimbangkan kesan-kesan imigran yang infektif. Selepas memperolehi parameter yang paling sensitif, beberapa strategi kawalan telah dipertimbangkan (pendidikan tentang kesihatan, rawatan dan penakaian). Simulasi berangka model telah dijalankan dan keputusan menunjukkan bahawa kombinasi ketiga-tiga parameter kawalan pada tiga situasi yang berbeza adalah yang paling efektif dalam mengawal penularan virus. Penakaian adalah satu parameter kawalan yang sangat penting dalam mengurangkan populasi cimpanzi sementara parameter kawalan lain seperti penggunaan kondom, rawatan, pendidikan kesihatan awam serta ujian HIV membantu mengurangkan insiden dan kelaziman HIV.

AN EXTENDED MATHEMATICAL MODEL FOR SIV TO HIV FROM CHIMPANZEES TO HUMAN

ABSTRACT

The purpose of this study is to investigate the transmission dynamics of SIV/HIV in humans, in the presence of chimpanzees that harbor Simian Immunodeficiency Virus (SIV) and to suggest some control strategies in sub-Saharan Africa. SIV was believed by some scientists to have ignited the emergence of HIV. This could be one of the reasons that make the disease endemic in sub-Saharan Africa where these chimpanzees are predominantly found. A basic model that consists of human and chimpanzee populations were formulated and the equilibrium points were determined. It was obtained that the disease free equilibrium point is locally asymptotically stable when the basic reproduction number is found to be less than unity and unstable otherwise. The model is extended to consider the effects of control strategies. Sensitivity analysis was carried out to obtain the most sensitive parameters that help most in disease spread. The result shows that the contact rate of susceptible human with the infected human and the contact rate of susceptible chimpanzees with infective chimpanzees are the most sensitive parameters. Some control parameters (condom use, treatment and culling) were considered in order to control the spread of the disease. The basic model was further extended to consider the effects of vertical transmission (mother to child) on both populations on the spread of the virus. Some basic properties of the extended model were investigated and basic reproduction number was computed using Next Generation Operator method. Sensitivity analysis of the model parameters was car-

ried out and Pontryagin's Maximum Principle is applied with some control parameters of (HIV testing, treatment and culling) to reduce the infective classes of human and chimpanzees with minimal intervention funds. Further, the basic model is extended to consider the effects of infective immigrants. After obtaining the most sensitive parameters, some control strategies were considered (public health education, treatment and culling). Numerical simulations of the models was carried out and the results indicate that combination of all the three control parameters in three different situation are most effective in controlling the spread of the virus. Culling is very essential in reducing the population of chimpanzees while the remaining other control parameters like condom use, treatment, public health education and HIV-testing will all help in reducing the incidence and prevalence of HIV.

CHAPTER 1

INTRODUCTION

1.1 Preliminaries

The persistence of Human Immunodeficiency Virus (HIV) since the 1980's has convinced scientists to devise more effective ways of controlling the spread of infectious diseases as a whole due to their socioeconomic effects (Naresh et al., 2009). This thesis will focus on the modeling the spread of HIV from chimpanzees to humans and its optimal control in sub-Saharan Africa.

The virus weakens the immune system resulting in life-threatening infections that occur more frequently. HIV is a disease typically responsible for long term sicknesses with a long maturation period (Douek et al., 2009). This chapter gives a brief introduction of HIV and Simian Immunodeficiency Virus (SIV) after reviewing the works done on HIV modeling. The link between the two viruses, motivations, problem statements, objectives of the research and thesis organization are presented.

1.2 Human Immunodeficiency Virus (HIV)

HIV causes gradual depletion of immune system that leads to Acquired Immune Deficiency Syndrome ($AIDS$). It has been a human disaster particularly in sub-Saharan Africa and may be attributed to poor development, poverty and lack of health services (Gayle, 2000). At the dissemination phase, the virus spread quickly to various parts of the globe due to population movements and thus planting the seeds for a volatile epidemic (Olshansky et al., 1998). There are two types of HIV, $HIV-1$ and $HIV-2$ and

the ordering is based on differences in genetic structure. The $HIV-2$ is the less common type and is found mainly in western Africa. Both types of virus are transferred in the same way and cause the same sicknesses. However, it appears that $HIV-2$ is more difficult to transmit and that the duration from infection to illness is longer (Jay, 1995). The $HIV-1$ is the major cause of global illness and death, when people mention HIV, what is meant is $HIV-1$ and this is the convention that will be used in this thesis.

HIV has a physiological impact on the immune system. It targets and attacks the Leucocytes cells or $CD4+$ cells which are part of immune system (Irwin, 2001). Chronic HIV infection causes continuing running down of the $CD4+$ cells (Kirschner et al., 1997). The virus is contained in the bodily fluids of a diseased person such as semen, blood, breast milk etc. The transmission of the HIV virus takes place when a sufficient amount of either of these fluids is transmitted to a vulnerable person from an infected person. All HIV positive individuals irrespective of their stages and whether on treatment or not can transmit the virus to a vulnerable individuals.

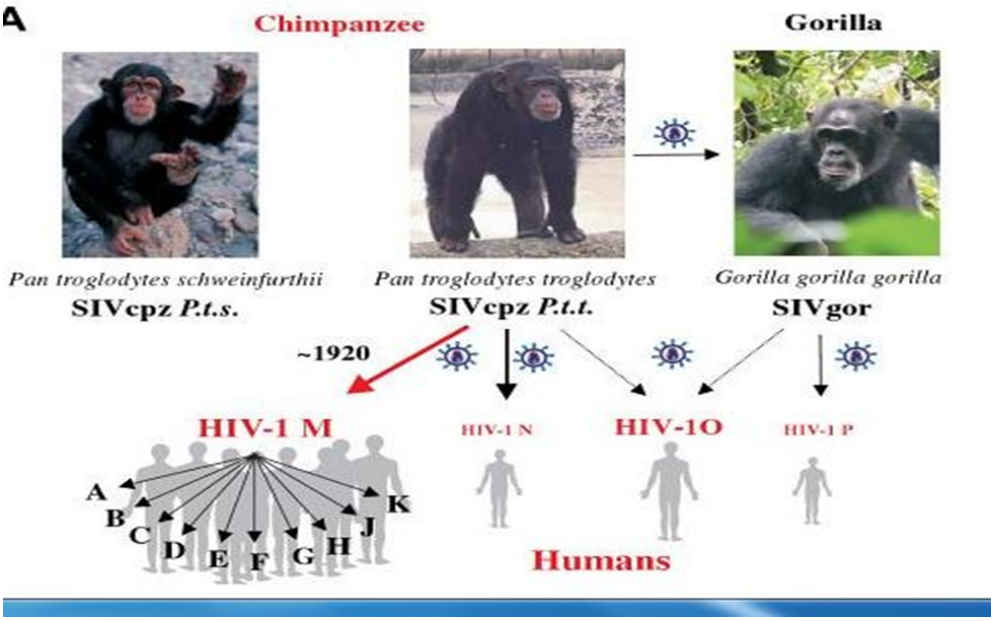
Due to high viral load at the early and late stages of infection (full blown *AIDS*) the risk of transmitting the virus is much higher at the early and late stage (Kaur and Mehra, 2009). At these stages, the virus can be transmitted via unsafe sex and use of unsterilized needles for intravenous drugs users. Transmission also takes place from an infected mother to its new born before, during, after delivery or during breast feeding. In addition, the virus can also be transmitted through transfusion of contaminated blood. Other ways include organ and tissue transplant (Lamptey et al., 2006).

Since the beginning of the worldwide epidemic in 1981, more than 75 million people were infected with the virus and roughly 40 million people so far have died of HIV related illnesses to date (Sued et al., 2016). As at December 2014, about 36.9 mil-

lion people were living with the virus globally (Mohammad Hoseinpour et al., 2015). Further, in 2014, about 1.2 million persons died from *HIV* related causes and about 2 million new infection worldwide (Sued et al., 2016). Sub saharan Africa is the most affected region with 25.8 million people living with the virus which is about 70% of the global infection (Mohammad Hoseinpour et al., 2015). Around two million individuals were newly infected with the virus in the same year. The burden of the epidemic continues to affect countries of sub-saharan Africa. The region remains harshly affected, with approximately 1 in every 20 adults living with the virus (UNAIDS, 2013).

1.3 Simian Immunodeficiency Virus (SIV)

Simian Immunodeficiency Viruses $(SIVs)$ are primate viruses that are found naturally in many African chimpanzee species. Two of *SIV* viruses, $SIVcpz$ from chimpanzees of P.t. Troglodytes type and $SIVsmm$ from chimpanzees of sooty mangabey type are able to generate cross-species transmission from primate (chimpanzees) to humans in a process called zoonosis (Sharp and Hahn, 2011; Gao et al., 1999). Coming in contact with the blood and tissues of infected chimpanzees as a result of hunting and eating of bush meat represent a source for human contagion. Hunting and eating of chimpanzees by humans are still taking place and hence the risk of further transfer of infections via this mode cannot be overruled (Nyamu, 2014). The diagram below illustrate the flow of the virus from non-human primate (chimpanzees) to human (Jasinska et al., 2013; Pancino et al., 2012).



Source: Pancino et al. (2012).

Figure 1.1: Flow diagram of SIV_{cpz} to $HIV-1$ sub-types

For a very long time certain viruses were known to be passing between different species (Sharp and Hahn, 2011). According to (Apetrei et al., 2004) the Lancet published an article in 2004 showing that crossover of viruses from non-human primates (chimpanzees) to human (hunters) is still taking place. For instance, about 1,099 individuals were considered as a sample and tested in Cameroon, (mostly hunters and those engaged in eating bush meat) and the results revealed that one percent (1%) of the sample was infected by Simian Foamy Virus (SFV), a virus like SIV which was before believed only to infect primates (Wolfe et al., 2004). All these types of transfer is thought to have happened via butchering and feeding on chimpanzees. It is therefore important to examine the spread of the virus and propose optimal control strategies by means of deterministic mathematical modeling. Research on mathematical models of HIV that include the population of these chimpanzees are not available to the best of

our knowledge.

1.4 Link between *SIV* and *HIV*

The two viruses (*SIV* and *HIV*) are groups of retroviruses capable of producing illnesses characterized by a delay in the onset of symptoms after infection in their respective host. The available evidence (Apetrei et al., 2004), leads scholars to believe *HIV* is a zoonotic disease i.e a virus transmitted from non-human primates (chimpanzees) to human primates based on similarities between *SIV* and *HIV* on the host identification and location, viral genetic levels, and on route of transmission (Sharp and Hahn, 2010, 2011). Through non-human primates and human interference, *SIV* became transmissible to humans and finally develop into *HIV*.

1.5 Motivation

Much effort and research have been done on the dynamics of *HIV* since when the virus was detected in 1981. Among the models are the work of (Anderson et al., 1986; Anderson, 1988; Al-Sheikh et al., 2011; Agusto and Adekunle, 2014) etc. Thus, this research is motivated by the presence of *P.t* Troglodytes chimpanzees in sub-Saharan Africa that harbor *SIV* and the non-availability of mathematical models on *HIV* initiated with the *SIV*.

1.6 Problem Statement

As highlighted, there are still dangers posed by the lack of understanding of the spread of *HIV* initiated by *SIV*. This lack of understanding can lead to continued health issues. Mathematical models of disease spread help in understanding how diseases are

transferred from nonhuman primate to human and from human to human. Thus, the extended mathematical model in this study will assist in understanding *HIV* spread initiated by *SIV* from chimpanzees to human. The model comprised of two interacting populations of humans and chimpanzees. Hence, this work intends to extend the model of Eduafo (2015) by incorporating the chimpanzees populations. At the same time, investigate the effects of vertical transmission and infected immigrants.

1.7 Objectives of the Research

The main objectives of this research is to extend an enhanced model of *HIV* through the incorporation of *SIV*. Three different aspects will be investigated such as follows:

1. To extend a mathematical model of Eduafo (2015) by incorporating the populations of chimpanzees, to show how *SIV* leads to the emergence of *HIV*.

2. To investigate the properties of the model such as invariant region, disease free and endemic disease equilibria. Local stability of the disease free equilibrium and stability of the endemic equilibrium state.

3. To investigate effects of certain control strategies on vertical transmission and infected immigrants on the model. Control strategies considered are condom use, treatment, *HIV* testing, public health education and culling, using optimal control method.

1.8 Research Methodology

Many mathematical models of infectious diseases were build using deterministic mathematical modeling approach such as works by Abiodun et al. (2013); Okosun et al. (2013b,a); Seidu et al. (2015); Duwal et al. (2015) and Huo et al. (2016) similar approach will also be adopted in this thesis. This is due to the fact that deterministic model is practically simple in formulation and need fewer data. Furthermore, the computer software are user friendly and generally accessible (Abdullah, 2015). The basic model considered is an extension of Eduafo et al. (2015) and it was choosen as it was formed as a standard model of $HIV/AIDS$ that has only three compartments of susceptible, infected and AIDS individuals. In this thesis,the model is extended by incorporating the population of chimpanzees. In this work, an effort will be made towards illustrating and explaining what occurs typically at the population level. Individuals in a population move from one compartment to other compartment, that is from susceptible class to infected and then to the *AIDS* class. The same movement also occurs in the population of chimpanzees from susceptible class to the infected and to the class of chimpanzees with AIDS-like symptoms. The rate at which such individuals transfer from one compartment to another is mathematically stated as derivatives or rate of change with respect to time.

The basic model comprised of six differential equations, three from each population of humans and chimpanzees. In order to investigate the validity of the model, invariant region (total population must be positive real number) and positivity of the solutions (all variables must be positive) was investigated. Similarly, the two equilibria, disease-free equilibrium point and its local stability with endemic equilibrium and its global stability were also examined. Furthermore, the basic model is extended to examine

the effects of time dependent control strategies (condom use, treatment and culling) using Optimal Control Theory. Pontryagin's Maximum Principle is then employed to examine the effects of time dependent control parameters (HIV-testing, treatment and culling) while conditions for the optimal control was obtained on the effects of vertical transmission (mother to child). Similarly, sensitivity analysis was carried out to obtain the parameters that help most in the virus transmission. Lastly, the basic model is extended to verify the effects of infective immigrants while the sensitivity analysis of the model parameters will be carried out and the optimal conditions were to be obtain using Optimal Control Theory. Computational experiments were conducted using Maple-17 software found suitable to obtain the basic reproduction numbers and conditions for optimal control problem. MATLAB-R2014a is used to carry out numerical simulations in chapter 5-7 as it is more appropriate in dealing with Runge-Kuta 4th order. MATHEMATICA-10 software is used to obtain the numerical simulations in chapter 4.

1.9 Thesis Organization

The structure of the research is as shown in Figure 1.2. In Chapter 1, an overview of HIV and SIV and the link between them was presented. Further, the research motivation, problem statement and objective of the study were briefly stated while research methodology and thesis organization are also presented. In Chapter 2, the presentation of related literature to the study is made. In Chapter 3, description of mathematical theories and assumptions connected to the planned research are made. The basic model comprising human and chimpanzee populations with analysis are presented in Chapter 4. In Chapter 5, the effect of control strategies such as condom use, treatment of the in-

fected human and culling are investigated. In Chapter 6 the basic model was extended to reflect the effect of mother to child transmission on the dynamics of the virus. In Chapter 7 the combined effects of infected immigrants are investigated. Finally, Chapter 8 present the concluding remarks and suggest some future work.

This chapter presents the modeling frameworks that are used in the research work. The idea of this chapter is to address various issues related to prior research in HIV/AIDS modeling. A synthesis of the earlier work provides an overview to the current study and supports the research questions provided.

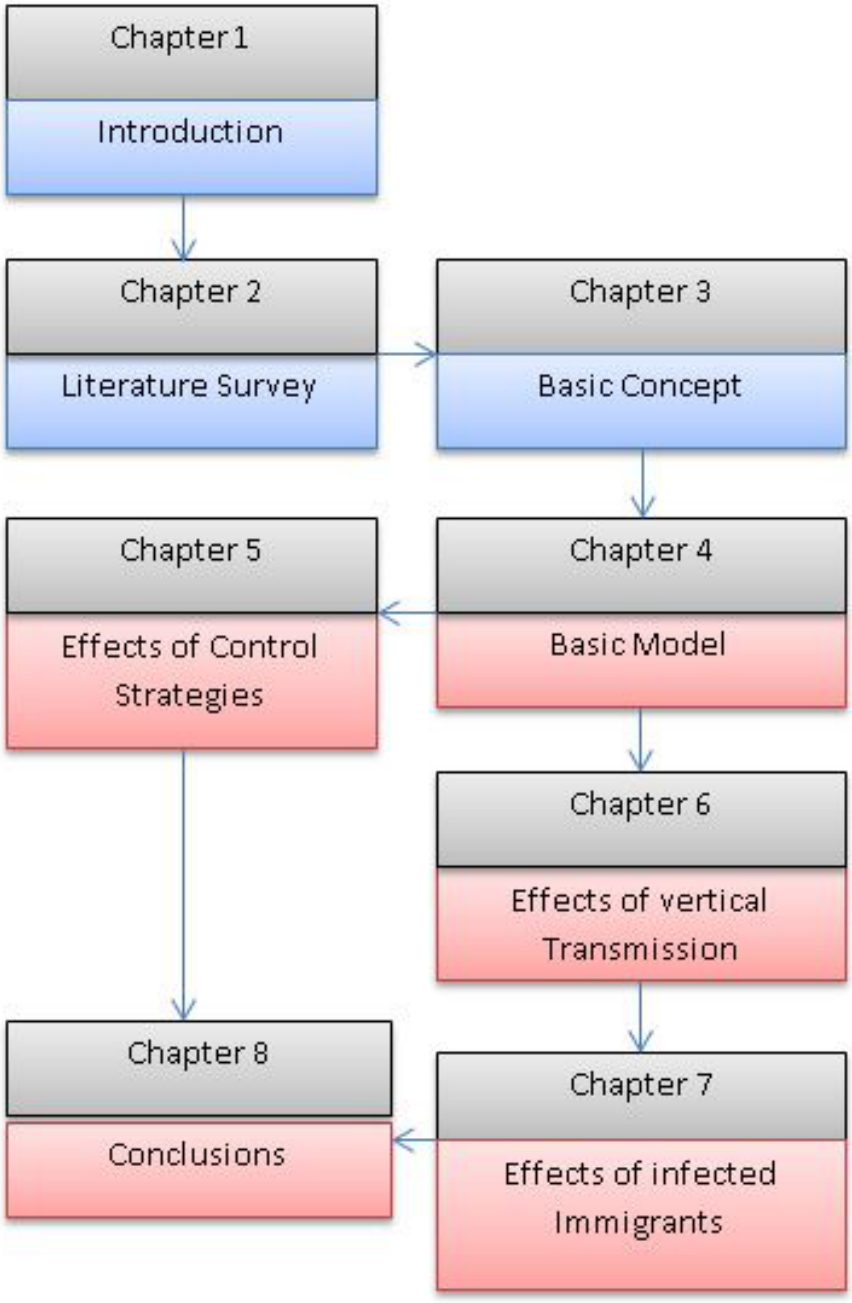


Figure 1.2: Flow chart of the thesis

CHAPTER 2

REVIEW OF THE LITERATURE

2.1 Introduction

This chapter presents the modeling frameworks that are used in the research work. The first part of the chapter gives a review of the past and present literature in relation to the HIV. This research deals with the mathematical modeling of SIV/HIV as opposed to many studies which deals with the mathematical modeling of $HIV/AIDS$.

2.2 Human Immunodeficiency Virus HIV

AIDS is caused by HIV transmission. There are many models on HIV transmission since its detection in 1981, such as (Okosun et al., 2013b; Abiodun et al., 2013; Seidu and Makinde, 2014; Seidu et al., 2015) and many more. However, these models have not taken into account SIV transmission which causes HIV which in turn causes AIDS. Modeling disease spread has helped in developing strategies to control of infectious diseases. It is developed by splitting the populace into diverse infection sections. Deterministic mathematical models that provide thorough account of transmittable disease dynamics were presented more than 100 years ago (Dietz and Heesterbeek, 2002). Mathematical models permit us to deduce from current information about the state and growth of an outbreak to forecast the future and to quantify the uncertainty in these forecasts. Some of the literature include the following;

In Okosun et al. (2013a), they presented a mathematical model by incorporating use of treatment, condom and screening of unaware infective as control measures. Op-

timal control was applied to examine the necessary conditions for the control of the disease and investigate the role played by unaware infective in the spread of the virus. Conditions for optimal control of the disease with effective use of the three control parameters was derived and analyzed. They conclude that the successful screening of unaware infectious individuals has a significant impact in reducing the endemicity of virus. This may be as a result of awareness by infective who also took necessary precautionary measures not to spread the disease. However, the model does not consider the immigration of infective individuals as well as vertical transmission of the virus. Furthermore, the model considered only humans populations.

Okosun et al. (2013b), considered another nonlinear mathematical model to analyze the recruitment effects of vulnerable and diseased individuals in order to measure the efficiency of an organizational labor force in the presence of HIV with defensive and highly active antiretroviral therapy $(HAART)$ treatment measures in improving the work force output. They further extend the model by incorporating the time-dependent control in order to derive the necessary conditions for the optimal control of the disease using pontryagins maximum principle. The model shows that combination of education/monitoring of employees and adherence to preventive measures against infection is the most cost effective strategy to combat the spread of the virus. However, the model does not consider the classification of individuals based on viral load (quantity of the virus within the infected humans), since the model is focusing on the recruitment of employees. Similarly, the model considered only humans populations which opposed to our formulations of humans and chimpanzees populations.

Abiodun et al. (2013), derived and analyzed a mathematical model that describes the dynamics of HIV infection among the immigrant youths and how parental care can

minimize or prevent the spread of the disease in the population. They analyze the model with both screening control and parental care, and then investigate its stability and sensitivity behavior. They also conduct both qualitative and quantitative analysis. It is observed that in the absence of infected youths, disease-free equilibrium is achievable and is globally asymptotically stable. They establish optimal strategies for the control of the disease with screening and parental care. The result shows that, the most effective combination of parental care and screening of immigrants gives the best results in controlling the spread of virus. Hence, the model does not consider the transmission of the virus from infected mothers to their newborn.

In 2014, Seidu and Makinde (2014) presented a mathematical model to study the optimal levels of numerous intervention plans needed to optimally decrease the spread of the virus and increase productivity. Optimal control was applied by integrating time-varying controls into the model and the condition for optimality was derived using Pontryagin's Maximum Principle. Numerical simulation of the resulting control problem was carried out to find out the efficiency of several combinations of the controls. The result shows that their approach that employs all control efforts is the most efficient in the battle against the virus. However, the model does not take consideration of infected immigrants as they contribute much on the spread of the virus.

Seidu et al. (2015), proposed a nonlinear deterministic model to study the dynamics and effects of HIV-malaria co-infection in the workplace. Basic reproduction numbers of sub-models are derived and are shown to have locally asymptotically stable (LAS) disease-free equilibria when their respective basic reproduction numbers are less than unity. Conditions for existence of endemic equilibria of sub-models are also derived. Unlike the HIV-only model, the malaria-only model is shown to exhibit a backward

bifurcation under certain conditions. Conditions for optimal control of the co-infection are derived using the Pontryagin's Maximum Principle. Numerical simulation on the resulting optimality system is performed. Using the incremental cost-effectiveness ratio, it is observed that combining preventative measures for both diseases is the best strategy for optimal control of *HIV*-malaria co-infection at the workplace. However, the model does not include the transmission from an infected mother to its newborn child.

In 2015, Duwal et al. (2015) presented a model using treatment as a control strategy in curtailing the spread of the virus. Antiviral treatment cannot cure patients, but it slows disease progression and may prevent *HIV* transmission by decreasing the amount of transmittable viruses in treated individuals. They provide a mathematical framework that allows assessing different treatment paradigms using optimal control theory together with modeling of within-host viral dynamics and drug resistance development. They use this framework to compute and evaluate two distinct optimal long-term treatment strategies for resource constrained settings. It was found that immediate treatment initiation rapidly decreases virus burden, which reduces the number of transmittable viruses and thereby the probability of infection. However, the model include only one control parameter and does not recognize the immigration of infected individuals.

Currently Huo et al. (2016) has presented an *HIV* model with inclusion of treatment compartment in order to halt the spread of the virus. Analysis of the model was carried out using stability theory. Model validity was then established through the investigation of basic reproduction number with disease free equilibrium point. Endemic equilibrium was also investigated with its global stability. The results obtained shows

that early treatment helps in combating the spread of the virus. Thus, the model only considered one control strategy and does not consider immigration of infected individuals.

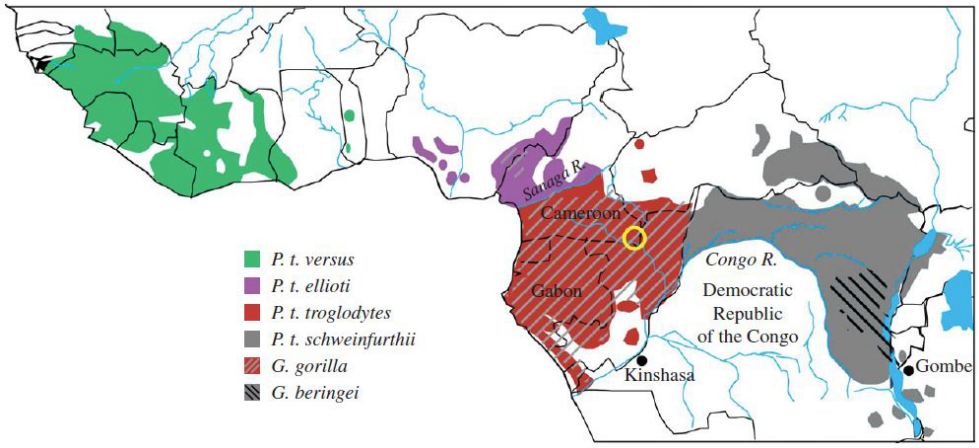
However, none of the above models were initiated by Simian Immunodeficiency Virus (SIV). As such, this work intends to extend a model of Eduafo (2015) on the dynamics of the HIV with SIV. Hence, incorporating some of the shortcomings of the reviewed literature of effects of vertical transmission and infected immigrants is the main trust of this current research.

2.3 Simian Immunodeficiency Virus (SIV)

It is a well known fact that for many years back some certain viruses were transferred from primates to human. These include Ebola and influenza (Miller, 2004; Faria et al., 2014). Zoonosis is the transfer of virus from non-human primates (chimpanzees) to humans (Pedersen and Davies, 2009; Pancino et al., 2012). SIV is a lentiviruses belonging to a family of retroviridae (Sharp et al., 2000). Lentivirus represents a genus of slow viruses and can be characterized by long incubation period. Retroviridae is a family of enveloped viruses that replicate in a host cell through the process of reverse transcription (Mansky and Temin, 1995). SIV have cross over species boundaries from simian hosts to humans on several occasions one of which led to the universal HIV disaster. Three separate crossover of SIV from the central African chimpanzee subspecies leads to the emergence of HIV group M, N and O (Nerrienet et al., 2005; Pancino et al., 2012; Kraiselburdi, 1995). The SIV is found to be identical with HIV in their genomic constituents comprising a specific gene, known as vpu that is not found in other lentiviruses (Huet et al., 1990).

The *SIV* (lentiviruses) is called immunodeficiency viruses due to their genetic and structural relationships to the human AIDS virus (Huet et al., 1990). This identical nature in genome organization made *SIV* a strong candidate as the origin of *HIV*. It is evident that African chimpanzees are reservoir of lentiviruses with potential for transmitting it to some other species (including humans) in their natural territories (Wain et al., 2007; Morin et al., 1994).

The existing literature indicate that $SIV's$ are transferred several times from non-human primates chimpanzees to human populations (Gao et al., 1999; Sharp et al., 2000; Hahn et al., 2000). However, the *HIV* sub-group M which is responsible for the great majority of all *HIV* infections worldwide appears to have arisen from one such cross-species transmission event (Sharp et al., 2000).



Source:Sharp and Hahn (2010).

Figure 2.1: Map of west and central Africa, showing the ranges of chimpanzee subspecies (colour coded).

The central common subspecies of P.t Troglodytes chimpanzees are geographically found in Democratic Republic of Congo, Gabon and southern Cameroon.

The main reason that P.t. Troglodytes is assumed to be the origin of *HIV* is that it harbor *SIV* virus that is genetically very close to the human virus *HIV* (Lemey et al., 2003; Sharp et al., 2000). In sub-Saharan Africa, there are at least 38 other primates that harbor different version of Simian Immunodeficiency Virus. Chimpanzees acquired *SIV* from two other primates of greater spot-nosed monkey (Cercopithecus Petaurista) and red-capped mangabey (Cercocebus Torquatus). They acquire this virus through hunting and consuming infected monkeys (Sharp and Hahn, 2010; Saenz et al., 2012).

Source: (Hahn, 2005)

Figure 2.2: Pan troglodytes:The Primate Source of *HIV*

The three different cross-over have led to three different consequences: group N strains have been found in a limited number of persons in Cameroon, group O strains are more prevalent but mainly limited to individuals from Cameroon and nearby countries. Group M strains have spread all over Africa and to the rest of the world (Wain et al., 2007; Pancino et al., 2012).

2.4 *HIV* Compartmental Modeling

Kermack and McKendrick (1927) formulated a model on the dynamics of infectious diseases using nonlinear dynamical system. Subsequently, Anderson and May (1979) also used nonlinear dynamical systems on the control of variety of infectious disease. The whole idea in a deterministic model is to describe epidemic by the number of vulnerable and infectious individuals with change of time. Deterministic modeling approach of infectious diseases involves the partitioning of the population of interest into a number of sub-classes called compartments. Thus, the resulting model is known as compartmental model.

In a model, diseases that confer immunity are represented by acronym *SIR* (susceptible, infected and removed/recovered) to describe the transition of individuals from susceptible to infected and finally to recovered/removed class. Diseases that do not confer immunity (no immunity against re-infection) were represented by the acronym *SIS* (susceptible, infected and susceptible). Other options includes acronyms of *SEIS* and *SEIR* models (susceptible, expose, infected and recovered) with an exposed class of being infected but cannot infect others. Hence, all the above examples are compartmental models that describe the transition of individuals from one compartment to others. The description listed below explain each compartment used in the formulations.

I. Susceptible human S_h:

   This compartment contains those individuals in a population that are not infected but are liable of contracting the disease when interacts with the infectious individuals.

II. Infected human I_h:

This class is a compartment of individuals who are infected with the disease and they can transfer the disease after an interaction with a susceptible individual.

III. Asymptomatic human I_1:

The class of infected individuals that does not show any sign of infection.

IV. Symptomatic human I_2:

The class of infected individuals that exhibits the symptoms of infections.

V. Pre-AIDS P:

This compartment covers individuals who are infected with the virus and at the stage of getting into AIDS stage.

VI. AIDS human A_h:

The class of infected individuals that developed full blown AIDS (the end stage of HIV).

The magnitudes of every class at any given time t are symbolized by $S(t), I(t), P(t), A(t)$ respectively with $N(t)$ symbolizing the overall population size.

Thus,

$$N(t) = S(t) + I(t) + P(t) + A(t). \tag{2.1}$$

Nevertheless, some other classes could be added depending on the disease and for the accuracy of the model. The dynamics of HIV model is considered through the following sub-populations of susceptible class S(t), the susceptible populations are in-

dividuals that are *HIV* negative but are prone to infection after interacting with the infectious classes sexually. The infective class I(t) individuals proceed with constant rate to develop AIDS A(t) that is,

$$N(t) = S(t) + I(t) + A(t). \tag{2.2}$$

The basic model will later be extended to consider the effects of control strategies, vertical transmission and effects of infected immigrants. Virus transmission from an infected individuals to the susceptible individuals can either be through horizontal process or vertical (mother to child) and in the case of *SIV* (chimpanzees to human), it is through blood contact during hunting and butchering of infected primates. Other important epidemic measures include basic reproduction number, incidence and prevalence. Incidence is defined as the number of individuals in the population who become infected in a given period of time (Huang et al., 2016) while prevalence is the proportion of the population that is infected at a given point in time. The basic reproduction number $\mathfrak{R}_0$ is a measure of the potential for disease spread in a population (Ball et al., 2014).

2.5 Summary

In this chapter, some literatures on Simian Immunodeficiency Virus, chimpanzees and its geographical location were briefly presented. Some nonlinear mathematical models on the spread of *HIV* were briefly discussed, which only address the interaction of human to human only. Some of the deficiencies of the models considered are, non inclusion of chimpanzees in the modeling processes, vertical transmission and effects of

infected immigrants. Hence, all the deficiencies mentioned are to be included into our proposed model. Description on the deterministic mathematical model formulation is briefly discussed. Model compartments were also described as used in the up-coming model. In the next chapter some basic concept regarding the model formulation and analysis in relation to the current study will be discussed.

CHAPTER 3

BASIC CONCEPTS, DEFINITIONS AND THEORIES

3.1 Introduction

In this chapter the introductory background, concepts, definitions and theories required for analysis of the extended models are presented. The concepts discussed are transmission function, basic reproduction number, sensitivity analysis and optimal control.

3.2 Transmission Function

According to Heesterbeek (2005), the probability of transmission during a given time period can be regarded as either a function of the number of infectious individuals in a given area or as a function of the prevalence of infection in the population. The contact rate depends on the size of the total host population and thus models are said to represent mass action (density dependent) transmission. The law of mass action states that the rate at which individuals of two types say, X and Y meet is proportional to the product of the densities of the respective sub population XY (susceptible and infected). William Hamer in 1906 Hamer (1906), while modeling the transmission of measles observed, that the incidence of new cases in a time interval was proportional to the product of SI (susceptible and infected) of the number of susceptible and infective in the population. Thus, the concept of mass action is fundamental in the modern theory of deterministic epidemic modeling (Krylova and Earn, 2013).

3.3 The Basic Reproduction Number

The basic reproduction number $\Re_0$ is a measure of the ability of the diseased to reproduce the disease in a population. It symbolizes number of secondary infectivity generated by an infected individual if introduced into a susceptible population. When $\Re_0$<1 every infected individual generates less than one new infected individual during its period of infectivity. In this situation, the infectivity will die out. But in a situation where $\Re_0$>1, every infected individual will produce more than one new infection and this situation leads to disease outbreaks. Large values of $\Re_0$ indicate the probability of a major epidemic. The method used for the computation of basic reproduction number is the next generation method introduced by Heesterbeek (2000) and later analyzed by Van den Driessche and Watmough (2002) as follows:

Consider a mathematical model with homogeneous compartments. Let the vector x indicate the state of the system and x_j is the number of individuals in compartment j. The compartments are classified in such a way that the first k compartments are not infected (susceptible) while the others are the infected compartments (latent, infected...) Van den Driessche and Watmough (2002).

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

• Let f_j be the rate of emergence of new infections in compartment j.

• $v_j^+(x)$, the rate of transfer of individuals into compartment j, by all other means.

• $v_j^-(x)$, the rate of transfer of individuals out of compartment j.

The dynamics of the compartment is defined by

$$\dot{x} = f_j(x) - v_j^+(x) - v_j^-(x). \tag{3.1}$$

It is assumed that each function is continuously differentiable at least twice in each variable. If we put $\nu_j(x) = \nu_j^+(x) - \nu_j^-(x)$ in system (3.1), it becomes,

$$\dot{x} = f_j(x) - \nu_j(x). \tag{3.2}$$

If x_0 is the disease free state of (3.2), then the infected compartments are empty. This equilibrium is called disease free equilibrium (DFE), that is $j > k, (x_0)_j = 0$. For biological reasons, to compute the basic reproduction number we have the following conditions:

I. $x \geq 0, f_j(x) \geq 0, \nu_j^+(x) \geq 0, \nu_j^-(x) \geq 0$. Since each function stands for a transfer of individuals, they are all non-negative.If a compartment is empty, then there can be no transfer of individuals out of the compartment by death, infection, or any other means.

II. If $x_i = 0$ then $\nu_j^-(x) = 0$. In particular, if we set $X_s = \{x \geq 0; x_i = 0, i = 1..., n\}$ and if $x \in X_s$ then $\nu_j^-(x) = 0$. In other words, there is no transfer from an empty compartment.

III. If $j \leq k$ then $f_j(x) = 0$ that is, if there is no immigration of infected individuals from the uninfected compartment.

IV. If x_0 is the disease free state, then $f_j(x_0) = 0$ and for $j \geq k$, $\nu_j^+(x_0) = 0$ if the population remains near the disease free equilibrium DFE, that is there is no disease, then introduction of a new infected individual will not result in an epidemic.

V. If $f(x)$ is set to zero, then all eigenvalues of $Df(x_0)$ have a negative real parts,