A MATHEMATICAL MODEL OF HIV/AIDS PANDEMIC WITH THE EFFECTS OF DRUG APPLICATION

BY

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CERTIFICATION

This thesis titled: A MATHEMATICAL MODEL OF HIV/AIDS PANDEMIC WITH THE EFFECT OF DRUG APPLICATION by SIRAJO ABDUL-RAHMAN meets the regulation governing the award of the degree of Master of Technology in Mathematics, Federal University of Technology, Minna and is approved for its contribution to knowledge and literary presentation.

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DEDICATION

TO MY PARENTS AND GRANDPARENTS

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ABSTRACT

This project proposes a mathematical model of the dynamics of HIV/AIDS pandemic and analyzes the equilibrium states for stability. The total population of the community in view is partitioned into three distinct compartments of Susceptibles, Removed and Infected classes, giving rise to a set of model equations with two ordinary differential equations and one partial differential equation. A parameter (k) is introduced to measure the effectiveness of anti-retroviral drugs application in slowing down the death of the members of the Infected class. It is observed that the zero equilibrium state will be stable if the birth rate is less than the death rate ($\beta<\mu$), while the non-zero equilibrium state, which is the state of population sustenance will be stable with the birth rate greater than the death rate ($\beta>\mu$) if k is high.

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CHAPTER ONE

INTRODUCTION

1.1 Background to the Study

Many real life situations can be transformed into mathematical models. The analysis of the model will then give an insight into the dynamics of the real life situation. The approach to this analysis brings about special schemes, which may be analytical or numerical. Problems such as the existence of equilibrium states and their stability are of great interest in the mathematical models of population dynamics as pointed out by Akinwande [2]. In this work, we propose a deterministic mathematical model of the dynamics of HIV/AIDS disease pandemic with a system of two ordinary and one partial differential equations [1,2,17]. The population $P(t)$ is partitioned into three compartments of the Susceptibles $S(t)$; this is the class in which members are virus-free but open to infection as they interact with the infected class. The second class is the Removed $R(t)$; this is the class of those assumed not susceptible to infection, possibly due to their yielding to warnings or changed behaviour as a result of public awareness campaign or enlightenment. And the third

class is the Infected *I(t)*; this is the class of those that have contracted the virus and are at various stages of the infection.

This work has been divided into five chapters. The first chapter is the introduction. In chapter two we review some literatures that are related to this work. The model equations are presented in chapter three with all the boundary conditions and the definition of parameters. The equilibrium states and the corresponding characteristic equation of the model are also obtained in chapter three. In chapter four we analyze the equilibrium states for stability. And finally, we have the conclusion and recommendations in chapter five.

1.2 Objectives of the Study

> "In the regulation of population, boundedness and stability of equilibria are two concepts most likely to be given prominence." Sowunmi [28]

The objective of this study is to analyze the equilibrium states of HIV/AIDS pandemic for stability or otherwise and the influence of antiretroviral drugs application in slowing down the death of the members of the infected class.

1.3 Significance of the Study

According to Collin Powel, U.S. former Secretary of State

"HIV doesn't just destroy immune systems; it also undermines the social, economic and political systems that underpin entire nations and regions." [9]

The studies of population have been of great relevance to the growth of a nation or community over the ages because of the practical influence it has on human life. " Population plays a vital role in the economic success of a nation to the extent that she cannot survive without adequate understanding of her population dynamics" [26]. Population studies are important for both short term and long term planning in fields such as education, health, employment, social security and environmental preservation. Such studies also provide the information needed for the formulation of government policies so as to achieve economic and social objectives.

Since the study of population is so vital, mathematical models have been of immense and reliable contribution in the study of various kinds of population dynamics. This research work is not an exception but of prime importance since it is an age-structured population model of the dynamics

of HIV/AIDS pandemic. This is so because of its closeness to the real situation as well as the use of partial differential equation in the population model.

1.4 Scope and Limitation of the Study

We partitioned the population into three compartments: S-R-I and hence a three dimensional mathematical model. The effectiveness of anti-retroviral drugs application in slowing down the death of the members of the infected class was also looked into. Accurate data are hard to come by, hence the use of hypothetical values in the analysis.

1.5 HIV/AIDS Pandemic

1.5.1 Overview of HIV/AIDS

Human Immunodeficiency Virus (HIV) is an infectious agent that causes Acquired Immunodeficiency Syndrome (AIDS), a disease that leaves a person vulnerable to life-threatening infections. Scientists have identified two types of this virus. HIV-1 is the primary cause of AIDS worldwide. HIV-2 is found mostly in West Africa.

HIV transmission occurs when a person is exposed to body fluids infected with the virus, such as blood, semen, vaginal secretions, and breast milk. The primary modes of HIV transmission are

(1) Sexual relations with an infected person

(2) Sharing hypodermic needles or accidental pricking by a needle contaminated with infected blood

(3) Transfer of the virus from an infected mother to her baby during birth or through breast-feeding.

(4) Blood transfusion

(5) Barbing and sharing of razor blades in incisions etc.

When HIV enters the body, it infects lymphocytes, white blood cells (CD4 T-cells) of the immune system. These cells are essential for the coordination of the body's immune system, which protect the body against infections. The virus commandeers the genetic material of the host cell, instructing the cell to replicate more viruses. The newly formed viruses break free from the host, destroying the cell in the process. The new viruses go on to infect and destroy other lymphocytes.

Over a period that may last from a few months to up to 15 years, HIV may destroy enough lymphocytes that the immune system becomes unable to function properly. An infected person develops multiple life-threatening illnesses from infections that normally do not cause illnesses in people with a healthy immune system. Some people who have HIV

infection may not develop any of the clinical illnesses that define the full-blown disease of AIDS for ten years or more. Doctors prefer to use the term AIDS for cases where a person has reached the final, life-threatening stage of HIV infection.

1.5.2 Signs and Symptoms of HIV Infection

The only way to know if one is infected is to be tested for HIV infection. We cannot rely on symptoms to know whether one is infected with HIV. Many people who are infected with HIV do not have any symptoms at all for many years.

The following **may be** warning signs of infection with HIV [8]:

- Rapid weight loss
- Dry cough
- Recurring fever or profuse night sweats
- Profound and unexplained fatigue
- Swollen lymph glands in the armpits, groin, or neck
- Diarrhea that last for more than a week
- White spots or unusual blemishes on the tongue, in the mouth, or in the throat
- Pneumonia

- Red, brown, pink, or purplish blotches on or under the skin or inside the mouth, nose, or eyelids
- Memory loss, depression, and other neurological disorders

However, no one should assume they are infected if they have any of these symptoms. Each of these symptoms can be related to other illnesses. Again, **the only way to determine whether one is infected is to be tested for HIV infection.**

1.5.3 Structure of HIV

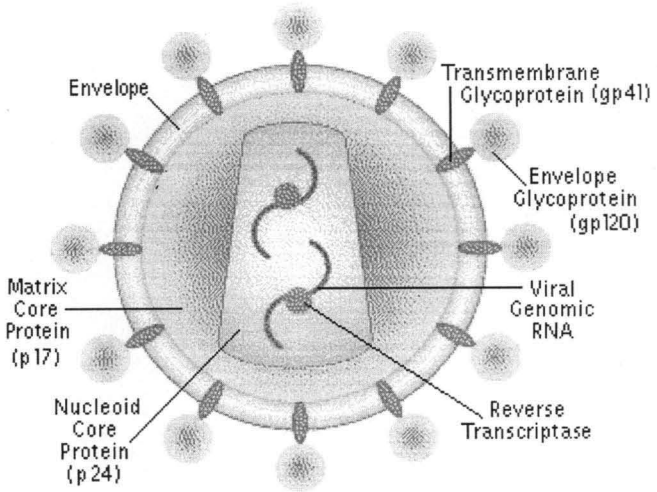

Fig. 1.1

Source: Microsoft [24]

The human immunodeficiency virus (HIV) consists of a nucleoid core and the surrounding protein matrix, both enclosed in a lipid envelope. The nucleoid core contains the viral genetic material and the

reverse transcriptase enzyme, which are used in viral replication. The transmembrane glycoprotein gp41 and the envelope glycoprotein gp120 are attached to the envelope; these proteins enable HIV to bind and fuse with a target host cell.

1.6 Mathematical Modeling

1.6.1 Overview of Mathematical Modeling

Mathematical Modeling, which is defined by Benyah [6] as "the process of creating a mathematical representation of some phenomenon in order to gain a better understanding of that phenomenon", has become an important scientific technique over the last 20 years. Mathematical Modeling provides an essential tool to capture a set of assumptions and to follow them to their precise logical conclusions. They allow us to generate new hypotheses, suggest experiments, and measure crucial parameters. Essentially, any real situation in the physical and biological world, whether natural or involving technology and human intervention, is subject to analysis by modeling if it can be described in quantitative terms. Thus, optimization and control theory may be used to model industrial processes, traffic patterns, sediment transport in streams, and other situations; information and communication theory may be used to

model message transmission, linguistic characteristics, and the like; and dimensional analysis and computer simulation may be used to model atmospheric circulation patterns, stress distribution in engineering structures, the growth and development of landforms, and a host of other processes in science and engineering.

Once a model has been developed and used to answer questions, it should be critically examined and often modified to obtain a more accurate reflection of the observed reality of that phenomenon. Mathematical modeling is an evolving process, as new insight is gained the process begins again as additional factors are considered [6]. Generally, the success of a model depends on how easily it can be used and how accurate are its predictions.

1.6.2 The Stages of Mathematical Modeling

Building a Mathematical Model for a real-life situation requires a thorough understanding of the underlying principles of the system to be modeled. During the process of building a Mathematical Model, the modeler will decide what factors are relevant to the problem and what factors can be de-emphasized. Different problems may require very different methods of approach. Benyah [6] outlined the following steps as

a general approach to the formulation of a real-life problem in Mathematical terms:

(a) Identify the problem

(b) Identify the important variables and parameters

(c) Determine how the variables relate to each other, stating the assumptions.

(d) Develop the equation(s) that express the relationship between the variables and constraints.

(e) Analyze and solve the resulting mathematical problem.

1.6.3 Mathematical Modeling with Differential Equations.

Differential Equations form very important mathematical tools used in producing models of physical and biological processes. They have been the subjects of a great deal of research for more than 100 years. Burghes and Wood [7] have this to say "..., it could even be claimed that the spread of modern industrial civilization, for better or for worse, is partly a results of man's ability to solve the Differential Equations which govern so many of our industrial processes, be they chemical or engineering."

1.7 Equilibrium and Stability

1.7.1 Equilibrium

Equilibrium is the state of a system whose configuration or large-scale properties do not change over time. For example, if a hot penny is dropped into a cup of cold water, the system of the water and penny will reach equilibrium when both are at the same temperature. At that point, the large-scale properties of the system, namely the temperature of the water and the penny, will not change over time. As another example, in mechanics a system is at equilibrium if the net force acting on a body is equal to zero. In the case of a stationary body, the large-scale property of the position of the body will remain unchanged over time. If the dynamics of a system is described by a differential equation (or a system of differential equations), then equilibria can be estimated by setting a derivative (all derivatives) to zero.

Example: Logistic model:

$$\frac{dN}{dt} = r_0 N\left(1 - \frac{N}{K}\right)$$

To find equilibria we have to solve the equation: $\frac{dN}{dt} = 0$:

i.e. $r_0 N\left(1 - \frac{N}{K}\right) = 0$. This equation has two roots: $N=0$ and $N=K$.

1.7.2 Stability

Stability in physics and engineering is the property of a body that causes it to return to its original position or motion as a result of the action of the so-called restoring forces, or torques, once the body has been disturbed from a condition of equilibrium or steady motion. In a moving or oscillating system, stability generally demands both restoring forces and damping factors. If the restoring forces in an electrical or mechanical oscillating system, such as a servomechanism, are not properly timed and if damping is insufficient, these forces cannot fulfill their function, rendering the system unstable and sending it out of control. For control surfaces of aircraft or for large suspension bridges, the interaction between the oscillating aerodynamic forces and the structure may lead to sudden large and disastrous vibrations, or flutter.

A solution $f(x)$ is said to be stable if any other solution of the equation that starts out sufficiently close to it when $x=0$ remains close to it for succeeding values of x. if the difference approaches zero as x increases, the solution is called asymptotically stable. If a solution does not have either of these properties, it is called unstable.

1.7.3 Illustrative Examples

An equilibrium may be stable or unstable. For example, the equilibrium of a pencil standing on its tip is unstable; The equilibrium of a picture on the wall is (usually) stable (Fig.1.2)

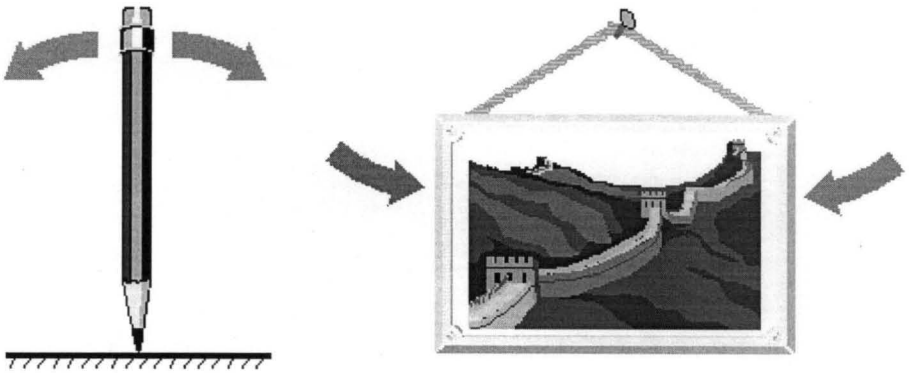

Fig. 1.2

Consider Fig 1.3 below, if a ball is pushed down a hill, it may end up in the positions indicated by Q or S, but it would be a lucky push indeed that results in the ball being positioned exactly at R. For this problem, the positions Q and S are stable equilibria for the ball, whereas R is an unstable equilibrium. Even if we carefully place the ball at point R, a gentle breeze or earth tremor will cause the ball to move away from R. In contrast, placing a ball at point Q or S will result in the ball staying near that stable equilibrium, even on a gusty day.

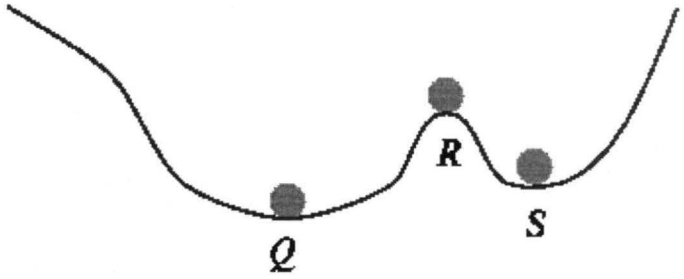

Fig. 1.3

Equilibrium is considered stable (for simplicity we will consider asymptotic stability only) if the system always returns to it after small disturbances. If the system moves away from the equilibrium after small disturbances, then the equilibrium is unstable.

The notion of stability can be applied to other types of attractors (limit cycle), however, the general definition is more complex than for equilibria. Stability is probably the most important notion in science because it refers to what we call "reality". Everything should be stable to be observable. For example, in quantum mechanics, energy levels are those that are stable because unstable levels cannot be observed.

CHAPTER TWO

LITERATURE REVIEW

2.1 Introduction

"Epidemiology is the mathematical study of the spread of disease. The most pressing problems in this area are to do with HIV/AIDS. It is estimated that 42 million individuals are living with HIV/AIDS, and of these 29 million are Africans. The rate of infection in most developing countries is high." Farai [15]

The purpose of this chapter is to review some literatures that are related to the dynamic of HIV/AIDS pandemic. Thousands of mathematical models have been developed on this topic with different purposes in mind. Hence, in order to ease our understanding, the literature review has been divided into the following sub sections:

- HIV and the Immune System
- HIV and its Transmission/Spread
- Prevention and Treatment
- The HIV – AIDS Connection

2.2 HIV and the Immune System

Understanding how the HIV actively diminishes the immune system's capability of response, and HIV's ability to mutate, which ultimately leads to drug therapy failure, are arguably some of the most important medical problems of the 21st century. In fact, while researchers worldwide are actively combating this disease, we still lack an understanding of many of the fundamental properties of its pathogenesis.

In 1995 a simple model for Human Immunodeficiency Virus-1 viral loads in the blood plasma of infected individuals was presented in a paper by David Ho et al. [12], which revolutionized our understanding of the disease. This work was the first to show that the infection pathogenesis was a rapidly varying dynamical process during which about twelve billion viral particles per day were being produced in infected individuals.

Dominik and Martin [14] review mathematical models of HIV dynamics, disease progression, and therapy. They start by introducing a basic model of virus infection and demonstrate how it was used to study HIV dynamics and to measure crucial parameters that lead to a new understanding of the disease process. They discuss the diversity threshold

model as an example of the general principle that virus evolution can drive disease progression and the destruction of the immune system. Finally, they show how mathematical models can be used to understand correlates of long-term immunological control of HIV, and to design therapy regimes that convert a progressing patient into a state of long-term non-progression.

Josef [19] examine the increasing of the HI-viruses in the human body. This model gives an answer to the question why the space of time between HI-infection and outbreak of AIDS differs to a great extent. It also gives insight into the phenomenon that our immune system is generally not able to root out HI-viruses completely. This example is interesting and well suited for lessons combining subjects like mathematics and biology. It demonstrates that even extensive simulations can be well done by the TI92/TI89 or DERIVE.

In a similar development Ibinaiye [18] developed a mathematical model of the immune deficiency in an HIV/AIDS patients and concluded that since the non-zero state equilibrium is unstable once the HIV is introduced into a blood system, recovery is mostly unlikely.

2.3 HIV and its Transmission/Spread

Research has revealed a great deal of valuable medical, scientific, and public health information about the ways in which HIV can be transmitted.

CDC [8] explain that HIV is spread by sexual contact with an infected person, by sharing needles and/or syringes (primarily for drug injection) with someone who is infected, or, less commonly through transfusions of infected blood or blood clothing factors. Babies born to HIV-infected women may become infected before or during birth or through breast-feeding after birth. On the fear of some people that HIV might be transmitted in other ways such as through air, water, or insects, CDC pointed out that, no scientific evidence to support any of these fears has been found, adding "If HIV were being transmitted through other routes, the pattern of reported cases would be much different from what has been observed. For example, if mosquitoes could transmit HIV infection, many more young children and preadolescents would have been diagnosed with AIDS."

In another development, WHO [31] reported that Mathematical modeling is being used to model Herpes Simplex Virus Type 2 (HSV2)

spread and control and the interactions between HSV2 and HIV. The modeling allows improved understanding of the mechanisms of STI spread by analyzing, interpreting and identifying gaps in empirical data and guiding future field studies. However, as the validity of the output depends on the validity of the input, modeling does not usually provide quantitative certainty. Modeling HSV2 spread has highlighted that sexual behaviour patterns, such as age mixing, and biomedical factors, such as the duration of the period with recurrences, are more important determinants of HSV2 incidence and prevalence than the frequency and duration of individual recurrences.

In an attempt to find out if genetic mutation influences spread of HIV/AIDS, Kirschner et al. [21] designed a model that compare the rate of HIV transmission in two populations. All the individuals in one group had two copies of the normal genetic mutation that protects people from HIV Infection (CCR5 gene). The second group was a combination of individuals -- some with two mutated CCR5 alleles, some with one mutated and one normal allele, and others with two copies of the normal gene. They found out that people with two copies or alleles of this mutation are almost completely protected against HIV, those with one

mutated and one normal copy can be infected, but they carry lower levels of the virus and take two years longer, on average, to develop AIDS. People with two normal copies of the CCR5 gene are most susceptible to HIV infection. In the model population without the protective mutation, the researchers found that HIV/AIDS prevalence increased logarithmically for the first 35 years of the epidemic, reaching 18 percent before leveling off. In the model population with the mutated CCR5 gene, the epidemic spread more slowly for the first fifty years and HIV/AIDS prevalence reached approximately 12 percent. Prevalence began to decline after 70 years.

Finally their results suggest that the CCR5 mutation limits the epidemic by decreasing the probability of infection due to lower viral loads in people with one copy of the mutated gene.

2.4 Prevention and Treatment of HIV/AIDS

David et al. [11] examine the impact of condom use on the sexual transmission of human immunodeficiency virus (HIV) and acquired immune deficiency syndrome (AIDS) amongst a homogeneously mixing male homosexual population. They first derive a multi-group SIR-type model of HIV/AIDS transmission where the homosexual population is

split into subgroups according to frequency of condom use. Both susceptible and infected individuals can transfer between the different groups. They then discuss in detail an important special case of their model, which includes two risk groups and perform an equilibrium and stability analysis for this special case. Their analysis shows that the model can exhibit unusual behaviour. As normal, if the basic reproduction number, R_0, is greater than unity then there is a unique disease-free equilibrium, which is locally unstable and a unique endemic equilibrium. However, when R_0 is less than unity two endemic equilibrium solutions can also co-exist simultaneously with the disease-free solution, which is locally stable. Numerical simulations using realistic parameter values confirm this and they find that in certain circumstances the disease-free solution and one of the endemic solutions are both locally asymptotically stable, while the other endemic solution is unstable. This unusual behaviour has important implications for control of the disease as reducing R_0 to less than unity no longer guarantees eradication of the disease. For a restricted special case of this two-group model they show that there is only the disease-free equilibrium for $R_0 \leq 1$ which is globally

stable. For $R_0 > 1$ the disease-free equilibrium is unstable and there is a unique endemic equilibrium which is locally stable.

Michael et al. [23] introduced a mathematical model to study the accelerating impact of HIV infection on the incidence rates of tuberculosis (TB) disease. A sexually active population (15-49 years) is followed cross-sectionally over a period of time. Beginning with the year in which HIV infection was probably first present in the population, the model calculates the growing yearly incidence rates of new TB disease in HIV-positive and in HIV-negative individuals. Model equations derived by an actual method, are developed recursively. Input information required for the calculations includes the age distribution of the study population, pre-HIV annual TB infection rates, annual HIV infection and mortality rates and estimates of annual TB disease breakdown rates in the absence and in the presence of HIV infection. With correct input data, the model provides a useful blueprint for health agencies in designing effective programmes for curbing the future course of these dual epidemics in the population.

The most interesting result of a simple dynamic model by Perelson et al. [27] establishing the existence of multiple equilibrium states, one of

which is virus-free, led to so many further research works. One of this is the depletion of lymphocytes as a therapy for AIDS, based on a population dynamic model, advocated by de Boer and Boucher [13]. They proposed that using a suitable immunosuppressant or CD4-killing drug in combination with an anti-viral therapy may eliminate the infection. The intervention by lymphocyte depletion will work as predicted by modeling only if other parameters of the system remain substantially unaffected. This is an unlikely outcome with immunosuppressive drugs. Results from limited attempts to use them in HIV-positive patients [3,4,10] are interesting, but not very encouraging. In fact, the observed rise in CD4+ counts runs *contrary* to the expected effect of depletion. Activation of latent CD4+ by OKT3 and IL-2 with intention to purge the virus has also been attempted by Van Praag et al. [30], but the outcome was a surprisingly prolonged depletion of CD4+ with little effect on the virus.

Research works on risk and benefits of medication for human immunodeficiency virus (HIV) shows that infected patients are at risk of developing fungal and bacterial infections that take the "opportunity" provided by a patient's weakened immune systems to attack the body.

Moore et al. [25] found out that the ability of zidovudine (ZDV) therapy to prolong survival in HIV-infected patients is limited to between 1 and 2 years in patients with CD4 cell counts of 500/mm3 or less, perhaps due to the emergence of ZDV-resistant HIV. Beyond 1 year of ZDV use, changing to an alternative therapy—such as didanosine, zalcitabine, stavudine, or combination therapy—may be appropriate, conclude the authors. They determined the duration of ZDV benefit in 393 patients who were receiving HIV care at a large urban clinic; 57 percent of the patients were injecting drug users. They compared the 235 patients who used ZDV with the 158 nonusers and found that the risk of dying was reduced by two-thirds when ZDV was used for less than a year. However, this hazard declined only 25 percent by the second year. These findings demonstrate an early, though limited, benefit of ZDV in an urban, predominantly black population with a relatively high proportion of women and injecting drug users. This study preceeded current work on combination therapies and contributed to the evolving knowledge base on treatment options for HIV-infected patients.

In another development, Maenza et al. [22] revealed that advanced immunosuppression, indicated by low CD4 cell count, and increased

exposure to oral azole medications increase the risk for developing fluconazole resistance. The researchers conducted a case control study to identify risk factors for development of this resistance in 25 patients with fluconazole-resistant candidiasis, whom they compared with controls who had treatment-responsive candidiasis. After their first episode of candidiasis, patients who later developed fluconazole resistance had more treated episodes than did matched controls (3.1 vs. 1.8) lower median CD4 cell counts (11 vs. 77/mm3), and greater median durations of all antifungal therapy (419 vs. 118 days) and systemic azole therapy (272 vs. 14 days). These findings raise the question of whether oropharyngeal candidiasis should be treated with topical agents whenever possible, reserving systemic azoles for patients with esophageal candidiasis or invasive mycoses, conclude the researchers.

Using a mathematical method called "uncertainty analysis," the University of California-Los Angeles researchers (UCLA) [29] led by Blower, calculated the impact of a range of variables on HIV infection in San Francisco. The researchers assumed that antiretroviral treatments lower the amount of virus contained in the bloodstream by at least half and possibly up to 100-fold, meaning that widespread antiretroviral use

will make it more difficult for HIV-positive individuals to transmit the virus to sexual partners. The mathematicians also assumed that drug-resistant strains of HIV will develop but will be less infectious. Even when "worst-case assumptions" -- such as the evolution of drug-resistant HIV that is infectious and an increase in unprotected sexual activity among people using antiretroviral drugs -- are factored in, the model predicts that antiretroviral treatment will stop the HIV/AIDS epidemic in San Francisco "well before" the end of the century.

Their prediction was with reactions from different angles. Gange [16] said that other studies conducted in Uganda and the United States have shown that antiretroviral treatment "only marginally affects a person's ability to infect" others with HIV. He added that the main reason why antiretroviral treatment will not slow the epidemic is that "in the real world, most patients manage to sustain a 50% or less reduction" in viral load, a smaller reduction than calculated in the UCLA study.

The researchers replied that their model is based on San Francisco data, where most patients on antiretroviral therapy have experienced decreases in viral loads of more than 50%. Therefore, the pandemic could only be slowed through widespread antiretroviral use because treating

only a small percentage of the HIV-positive population would have "very little impact" on HIV transmission. The researchers concluded that regardless of whether antiretroviral drugs can reverse the HIV/AIDS pandemic, the drugs "should be available to all who need them, regardless of poverty," because they help extend life expectancy.

2.5 The HIV – AIDS Connection

Some persons are of the opinion that AIDS is not caused by an infectious agent or is caused by a virus that is not HIV. "This is not only misleading," observed CDC [8], "but may have dangerous consequences." Prior to 1996, scientist estimated that about half the people with HIV would develop AIDS within 10 years after becoming infected. This time varied greatly from person to person and depended on may factors, including a person's health status and their health-related behaviors. "Since 1996, the introduction of powerful anti-retroviral therapies has dramatically changed the progression time between HIV infection and the development of AIDS," pointed out CDC [8].

The amount of time that it will take for patients infected with the human immunodeficiency virus (HIV) to develop AIDS can be predicted by the amount of viral RNA in their blood, according to a study Lau et al.

[22] which was supported in part by the Agency for Health Care Policy and Research (HS07782).

The investigators constructed a mathematical model to predict the time to symptomatic disease based on viral load measurements from longitudinal observations of untreated patients with asymptomatic HIV infection and CD4 cell counts greater than 500. For different viral loads, they calculated the time to progression to AIDS using a wide range of estimates for the time since seroconversion and the rate of change of viral load over time.

The investigators found that without antiretroviral treatment, asymptomatic HIV-infected patients with a viral load of 105 copies of viral RNA/ml serum are at risk of developing AIDS in less than 3 years, and patients with a viral load that is half a log higher (105.5) may develop AIDS in less than 1 year. In stark contrast, for patients with a viral load of 104.5, it may be at least 2 years or as many as 8 years before they develop AIDS; patients who have a viral load of 104 have 3 to 19 years before developing AIDS, according to the study.

Using viral load as a marker of disease status is important for guiding therapy during all stages of the disease, especially when the CD4

cell count, a marker of immune system deficiency, is maintained at levels close to normal (about 1,000). This is true even if the exact time of seroconversion (development of antibodies to HIV in the blood, the signal of infection) is unknown, points out John et al. [20]. Adding that "In patients with advanced stages of disease, CD4 cell counts may provide better information than viral load for long-term outcomes, but changes over time in viral load may be more useful in determining the efficacy of antiretroviral treatment."

CHAPTER THREE

THE MODEL EQUATIONS AND EQUILIBRIUM STATES

3.1 Introduction

The population is partitioned into three compartments of the Susceptibles *S(t)*, Removed *R(t)* ant the Infected *I(t)* as earlier explain in chapter one.

The infected class *I(t)* is structured by the infection age with the density function $\rho(t,\tau)$, where t is the time parameter and τ is the infection age. There is a maximum infection age T at which a member of the infected class *I(t)* must leave the compartment via death; and so $0 \leq \tau < T$. This notwithstanding, a member of the class could still die by natural causes at a rate μ, the latter is also applicable to the Susceptibles class *S(t)* and the Removed class *R(t)*.

Members of the class *S(t)* move into the class *R(t)* due to change in behaviour or/and as a result of effective public campaign at a rate γ.

The death rate via infection is given by :

$$\delta \tan \frac{\pi\tau}{2Tk}$$

where k is a control parameter which could be associated with the measure of slowing down the death of the infected, such as the

effectiveness of anti-retroviral drugs which give the victims longer life-span. A high value of k means high effectiveness of such measure and vice versa.

It is assumed that while the new births in *S(t)* are born as Susceptibles, the offspring of *I(t)* are divided between *S(t)* and *I(t)* in the proportions θ and $(1-\theta)$ respectively, i.e. a proportion $(1-\theta)$ of the offspring of *I(t)* are born with the virus.

3.2 The Model Equations

The model equations are given by (3.1) to (3.8) below; with the infected class structured into the infection age using the pattern of Gurtin and MacCamy [17].

$$P(t) = S(t) + R(t) + I(t) \tag{3.1}$$

$$\frac{dS(t)}{dt} = \beta(S(t)+R(t)) - (\gamma+\mu)S(t) + \theta\beta I(t) - \alpha S(t)I(t) \tag{3.2}$$

$$\frac{dR(t)}{dt} = \gamma S(t) - \mu R(t) \tag{3.3}$$

$$\frac{\partial \rho(t,\tau)}{\partial t} + \frac{.\partial \rho(t,\tau)}{\partial \tau} + \sigma(\tau)\rho(t,\tau) = 0 \tag{3.4}$$

$$\sigma(\tau) = \mu + \delta \tan\frac{\pi\tau}{2Tk} \tag{3.5}$$

$$I(t) = \int_0^T \rho(t,\tau)d\tau \tag{3.6}$$

$$\rho(t,0) = B(t) = \alpha S(t)I(t) + (1-\theta)\beta I(t);\ \rho(0,\tau) = \phi(\tau) \qquad (3.7)$$

$$S(0) = S_0; R(0) = R_0; I(0) = I_0 \qquad (3.8)$$

The parameters are defined as follows:

β = natural birth rate for the population *P(t)*.

μ = natural death-rate for the population *P(t)*.

α = rate of contracting the HIV virus, via interaction of *S(t)* and *I(t)*.

$\sigma(\tau)$ = the gross death rate of the infected class *I(t)*.

δ = an additional burden from infection which is being regulated by environmental factors such as the social status of the infected person. $0 \leq \delta < 1$.

k = measure of the effectiveness of application of anti-retroviral drugs at slowing down the death of infected members in *I(t)*.

γ = rate of removal of the Susceptible *S(t)* into the Removed class *R(t)*; due to public campaign; i.e. the measure of the effectiveness of the public campaign against infection.

θ = the proportion of the offspring of the infected class *I(t)* which are virus-free at birth; with $0 \leq \theta \leq 1$.

t = time; τ = infection age.

T = maximum infection age; $\sigma(\tau)\to\infty$ as $\tau\to kT$, $0\le\tau<kT$.

3.3 Equilibrium States of the Model

At the equilibrium states let

$$S(0)=x;\ R(0)=y;\ I(0)=z \tag{3.9}$$

So that from (3.6) and (3.9) we have

$$z=\int_0^T\phi(\tau)d\tau \tag{3.10}$$

from (3.7) and (3.9) we have

$$\phi(0)=B(0)=\alpha xz+(1-\theta)\beta z \tag{3.11}$$

substituting (3.9) – (3.10) into (3.2) – (3.4) give:

$$\beta(x+y)-(\gamma+\mu)x+\theta\beta z-\alpha xz=0 \tag{3.12}$$

$$\gamma x-\mu y=0 \tag{3.13}$$

$$\frac{d\phi(\tau)}{d\tau}+\sigma(\tau)\phi(\tau)=0; \tag{3.14}$$

$$\phi(\tau)=\phi(0)\exp\left\{-\int_0^\tau\sigma(s)ds\right\} \tag{3.15}$$

let

$$\psi(\tau)=\exp\left\{-\int_0^\tau\sigma(s)ds\right\} \tag{3.16}$$

equation (3.15) becomes

$$\phi(\tau)=\phi(0)\psi(\tau) \tag{3.17}$$

Substituting (3.17) into (3.10), we have,

$$z = \int_0^T \phi(0)\psi(\tau)d\tau$$

$$z = \phi(0)\int_0^T \psi(\tau)d\tau$$

$$z = \phi(0)\overline{\psi} \tag{3.18}$$

Where $\overline{\psi} = \int_0^T \psi(\tau)d\tau$ (3.19)

Using equations (3.11) and (3.18) gives

$$z = \{\alpha xz + (1-\theta)\beta z\}\overline{\psi} \tag{3.20}$$

We then solve equations (3.12), (3.13) and (3.20) simultaneously for x,y, and z.

From (3.20), we have,

$$\{\alpha xz + (1-\theta)\beta z\}\overline{\psi} = z$$

$$\{\alpha x + (1-\theta)\beta\}\overline{\psi} = 1$$

$$\alpha\overline{\psi}x + (1-\theta)\beta\overline{\psi} = 1$$

$$\alpha\overline{\psi}x = 1 - (1-\theta)\beta\overline{\psi}$$

$$x = \frac{1-(1-\theta)\beta\overline{\psi}}{\alpha\overline{\psi}} \tag{3.21}$$

Substitute (3.21) into (3.13) to get y,

i.e. $-\mu y = -\gamma x$

$$-\mu y = \frac{-\gamma\,(1-(1-\theta)\beta\overline{\psi})}{\alpha\overline{\psi}}$$

$$y = \frac{\gamma[1-(1-\theta)\beta\overline{\psi}]}{\alpha\mu\overline{\psi}} \qquad (3.22)$$

From (3.12) we have,

$$\beta x + \beta y - \gamma x - \mu x + \theta\beta z - \alpha x z = 0$$

Substitute (3.21) and (3.22) to get z,

$$\frac{\beta[1-(1-\theta)\beta\overline{\psi}]}{\alpha\overline{\psi}} + \frac{\beta[\gamma\,(1-(1-\theta)\beta\overline{\psi}]}{\alpha\mu\overline{\psi}} - \frac{\gamma[1-(1-\theta)\beta\overline{\psi}]}{\alpha\overline{\psi}}$$

$$- \frac{\mu[1-(1-\theta)\beta\overline{\psi}]}{\alpha\overline{\psi}}) + \theta\beta z - \frac{\alpha z[1-(1-\theta)\beta\overline{\psi}]}{\alpha\overline{\psi}} = 0$$

Multiply through by the L.C.M. ($\alpha\mu\overline{\psi}$)

$$\beta\mu\,\{1-(1-\theta)\beta\overline{\psi}\} + \beta\gamma\{1-(1-\theta)\beta\overline{\psi}\} - \mu\gamma\{1-(1-\theta)\beta\overline{\psi}\}$$

$$-\mu^2\{1-(1-\theta)\beta\overline{\psi}\} + \theta\,\beta\alpha\mu\overline{\psi}\,z - \mu\alpha z\{1-(1-\theta)\beta\overline{\psi}\} = 0$$

$$(\beta\mu+\beta\gamma-\mu\gamma-\mu^2)(1-(1-\theta)\beta\overline{\psi}) - \{\alpha\mu(1-(1-\theta)\beta\overline{\psi}) - \alpha\beta\mu\overline{\psi}\,\theta\}z = 0$$

i.e.

$$z = \frac{\left(\beta\mu+\beta\gamma-\mu^2-\mu\gamma\right)(1-(1-\theta)\beta\overline{\psi})}{\alpha\mu(1-(1-\theta)\beta\overline{\psi}) - \alpha\beta\mu\overline{\psi}\theta}$$

$$z = \frac{(\beta-\mu)(\gamma+\mu)(1-(1-\theta)\beta\overline{\psi})}{\alpha\mu(1-\beta\overline{\psi})} \qquad (3.23)$$

The Equilibrium states are

(a) the zero equilibrium states given by (x,y,z) = (0,0,0), and

(b) The non-zero equilibrium states (x,y,z) given by :

$$x = \frac{1-(1-\theta)\beta\overline{\psi}}{\alpha\overline{\psi}}$$

$$y = \frac{\gamma[1-(1-\theta)\beta\overline{\psi}]}{\alpha\mu\overline{\psi}}$$

$$z = \frac{(\beta-\mu)(\gamma+\mu)(1-(1-\theta)\beta\overline{\psi})}{\alpha\mu(1-\beta\overline{\psi})}.$$

3.4 The Characteristic Equation

We perturb the equilibrium state as follows: Let

$$S(t) = x + p(t);\ p(t) = \overline{p}\, e^{\lambda t} \tag{3.24}$$

$$R(t) = y + rp(t);\ p(t) = \overline{r}\, e^{\lambda t} \tag{3.25}$$

$$I(t) = z + q(t);\ q(t) = \overline{q}\, e^{\lambda t} \tag{3.26}$$

Where $\overline{p}$, $\overline{q}$, $\overline{r}$ are constants.

$$\rho(t,\tau) = \phi(\tau) + \eta(\tau)e^{\lambda t} \tag{3.27}$$

with $$\overline{q} = \int_0^T \eta(\tau)d\tau \tag{3.28}$$

Substituting (3.24) to (3.27) into the model equation (3.2) to (3.4), we have

$$\frac{d\left(x+\bar{p}e^{\lambda t}\right)}{dt}=\beta\left(x+\bar{p}e^{\lambda t}\right)+\beta\left(y+\bar{r}e^{\lambda t}\right)-\gamma\left(x+\bar{p}e^{\lambda t}\right)$$

$$-\mu\left(x+\bar{p}e^{\lambda t}\right)+\theta\beta\left(z+\bar{q}e^{\lambda t}\right)-\alpha\left(x+\bar{p}e^{\lambda t}\right)\left(z+\bar{q}e^{\lambda t}\right) \qquad (3.29)$$

giving

$$\lambda\bar{p}e^{\lambda t}=\beta x+\beta\bar{p}e^{\lambda t}+\beta y+\beta\bar{r}e^{\lambda t}-\gamma x-\gamma\bar{p}e^{\lambda t}-\mu x-\mu\bar{p}e^{\lambda t}+\theta\beta z$$

$$+\theta\beta\bar{q}e^{\lambda t}-\alpha\left(\alpha z+x\bar{q}e^{\lambda t}+z\bar{p}e^{\lambda t}+\bar{p}\bar{q}e^{2\lambda t}\right)$$

$$=\beta x+\beta\bar{p}e^{\lambda t}+\beta y+\beta\bar{r}e^{\lambda t}-\gamma x-\gamma\bar{p}e^{\lambda t}-\mu x-\mu\bar{p}e^{\lambda t}+\theta\beta z$$

$$+\theta\beta\bar{q}e^{\lambda t}-\alpha xz-\alpha x\bar{q}e^{\lambda t}-\alpha z\bar{p}e^{\lambda t}-\alpha\bar{p}\bar{q}e^{2\lambda t}$$

$$=\beta x+\beta y-\gamma x-\mu x+\theta\beta z-\alpha xz+\beta\bar{p}e^{\lambda t}+\beta\bar{r}e^{\lambda t}-\gamma\bar{p}e^{\lambda t}$$

$$-\mu\bar{p}e^{\lambda t}+\theta\beta\bar{q}e^{\lambda t}-\alpha x\bar{q}e^{\lambda t}-\alpha z\bar{p}e^{\lambda t}-\alpha\bar{p}\bar{q}e^{2\lambda t}$$

Using equation (3.12) and neglecting terms of order 2 in λt gives

$$\lambda\bar{p}e^{\lambda t}=\beta\bar{p}e^{\lambda t}+\beta\bar{r}e^{\lambda t}-\gamma\bar{p}e^{\lambda t}-\mu\bar{p}e^{\lambda t}+\theta\beta\bar{q}e^{\lambda t}$$

$$-\alpha x\bar{q}e^{\lambda t}-\alpha z\bar{p}e^{\lambda t}$$

Dividing through by $e^{\lambda t}$ gives

$$\lambda\bar{p}=\beta\bar{p}+\beta\bar{r}-\gamma\bar{p}-\mu\bar{p}+\theta\beta\bar{q}-\alpha x\bar{q}-\alpha z\bar{p}$$

$$0=\beta\bar{p}-\gamma\bar{p}-\mu\bar{p}-\lambda\bar{p}-\alpha z\bar{p}+\beta\bar{r}+\theta\beta\bar{q}-\alpha x\bar{q}$$

$$(\beta - \gamma - \mu - \lambda - \alpha z)\bar{p} + \beta\bar{r} + (\theta\beta - \alpha x)\bar{q} = 0 \tag{3.30}$$

Also from equation (3.3), we obtain

$$\frac{d\left(y + \bar{r}e^{\lambda t}\right)}{dt} = \gamma\left(x + \bar{p}e^{\lambda t}\right) - \mu\left(y + \bar{r}e^{\lambda t}\right) \tag{3.31}$$

giving,

$$\lambda\bar{r}e^{\lambda t} = \gamma x + \gamma\bar{p}e^{\lambda t} - \mu y - \mu\bar{r}e^{\lambda t}$$

Taking cognizance of equation (3.13) gives the above equation as

$$\lambda\bar{r}e^{\lambda t} = \gamma\bar{p}e^{\lambda t} - \mu\bar{r}e^{\lambda t}$$

Dividing through by $e^{\lambda t}$, gives

$$\lambda\bar{r} = \gamma\bar{p} - \mu\bar{r}$$

$$\lambda\bar{r} + \mu\bar{r} - \gamma\bar{p} = 0$$

$$(\lambda + \mu)\bar{r} - \gamma\bar{p} = 0$$

or

$$\gamma\bar{p} - (\lambda + \mu)\bar{r} = 0 \tag{3.32}$$

Also equations (3.27) and (3.28) when substituted into (3.4) gives

$$\frac{\partial(\phi(\tau) + \eta(\tau)e^{\lambda t})}{\partial t} + \frac{\partial(\phi(\tau) + \eta(\tau)e^{\lambda t})}{\partial\tau} + \sigma(\tau)(\phi(\tau) + \eta(\tau)e^{\lambda t}) = 0 \tag{3.33}$$

giving,

$$\lambda\eta(\tau)e^{\lambda t} + \frac{d\phi(\tau)}{d\tau} + e^{\lambda t}\frac{d\eta(\tau)}{d\tau} + \sigma(\tau)\phi(\tau) + \phi(\tau)\eta(\tau)e^{\lambda t} = 0$$

Using equation (3.14) reduces the above equation to

$$\lambda\eta(\tau)e^{\lambda t} + e^{\lambda t}\frac{d\eta(\tau)}{d\tau} + \phi(\tau)\eta(\tau)e^{\lambda t} = 0$$

Dividing through by $e^{\lambda t}$, we have

$$\frac{d\eta(\tau)}{d\tau} + (\phi(\tau) + \lambda)\eta(\tau) = 0 \qquad (3.34)$$

Solving the ODE (3.34) gives,

$$\eta(\tau) = \eta(0)\exp\left\{-\int_0^{\tau}(\lambda + \sigma(s)ds\right\} \qquad (3.35)$$

Integrating (3.35) over [0,T] gives

$$\int_0^T \eta(\tau)d\tau = \eta(0)\int_0^T \exp\left\{-\int_0^{\tau}(\lambda + \sigma(s)ds\right\}d\tau$$

Using equation (3.28) in the above reduces it to

$$\bar{q} = \eta(0)\int_0^T \exp\left\{-\int_0^{\tau}(\lambda + \sigma(s)ds\right\}d\tau$$

$$\bar{q} = \eta(0)b(\lambda) \qquad (3.36)$$

with

$$b(\lambda) = \int_0^T \exp\left\{-\int_0^{\tau}(\lambda + \sigma(s)ds\right\}d\tau \qquad (3.37)$$

Now, we need to find $\eta(0)$ as follows:

from equation (3.11)

$$\phi(0) = B(0) = \alpha xz + (1-\theta)\beta z$$

from equation (3.27)

$$\rho(t,\tau) = \phi(\tau) + \eta(\tau)e^{\lambda t}$$

$$\rho(t,0) = \phi(0) + \eta(\tau)e^{\lambda t} = B(t) \qquad (3.38)$$

and $B(t) = \alpha S(t)I(t) + (1-\theta)\beta I(t)$ from equation (3.7)

We substitute (3.24) to (3.28) into (3.7), then use (3.11) and (3.38) to get;

$$B(t) = \alpha\left(x + \bar{p}e^{\lambda t}\right)\left(z + \bar{q}e^{\lambda t}\right) + (1-\theta)\beta\left(z + \bar{q}e^{\lambda t}\right)$$

$$B(t) = \alpha\left(xz + x\bar{q}e^{\lambda t} + z\bar{p}e^{\lambda t} + \bar{p}\bar{q}e^{2\lambda t}\right) + (1-\theta)\beta z + (1-\theta)\beta\bar{q}e^{\lambda t}$$

$$= \alpha xz + \alpha x\bar{q}e^{\lambda t} + \alpha z\bar{p}e^{\lambda t} + \alpha\bar{p}\bar{q}e^{2\lambda t} + (1-\theta)\beta z + (1-\theta)\beta\bar{q}e^{\lambda t}$$

Comparing this with (3.38), and using (3.11) for $\phi(0)$ gives

$$\phi(0) + \eta(0)e^{\lambda t} = B(t)$$

$$\alpha xz + (1-\theta)\beta z + \eta(0)e^{\lambda t} = B(t)$$

i.e.

$$\alpha xz + (1-\theta)\beta z + \eta(0)e^{\lambda t} =$$

$$\alpha xz + \alpha x\bar{q}e^{\lambda t} + \alpha z\bar{p}e^{\lambda t} + \alpha\bar{p}\bar{q}e^{2\lambda t} + (1-\theta)\beta z + (1-\theta)\beta\bar{q}e^{\lambda t}$$

$$\eta(0)e^{\lambda t} = \alpha x\bar{q}e^{\lambda t} + \alpha z\bar{p}e^{\lambda t} + \alpha\bar{p}\bar{q}e^{2\lambda t} + (1-\theta)\beta\bar{q}e^{\lambda t}$$

Neglecting term of order 2 in λt and dividing through by $e^{\lambda t}$, gives

$$\eta(0) = \alpha x\bar{q} + \alpha z\bar{p} + (1-\theta)\beta\bar{q} \qquad (3.39)$$

Substituting for $\eta(0)$ in (3.34) gives

$$\bar{q} = (\alpha x\bar{q} + \alpha z\bar{p} + (1-\theta)\beta\bar{q})b(\lambda) \tag{3.40}$$

$$0 = (\alpha x\bar{q} + \alpha z\bar{p} + (1-\theta)\beta\bar{q})b(\lambda) - \bar{q}$$

$$\alpha z b(\lambda)\bar{p} + \{(\alpha x + (1-\theta)\beta)b(\lambda) - 1\}\bar{q} = 0 \tag{3.41}$$

The coefficients of $\bar{p}, \bar{r}$ *and* $\bar{q}$ in (3.30), (3.32) and (3.41) give the Jacobian determinant for the system with the eigenvalue λ.

$$\begin{vmatrix} \beta - \gamma - \mu - \lambda - \alpha z & \beta & \theta\beta - \alpha x \\ \gamma & -(\lambda + \mu) & 0 \\ \alpha z b(\lambda) & 0 & [\alpha x + (1-\theta)\beta]b(\lambda) - 1 \end{vmatrix} = 0 \tag{3.42}$$

and the characteristics equation for the model is therefore given by

$$-(\beta - \gamma - \mu - \lambda - \alpha z)(\lambda + \mu)\{(\alpha x + (1-\theta)\beta)b(\lambda) - 1\}$$
$$-\gamma\beta\{(\alpha x + (1-\theta)\beta)b(\lambda) - 1\} + \alpha z(\lambda + \mu)(\theta\beta - \alpha x)b(\lambda) = 0$$

i.e.

$$\{(\lambda + \mu)(\beta - \gamma - \mu - \lambda - \alpha z) + \gamma\beta\}\{(\alpha x + (1-\theta)\beta)b(\lambda) - 1\}$$
$$-\alpha z(\lambda + \mu)(\theta\beta - \alpha x)b(\lambda) = 0 \tag{3.43}$$

CHAPTER FOUR

STABILITY ANALYSIS OF THE EQUILIBRIUM STATES

4.1 Stability of the Zero Equilibrium State

At the zero equilibrium state (x,y,z) = (0,0,0). The characteristic equation (3.43) takes the form:

$$\{(\lambda+\mu)(\beta-\gamma-\lambda-\mu)+\beta\gamma\}\{((1-\theta)\beta)b(\lambda)-1\}=0 \qquad (4.1)$$

i.e. either

$$(\lambda+\mu)(\beta-\gamma-\lambda-\mu)+\beta\gamma=0 \qquad (4.2)$$

or

$$(1-\theta)\beta b(\lambda)-1=0 \qquad (4.3)$$

Now consider (4.2)

$$(\lambda+\mu)(\beta-\gamma-\lambda-\mu)+\beta\gamma=0$$

$$\lambda(\beta-\gamma-\lambda-\mu)+\mu(\beta-\gamma-\lambda-\mu)+\beta\gamma=0$$

$$-\lambda^2+\lambda(\beta-\gamma-\mu)-\lambda\mu+\mu(\beta-\gamma-\mu)+\beta\gamma=0$$

$$-\lambda^2+(\beta-\gamma-2\mu)\lambda+\beta\gamma+\mu(\beta-\gamma-\mu)=0$$

$$-\lambda^2+(\beta-\gamma-2\mu)\lambda+\beta\gamma-\mu\gamma+\mu(\beta-\mu)=0$$

$$-\lambda^2+(\beta-\gamma-2\mu)\lambda+(\beta-\mu)\gamma+\mu(\beta-\mu)=0$$

$$-\lambda^2+(\beta-\gamma-2\mu)\lambda+(\gamma+\mu)(\beta-\mu)=0$$

i.e.

$$\lambda = \frac{1}{2}\{(\beta - \gamma - 2\mu) \pm \sqrt{(\beta - \gamma - 2\mu)^2 + 4(\gamma + \mu)(\beta - \mu)}\}$$

$$= \frac{1}{2}\{(\beta - \mu - \mu - \gamma) \pm \sqrt{(\beta - \mu - \mu - \gamma)^2 + 4(\gamma + \mu)(\beta - \mu)}\}$$

$$= \frac{1}{2}\{(\beta - \mu) - (\gamma + \mu) \pm \sqrt{((\beta - \mu) - (\gamma + \mu))^2 + 4(\gamma + \mu)(\beta - \mu)}\}$$

$$= \frac{1}{2}\{(\beta - \mu) - (\gamma + \mu) \pm \sqrt{(\beta - \mu)^2 - 2(\beta - \mu)(\gamma + \mu) + (\mu + \gamma)^2 + 4(\gamma + \mu)(\beta - \mu)}\}$$

$$= \frac{1}{2}\{(\beta - \mu) - (\gamma + \mu) \pm [(\beta - \mu) + (\gamma + \mu)]\}$$

i.e.

$$\lambda_1 = \frac{1}{2}\{(\beta - \mu) - (\gamma + \mu) + [(\beta - \mu) + (\gamma + \mu)]\}$$

$$= \frac{1}{2}\{2(\beta - \mu)\}$$

$$= \beta - \mu$$

and $$\lambda_2 = \frac{1}{2}\{(\beta - \mu) - (\gamma + \mu) - [(\beta - \mu) + (\gamma + \mu)]\}$$

$$= \frac{1}{2}\{-2(\gamma + \mu)\}$$

$$= -(\gamma + \mu)$$

This shows that:

$$\lambda_1 < 0 \ \textit{if} \ \beta < \mu \qquad (4.4)$$

$$\lambda_2 < 0 \tag{4.5}$$

In order to investigate the nature of the roots of the transcendental equation (4.3), we first of all consider $b(\lambda)$

from equation (3.37)

$$b(\lambda) = \int_0^T \exp\left\{-\int_0^\tau (\lambda + \sigma(s))ds\right\} d\tau$$

i.e.

$$b(iw) = \int_0^T e^{-\lambda\tau}\psi(\tau)d\tau \tag{4.6}$$

If we set $\lambda = iw$ in (4.6) we have that

$$b(iw) = \int_0^T [\cos w\tau - i\sin w\tau]\psi(\tau)d\tau = f(w) + ig(w) \tag{4.7}$$

and so

$$f(w) = \int_0^T \psi(\tau)\cos w\tau d\tau \tag{4.8}$$

$$g(w) = -\int_0^T \psi(\tau)\sin w\tau d\tau \tag{4.9}$$

and so

$$f(0) = \int_0^T \psi(\tau)d\tau = \overline{\psi}\,;\ g(0) = 0 \tag{4.10}$$

also

$$f'(w) = -\int_0^T \tau\psi(\tau)\sin w\tau d\tau \tag{4.11}$$

and so

$$f'(0) = 0 \tag{4.12}$$

$$g'(w) = -\int_0^T \tau\psi(\tau)\cos w\tau d\tau \tag{4.13}$$

and

$$g'(0) = -\int_0^T \tau\psi(\tau)d\tau = -A \tag{4.14}$$

As applied in [2], the result of Bellman and Cooke [5] (See Appendix I) is used next to analyze equation (4.3) for stability or otherwise of the zero equilibrium state. Let equation (4.3) takes the form:

$$H_1(\lambda) = (1-\theta)\beta b(\lambda) - 1 = 0 \tag{4.15}$$

if we set $\lambda = iw$ in (4.15) we have that

$$H_1(iw) = F_1(w) + iG_1(w) \tag{4.16}$$

The condition for $\mathrm{Re}\lambda < 0$ will then be given by the inequality

$$F_1(0)G_1'(0) - F_1'(0)G_1(0) > 0 \tag{4.17}$$

From the above equations:

$$F_1(w) = (1-\theta)\beta f(w) - 1 \tag{4.18}$$

$$G_1(w) = (1-\theta)\beta g(w) \tag{4.19}$$

$$F_1'(w) = (1-\theta)\beta f'(w) \tag{4.20}$$

$$G_1'(w) = (1-\theta)\beta g'(w) \tag{4.21}$$

$$F_1(0) = (1-\theta)\beta\overline{\psi} - 1 \tag{4.22}$$

$$G_1(0) = 0 \tag{4.23}$$

$$F_1'(0) = 0 \tag{4.24}$$

$$G_2'(0) = -(1-\theta)\beta A \tag{4.25}$$

The inequality (4.17) then gives

$$[(1-\theta)\beta\overline{\psi} - 1][(1-\theta)\beta A] < 0 \tag{4.26}$$

Since

$$(1-\theta)\beta A > 0$$

the inequality (4.26) holds if

$$(1-\theta)\beta\overline{\psi} - 1 < 0 \tag{4.27}$$

from (3.16) and (3.19), we have that

$$\overline{\psi} = \int_0^T \exp\left\{-\int_0^\tau \sigma(s)ds\right\}d\tau$$

$$= \int_0^T \exp\left\{-\int_0^\tau (\mu + \delta \tan\frac{\pi s}{2Tk})ds\right\}d\tau$$

consider

$$\int_0^{\tau} (\mu + \delta \tan\frac{\pi s}{2Tk})ds = \left|\mu s - \frac{2\delta Tk}{\pi}\ln\left|\cos\frac{\pi s}{2Tk}\right|\right|_0^{\tau}$$

$$= \mu\tau - \frac{2\delta Tk}{\pi}\ln\left|\cos\frac{\pi\tau}{2Tk}\right|$$

then,

$$\overline{\psi} = \int_0^T \exp\left\{-\left(\mu\tau - \frac{2\delta Tk}{\pi}\ln\left|\cos\frac{\pi\tau}{2Tk}\right|\right)\right\}d\tau$$

$$= \left|\frac{-1}{\mu + \delta \tan\frac{\pi\tau}{2Tk}}\exp\left\{-\left(\mu\tau - \frac{2\delta Tk}{\pi}\ln\left|\cos\frac{\pi\tau}{2Tk}\right|\right)\right\}\right|_0^T$$

$$= \left[\frac{-1}{\left(\mu + \delta \tan\frac{\pi T}{2Tk}\right)}\exp\left\{-\left(\mu T - \frac{2\delta Tk}{\pi}\ln\left|\cos\frac{\pi T}{2Tk}\right|\right)\right\}\right] - \left[\frac{-1}{\mu}\right]$$

Hence,

$$\overline{\psi} = \frac{1}{(\mu)} - \frac{\exp\left(\frac{2\delta Tk}{\pi}\ln\left|\cos\frac{\pi}{2k}\right| - \mu T\right)}{\left(\mu + \delta \tan\frac{\pi}{2k}\right)} \qquad (4.28)$$

From (4.27) and (4.28) we define, after substitution for $\overline{\pi}$

$$J_1(k) = (1-\theta)\beta(\mu + \delta \tan\frac{\pi}{2k}) - \mu(\mu + \delta \tan\frac{\pi}{2k})$$
$$-(1-\theta)\beta\mu\exp\left(\frac{2\delta Tk}{\pi}\ln\left|\cos\frac{\pi}{2k}\right| - \mu T\right) \qquad (4.29)$$

So the origin will be stable when $\beta < \mu$ and $J_1(k) < 0$.

Using Mathcad, hypothetical parameter values were used to generate a table of values for $J_1(k)$, so as to verify the result of the analysis. Some of the values obtained are presented in the table 4.1 below:

Table 4.1: Computer simulation for $J_1(k)$

$\delta = 0.003, \theta = 0.4, T = 10$

K	$J_1(k)$ $\beta = 0.15$ $\mu = 0.25$		$J_1(k)$ $\beta = 0.12$ $\mu = 0.36$		$J_1(k)$ $\beta = 0.31$ $\mu = 0.12$		$J_1(k)$ $\beta = 0.38$ $\mu = 0.15$	
0.3	**-0.0410123**	**S**	**-0.1028962**	**S**	**0.0008826**	**I**	**0.0036957**	**I**
0.4	**-0.0423235**	**S**	**-0.1052531**	**S**	**0.0014138**	**I**	**0.0043240**	**I**
0.5	**-0.0418475**	**S**	**-0.1043893**	**S**	**0.0011976**	**I**	**0.0040692**	**I**
0.6	**-0.0415674**	**S**	**-0.1038895**	**S**	**0.0010943**	**I**	**0.0039467**	**I**
0.7	**-0.0412345**	**S**	**-0.1033024**	**S**	**0.0009917**	**I**	**0.0038240**	**I**
0.8	**-0.0406638**	**S**	**-0.1022967**	**S**	**0.0008181**	**I**	**0.0036162**	**I**
0.9	**-0.0390812**	**S**	**-0.0994874**	**S**	**0.0002778**	**I**	**0.0029729**	**I**

S and I implies Stability and Instability respectively.

From table 4.1 above, it can be seen that :

1. $J_1(k) < 0$ when $\beta > \mu$
2. $J_1(k) > 0$ when $\beta < \mu$

Note however that the result presented in table 4.1 above is for δ = 0.003, θ = 0.4; the profile remains the same when these values range between 0 and 1.

4.2 Stability of the Non-zero Equilibrium State

At the non-zero equilibrium states

$$x = \frac{1-(1-\theta)\beta\overline{\psi}}{\alpha\overline{\psi}}$$

$$y = \frac{\gamma[1-(1-\theta)\beta\overline{\psi}]}{\alpha\mu\overline{\psi}}$$

$$z = \frac{(\beta-\mu)(\gamma+\mu)(1-(1-\theta)\beta\overline{\psi})}{\alpha\mu(1-\beta\overline{\psi})}.$$

In order to analyze the non-zero state for stability, we shall similarly apply the result of Bellman and Cooke [5] to equation (3.43), taking it in the form

$$H_2(\lambda) = \{(\lambda+\mu)(\beta-\gamma-\mu-\lambda-\alpha z)+\gamma\beta\}\{(\alpha x+(1-\theta)\beta)b(\lambda)-1\} - \alpha z(\lambda+\mu)(\theta\beta-\alpha x)b(\lambda) = 0 \quad (4.30)$$

If we set $\lambda = iw$, we have that

$$H_2(iw) = F_2(w) + iG_2(w) \quad (4.31)$$

The condition for $\mathrm{Re}\lambda < 0$, will then be given by the inequality

$$F_2(0)G_2'(0) - F_2'(0)G_2(0) > 0 \quad (4.32)$$

i.e.

$$H_2(iw) = \{(\mu + iw)(\beta - \gamma - \mu - \alpha z - iw) + \gamma\beta\}$$
$$\{(\alpha x + \beta + \theta\beta)(f(w) + ig(w)) - 1\}$$
$$-\alpha z(\mu + iw)(\theta\beta - \alpha x)(f(w) + ig(w))$$

$$= \{\mu(\beta - \gamma - \mu - \alpha z - iw) + iw(\beta - \gamma - \mu - \alpha z - iw) + \gamma\beta\}$$
$$\{(\alpha x + \beta + \theta\beta)f(w) + (\alpha x + \beta + \theta\beta)ig(w) - 1\}$$
$$-\alpha z\mu(\theta\beta - \alpha x)f(w) - \alpha z\mu(\theta\beta - \alpha x)ig(w)$$
$$-\alpha ziw(\theta\beta - \alpha x)f(w) - \alpha ziw(\theta\beta - \alpha x)ig(w)$$

$$= \{\mu(\beta - \gamma - \mu - \alpha z) - iw\mu + iw(\beta - \gamma - \mu - \alpha z) - (iw)^2 + \gamma\beta\}$$
$$\{(\alpha x + \beta + \theta\beta)f(w) + (\alpha x + \beta + \theta\beta)ig(w) - 1\}$$
$$-\alpha z\mu(\theta\beta - \alpha x)f(w) - \alpha z\mu(\theta\beta - \alpha x)ig(w)$$
$$-\alpha ziw(\theta\beta - \alpha x)f(w) - \alpha ziw(\theta\beta - \alpha x)ig(w)$$

$$= \left\{\mu(\beta - \gamma - \mu - \alpha z) + iw(\beta - \gamma - 2\mu - \alpha z) + w^2 + \gamma\beta\right\}$$
$$\{(\alpha x + \beta + \theta\beta)f(w) + (\alpha x + \beta + \theta\beta)ig(w) - 1\}$$
$$-\alpha z\mu(\theta\beta - \alpha x)f(w) - \alpha z\mu(\theta\beta - \alpha x)ig(w)$$
$$-\alpha ziw(\theta\beta - \alpha x)f(w) - \alpha ziw(\theta\beta - \alpha x)ig(w)$$

$$
\begin{aligned}
&= \mu(\beta-\gamma-\mu-\alpha z)(\alpha x+\beta+\theta\beta) f(w) \\
&+ \mu(\beta-\gamma-\mu-\alpha z)(\alpha x+\beta+\theta\beta) ig(w) \\
&- \mu(\beta-\gamma-\mu-\alpha z) \\
&+ iw(\beta-\gamma-2\mu-\alpha z)(\alpha x+\beta+\theta\beta) f(w) \\
&- w(\beta-\gamma-2\mu-\alpha z)(\alpha x+\beta+\theta\beta) g(w) \\
&- iw(\beta-\gamma-2\mu-\alpha z) \\
&+ w^2(\alpha x+\beta+\theta\beta) f(w) \\
&+ w^2(\alpha x+\beta+\theta\beta) ig(w) \\
&- w^2 \\
&+ \gamma\beta(\alpha x+\beta+\theta\beta) f(w) \\
&+ \gamma\beta(\alpha x+\beta+\theta\beta) ig(w) \\
&- \gamma\beta \\
&- \alpha z\mu(\theta\beta-\alpha x) f(w) - \alpha z\mu(\theta\beta-\alpha x) ig(w) \\
&- \alpha z iw(\theta\beta-\alpha x) f(w) + \alpha z w(\theta\beta-\alpha x) g(w)
\end{aligned}
$$

$$
\begin{aligned}
F_2(w) &= \mu(\beta-\gamma-\mu-\alpha z)(\alpha x+\beta+\theta\beta) f(w) \\
&- \mu(\beta-\gamma-\mu-\alpha z) \\
&- w(\beta-\gamma-2\mu-\alpha z)(\alpha x+\beta+\theta\beta) g(w) \\
&+ w^2(\alpha x+\beta+\theta\beta) f(w) \\
&- w^2 \\
&+ \gamma\beta(\alpha x+\beta+\theta\beta) f(w) \\
&- \gamma\beta \\
&- \alpha z\mu(\theta\beta-\alpha x) f(w) + \alpha z w(\theta\beta-\alpha x) g(w)
\end{aligned}
$$

and

$$
\begin{aligned}
G_2(w) &= \mu(\beta-\gamma-\mu-\alpha z)(\alpha x+\beta+\theta\beta) g(w) \\
&+ w(\beta-\gamma-2\mu-\alpha z)(\alpha x+\beta+\theta\beta) f(w) \\
&- w(\beta-\gamma-2\mu-\alpha z) \\
&+ w^2(\alpha x+\beta+\theta\beta) g(w) \\
&+ \gamma\beta(\alpha x+\beta+\theta\beta) g(w) \\
&- \alpha z\mu(\theta\beta-\alpha x) g(w) - \alpha z w(\theta\beta-\alpha x) f(w)
\end{aligned}
$$

$$
\begin{aligned}
F_2'(w) = {} & \mu(\beta - \gamma - \mu - \alpha z)(\alpha x + \beta + \theta\beta) f'(w) \\
& - (\beta - \gamma - 2\mu - \alpha z)(\alpha x + \beta + \theta\beta)[w g'(w) + g(w)] \\
& + (\alpha x + \beta + \theta\beta)\left[w^2 f'(w) + 2w f(w) \right] \\
& - 2w \\
& + \gamma\beta(\alpha x + \beta + \theta\beta) f'(w) \\
& - \alpha z \mu(\theta\beta - \alpha x) f'(w) \\
& + \alpha z(\theta\beta - \alpha x)[w g'(w) + g(w)]
\end{aligned}
$$

and

$$
\begin{aligned}
G_2'(w) = {} & \mu(\beta - \gamma - \mu - \alpha z)(\alpha x + \beta + \theta\beta) g'(w) \\
& + (\beta - \gamma - 2\mu - \alpha z)(\alpha x + \beta + \theta\beta)[w f'(w) + f(w)] \\
& - (\beta - \gamma - 2\mu - \alpha z) \\
& + (\alpha x + \beta + \theta\beta)\left[w^2 g'(w) + 2w g(w) \right] \\
& + \gamma\beta(\alpha x + \beta + \theta\beta) g'(w) \\
& - \alpha z \mu(\theta\beta - \alpha x) g'(w) \\
& - \alpha z(\theta\beta - \alpha x)[w f'(w) + f(w)]
\end{aligned}
$$

setting $w=0$, we have

$$
\begin{aligned}
F_2(0) = {} & \mu(\beta - \gamma - \mu - \alpha z)(\alpha x + \beta + \theta\beta)\bar{\pi} \\
& - \mu(\beta - \gamma - \mu - \alpha z) \\
& + \gamma\beta(\alpha x + \beta + \theta\beta)\bar{\pi} \\
& - \gamma\beta \\
& - \alpha z \mu(\theta\beta - \alpha x)\bar{\pi}
\end{aligned}
\tag{4.33}
$$

$$
G_2(0) = 0 \tag{4.34}
$$

$$
F_2'(0) = 0 \tag{4.35}
$$

$$
\begin{aligned}
G_2'(0) = {} & \mu(\beta - \gamma - \mu - \alpha z)(\alpha x + \beta + \theta\beta)(-A) \\
& + (\beta - \gamma - 2\mu - \alpha z)(\alpha x + \beta + \theta\beta)\bar{\pi} \\
& - (\beta - \gamma - 2\mu - \alpha z) \\
& + \gamma\beta(\alpha x + \beta + \theta\beta)(-A) \\
& - \alpha z\mu(\theta\beta - \alpha x)(-A) \\
& - \alpha z(\theta\beta - \alpha x)\bar{\pi}
\end{aligned}
\tag{4.36}
$$

i.e.

$$
\begin{aligned}
G_2'(0) = {} & -\mu(\beta - \gamma - \mu - \alpha z)(\alpha x + \beta + \theta\beta)A \\
& + (\beta - \gamma - 2\mu - \alpha z)(\alpha x + \beta + \theta\beta)\bar{\pi} \\
& - (\beta - \gamma - 2\mu - \alpha z) \\
& - \gamma\beta(\alpha x + \beta + \theta\beta)A \\
& + \alpha z\mu(\theta\beta - \alpha x)A \\
& - \alpha z(\theta\beta - \alpha x)\bar{\pi}
\end{aligned}
\tag{4.37}
$$

The inequality (4.32) then gives

$$F_2(0)G_2'(0) > 0 \tag{4.38}$$

Let

$$J_2(k) = F_2(0)G_2'(0) \tag{4.39}$$

So the non –zero state will be stable when

$$J_2(k) > 0 \tag{4.40}$$

Using Mathcad, hypothetical parameter values were used to generate a table of values for $J_2(k)$, so as to verify the result of the

analysis. Some of the values obtained are presented in the table 4.2 below:

Table 4.2: Computer simulation for $J_2(k)$

$\alpha = 0.02, \delta = 0.003, \gamma = 0.45, \theta = 0.4, T = 10$

K	$J_2(k)$ $\beta = 0.44$ $\mu = 0.22$		$J_2(k)$ $\beta = 0.29$ $\mu = 0.13$		$J_2(k)$ $\beta = 0.45$ $\mu = 0.15$		$J_2(k)$ $\beta = 0.15$ $\mu = 0.25$	
0.3	-0.0552911	I	-0.0030424	I	-0.0083783	I	-0.0006479	I
0.4	-0.0568963	I	0.0033941	S	0.0093484	S	-0.0002959	I
0.5	0.0563110	S	0.0032447	S	0.0089637	S	-0.004445	I
0.6	0.0559693	S	0.0031791	S	0.0087707	S	-0.0005106	I
0.7	0.0555653	S	0.0031197	S	0.0085694	S	-0.0005712	I
0.8	0.0548731	S	0.0030201	S	0.0082274	S	-0.0006730	I
0.9	0.0529469	S	0.0026893	S	0.0071971	S	-0.0010079	I

S and I implies Stability and Instability respectively.

From table 4.2 above, it can be seen that:

1. $J_2(k) < 0$ when $\beta < \mu$
2. $J_2(k) < 0$ when $\beta > \mu$ and k is low
3. $J_2(k) > 0$ when $\beta > \mu$ and k is high

Note however that the result presented in table 4.2 above is for α=0.02, δ = 0.003, γ=0.45, θ = 0.4; the profile remains the same when these values range between 0 and 1.

CHAPTER FIVE

CONCLUSION AND RECOMMENDATION

5.1 Conclusion

From the above observations, it can be seen that the zero equilibrium state which is the state of population extinction will be stable when the birth rate is unusually less than the death rate.

However, in situations where the birth rate is greater than the death rate and the application of anti-retroviral drugs *(k)* is low, the non-zero equilibrium state will be unstable. But a high level of k revealed stability of the non-zero state, which is the state of population sustenance. Hence, we can conclude that once the virus is introduced into a population, the application of anti-retroviral drugs can at best slow down the eventual extinction of that population.

5.2 Recommendation

1. Controlling HIV requires our collective global commitment—governmental, societal, and personal by:
    (i) Ensuring access for all to life-sustaining drugs, so that HIV-positive parents may provide and care for their children.
    (ii) Reducing AIDS-related stigma and discrimination, so that more people will get tested for HIV and receive prevention counseling
    (iii) Respecting and enforcing the rights of women, so that they may control their bodies, reject unwanted sexual advances, and insist upon the use of condoms to protect against HIV infection
    (iv) Ending modern-day slavery and reducing the spread of HIV by eradicating human sex trafficking
2. Further research work can be carried out such as the economic, social, or political effect of HIV/AIDS in national development with computer simulation.

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APPENDIX I

THEOREM (BELLMAN AND COOKE, [5])

Theorem: Let $\Delta(z) = p(z,e^z)$ where $p(z,w)$ is a polynomial with principal term. Suppose $\Delta(iy)$, $y \in \mathbb{R}$, is separated into its real and imaginary parts,

$\Delta(iy) = F(y) + iG(y)$. if all zeros of $\Delta(z)$ have negatives real parts, then the zeros of $F(y)$ and $G(y)$ are real, simple, alternate and

$$F(0)G'(0) - F'(0)G(0) > 0 \qquad \text{(A)}$$

for $y \in \mathbb{R}$, conversely, all zeros of $\Delta(z)$ will be in the left half-plane provided that either of the following conditions is satisfied:

(i) All the zeros of $F(y)$ and $G(y)$ are real simple, and alternate and inequality (A) is satisfied for at least one y.

(ii) All the zeros of $F(y)$ are real and, for each zero, Relation (A) is satisfied.

(iii) All the zeros of $G(y)$ are real and, for each zero, Relation (A) is satisfied.

(iv) All the zeros of $G(y)$ are real and, for each zero,