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INTRODUCTION

1.1 OVERVIEW

Acquired Immunodeficiency Syndrome (AIDS) and its etiologic agent Human Immunodeficiency Virus (HIV) are two viral infections that have been most studied world wide since their first discovery in 1981 and 1983 respectively with 60 million people infected, 20 million deaths from AIDS and 14,000 daily new infections of which 95% is in developing world countries (WHO HIV statistics 2007). Statistics showed that around 33.2 million people were living with HIV at the end of 2007 of which 2.5 million were children, and a greater proportion of the population infected coming from Africa and Asia continents. Compared to approximately 47,000 cases of AIDS in the United States with 58% of the patients already dead since the first cases were reported in summer 1981 until 1 December, 1987 (Barker et al. 1998, Fauci 1988, Feinberg 1996). This shows that HIV appears to be progressive and irreversible with a high mortality rate that may approach 100 percent over several years if not put in check.

Presently only two types of HIV are known to infect humans, namely the HIV-1 and HIV-2. These two viruses evolved independently and may have crossed the monkey-human species barrier at several independent occasions (Groot, 2006). HIV-1 is believed to have originated from wild chimpanzees (Pan troglodytes) virus (SIVcpz) of the southern Cameroon of West Africa, while HIV-2 originated from sooty mangabey monkey (cercocebus atys) virus (SIV variant) of Guinea-Bissau, Gabon and Cameroon of Africa (Groot, 2006, HIV Wikipedia 2008).

Studies have reported cases of infection with HIV-2 such as the Portuguese man infected in Guinea-Bissau who had a clinical latency duration of 19 years (Ancelle et al. 1987), a Portuguese woman infected through blood transfusion and she had a clinical latency of 27

years (Mota-Miranda et al., 1995) and a Japanese man (first report of HIV-2 infected Japanese individual) with clinical latency of 35 years (Utsumi et al. 2007). One can effectively induce that HIV-2 has a longer clinical latency period than that of HIV-1. HIV-2 also has a lower transmission rate (this was pointed out by Utsumi et al. (2007), when they noted that the man had sexual acts with his 77 years old wife and both she and their 37 years old son were HIV negative). Also HIV-2 has less immune activation (see Levy 2009). Hence these have posed as very good advantages for the research into vaccine and cure of HIV-2 unlike its counterpart which has a shorter clinical latency period (10 years on average) and it is the more common viral infection in the world (http://en.wikipedia.org/wiki/HIV). Thus concentration has been placed on the HIV-1 strains among human and not the HIV-2 strains in this thesis solely because HIV-1 is more virulent, easily transmitted, has a lesser clinical latency duration (of say 10 years) and according to WHO reports, it is the cause of the majority of HIV infections globally. Unlike HIV-2 which is quite mild in nature, not easily transmitted, has a clinical latency duration of 20 – 40 years and it is less common among humans.

Our aim in this thesis is to use stochastic modelling to determine number of uninfected T4 cells, infected T4 cells and free HIV in an infected individual by examining the pathogenesis, progression and combined treatment of HIV. This is important because it helps in determining the efficacy of methods used in the research of pathogenesis, progression and combined treatment of HIV. We also looked at different ways that research has tried to go about eliminating the virus (section 2.3) in an infected person.

1.2 ACRONYMS AND TERMINOLOGIES

AIDS **A**cquired **I**mmune **D**eficiency **S**yndrome

APOBEC3G	**Apo**liprotein **B** mRNA **e**diting enzyme **c**atalytic polypeptide-like **3G**
$CD4^+$T cells	CD4 positive T lymphocytes
$CD8^+$T cells	CD8 positive T lymphocytes
DNA	**D**eoxyribo**n**ucleic **a**cid
Env	**Env**elope; precursor to envelope glycoproteins
Gag	**G**roup - **a**nti**g**en ; precursor to internal structural proteins
HIV	**H**uman **I**mmunodeficiency **V**irus
IT	**In**te**t**egrase
LTR	**L**ong **t**erminal **r**epeat
mRNA	**M**emory **R**ibo**n**ucleic **a**cid
PR	**Pr**otease
Pro	PR enzyme
Pol	**Pol**ymerase; precursor to RT and IT enzymes
Rev	regulates splicing/RNA transport
RNA	**R**ibo**n**ucleic **a**cid
RRE	**R**ev **r**esponse **e**lements
RT	**R**everse **t**ranscriptase
TAR	**T**rans**a**ctivation-**r**esponse element
Tat	activates transcription
Vif	affects infectivity of viral particles
vpr and/or vpx nef	is present in viron; has nuclear localization signal; facilitates infectivity in quiescent cells; triggers CD4 endocytosis, alters signal transduction in T cells; enhances viron infectivity
vpu	integral membrane protein; triggers CD4 degradation; enhances viron release

1.3 ROLE OF MATHEMATICAL AND STATISTICAL MODELING IN HIV/AIDS EPIDEMIC

Mathematical and statistical models of HIV/AIDS infection have become extremely important not only because medical scientists cannot combat the problems of these viruses alone (since not all problems can be replicated or solved experimentally as human lives are involved), but also to give better understanding of the HIV/AIDS epidemic and for reasons such as:

i. the models based on underlying transmission mechanism of the HIV/AIDS infection can help the medical and/or scientific world to understand and evaluate the epidemiology of these viral infections hence giving insight into different strategies of prevention and control that can be applied according to the severity of the epidemic in the different areas (Tan 2000)

ii. the mathematical and statistical models can provide qualitative insights even when data are lacking or not readily available, and this can help prioritize data collection (Hyman and Stanley 1988, Tan 2000)

iii. the models can be used to provide in-depth understanding of some basic features and principles of the epidemic and its pathogenesis, thus aiding in the study of suitable treatments and/or vaccine and maybe a cure in the near future (Tan 2000)

iv. the models can help reveal important parameters and co-factors of the infection and also shed light on their consequences

v. the impacts of risk factors may be assessed, thereby screening for important risk variables for the purpose of prevention and control of the infections (Hyman and Stanley 1988, Tan 2000)

vi. mathematical and statistical models based on the transmission of the infections can show how early or late infection, behavioural changes and medical advances such as

treatments and vaccines will affect the future course of the HIV/AIDS epidemic (Hyman and Stanley, 1988)

vii. the knowledge of parameters and co-factors can help develop both mathematical and statistical models which can give computer simulations to compare different treatment outcomes etc.; these computer simulations can save time, lives and resources as compared with using other means such as animals and running trials on humans

viii. models can be used to estimate unknown data on the basis of the known facts. For example, the past distribution of HIV infection can be estimated from the current AIDS caseload and the distribution of times from infection to AIDS (see Back-calculation method in section 3.4). To determine the consistency of the generated data a formal mathematical model similar to the one that was designed is required. The available data can also be assessed indirectly to determine their internal consistency by leaving some data out, generating estimates of the missing data based on one or more models, and then comparing the two data sets (lifted directly from Hyman and Stanley, 1988).

1.4 HIV MODELING

In the bid to combat the two deadliest viral infections in the 20th and 21st century, the onus have not been only on the medical scientist to find a cure but also partnership with mathematical, statistical, computational and engineering scientist have become inevitable. Hence the mathematical and computational modeling of HIV/AIDS have become a novel approach with great impact in the different areas of study of the epidemic. Among those who pioneered mathematical modelling (quantitation) of HIV is David Ho. His research into HIV/AIDS in the last 27 years has helped formed the basis for combined antiretroviral

treatments and also in understanding the dynamic nature of HIV replication *in vivo*. Research into the dynamics of HIV *in vivo* has helped in further understanding of the pathogenesis and growth of HIV, the replication and progression of the virus, means of determining HIV progression by T4 cell count or HIV-1 RNA viral load count, results of single and combined antiretroviral treatments, when to commence such treatment and also mathematical and computational modeling of these processes.

To ascertain the progression of HIV in an infected individual, the T4 cell count, the HIV-1 RNA viral and viral decay approach have not only become common but also reliable means used to predict the outcome of a patient in terms of duration to regressing to AIDS and also to determine when to commence ARV or HAART. Also methods that have permitted missing data analysis have become extremely important in HIV modelling because most patients don't know when they are infected and data on some patients are incomplete due to inconsistency in attending ART clinics. De Gruttola et al. (1991) modelled the progression of HIV infection using the T4 cells as its measure, more likely because of the availability of data on the T4 cell counts. They used the parametric linear growth curve model because it permits analysis of incomplete data assuming the data are missing at random. Also autoregressive models were fitted to short series of the T4 cell counts because this method allowed the estimation of annual decline averaged over all individuals. The setback of these methods was that the variability in the rates of decline of the T4 cell cannot be estimated and the modeling of the entire process from infection to AIDS cannot be done.

Tan and Wu (1998) developed a stochastic model for the interaction between $CD4^{+}$T cells and the human immunodeficiency virus. Stochastic differential equations were obtained for the numbers of uninfected T cells, latently infected T cells, actively infected T cells and free

HIV through binomial and multinomial distributions. They modelled the generation of new uninfected T cells by a pure birth process (Poisson process) and the growth of uninfected $CD4^{+}$T cells by simulating the antigens using a stochastic logistic pure birth process. The results of the Monte Carlo simulations showed that the probability distributions of the CD4+T cells and free HIV were skewed in the earlier stage of infection and eventually converged to normal distributions in later years.

Sridharah and Jayashree (1993) also used the stochastic point process to model the population of infected T4 cells. In the model, they made use of phases with special types of time-dependencies whose durations were independent and exponentially distributed. The first and second moments of the infected T4 cells were generated from explicit differential equations obtained.

Wu and Ding (1999) gave a model with a sum of exponentials which gave a good fit to the observed clinical data of HIV-1 dynamics i.e. HIV-1 RNA copies after starting antiretroviral treatments. The other advantage about this model was that it can also be used as a biological compartment model for the interaction between HIV and its host cells. Thus enjoying both worlds of biological interpretability and mathematical simplicity after re-parameterization and simplification. Finally the use of hierarchical nonlinear mixed-effect model approach for parameter estimation and other statistical inferences was illustrated using real life data.

Wu et al. (1999) revised four model-fitting procedures for biphasic viral decay data in clinical studies. This was because the estimates obtained when these methods were applied differed significantly. The methods were Single method, Perelson steady state (PSS) method, Wu and Ding (WD) method and Perelson and Neumann steady state (PNSS) method. Pros and cons

of these methods were discussed. For example, the simple method which fitted a bi-exponential model to the biphasic viral load was good because it included all data from baseline onward. The disadvantage of this method was the biased estimates of viral load obtained due to effect of the initial 'shoulder' that was ignored. Ding and Wu (1999) suggested the fitting of the model only after the effect of the 'shoulder' is considered.

Ding and Wu (1999) also worked in detail on the four model-fitting procedure given in Wu et al. (1999), evaluating the performance of these procedures through extensive use of Monte Carlo simulations. Guidelines on how to select appropriate method for data analysis was given and real life data was used to backup the guidelines.

Joshi (2002) derived an optimal control of an HIV immunology model by using a system of ordinary differential equation model taken from Kirschner and Webb (1998). This system of ODE described the interaction of the T4 cells and HIV in the immune system. He used the boundedness of solutions of the ODE system for finite time interval to prove the existence of an optimal control pair. Thus the optimal control pair obtained gave an optimal treatment strategy for the HIV infected patient under two types of drug treatments, namely, treatment that aimed at reducing viral population and treatment that aimed at improving the immune response. Joshi (2002) solved the optimality system by using an iterative method with a Runge-Kutta fourth order scheme. Joshi (2002) noted that the format of the optimal controls he obtained agreed with those of Butler et al. (1995), Kirschner et al. (1997) and Fister et al. (1998) where only one control instead of two was used.

Bortz and Nelson (2006) considered six deterministic models and made comparisons with respect to their ability to represent HIV infected patients undergoing antiretroviral treatment,

(to be precise reverse transcriptase mono-therapy). Bortz and Nelson (2005) created a statistical model using the hierarchical mixed-effects approach to characterize factors such as inter-individual and intra-individual variability in the patient population. Their aim was to derive mathematical model(s) of *in vivo* HIV infection dynamics. Bortz and Nelson (2005) were able to obtain higher viral clearance rate c as was done in earlier work by Louie et al. (2003) by using linear parameter fits as opposed to non-linear parameter fits.

Other method that have been used is the Bayesian modeling. Frost (2001) used this method to model the viral dynamics and evolution of HIV, Putter et al. (2002) estimated parameters in HIV dynamic models and Han et al. (2002) developed the Bayesian analysis method for the population dynamic HIV. Also Huang and Wu (2006) examined the Bayesian approach for estimation of antiretroviral efficacy.

1.5 THESIS OUTLINE

In this thesis, we have combated some of the issues of the two most deadly viruses namely human immunodeficiency virus (HIV) and acquired immunodeficiency syndrome (AIDS), that have invaded the human race in the last thirty years by concentrating on the stochastic modelling of the dynamics of the viruses. Although availability of efficient vaccines or cure for these infections is still like groping in the dark, medical scientists, pharmacologist, epidemiologists and even the mathematical and social scientists are eagerly working hand in hand to see a dream come true. The collaboration of medical scientists with scientist and theorists have in recent times made a big positive influence in better containing the viruses. This thesis has six chapters and they are outlined below.

In the first chapter an overview of the HIV is given and HIV modelling done by some scientists are reviewed. The second chapter deals with the pathogenesis of the viruses by delving into the genetic variation of the HIV. This is because the pathogenesis of the HIV infection can be understood only when the genetic variation in HIV and the receptor-specific HIV infection are given their due importance.

In chapter three, incubation period and seroconversion time are determined by using data on homosexuals given in Lui et al. (1988). Two stochastic models are used to determine the distribution function of the gay-life and the incubation period. Also the back-calculation method was used to project AIDS incidence.

Chapter four deals with the formulation of stochastic model of the dynamics of HIV in an infected individual. In this chapter, two stochastic models are proposed and analysed for the dynamics of the viral load in a HIV infected person and the multiplication process of the virons inside an infected T4 cell. Also numerical illustration of these stochastic models is given.

In chapter five, the T4 cell count which is considered one of the markers of disease progression in HIV infected individual is examined. WHO has recently advocated that countries encourage HIV infected individuals to commence antiretroviral treatments once their T4 cell count is 350 cells per ml of blood (was formerly 200 cells per ml of blood). This is because when the T4 cell count is low, the T4 cells are unable to mount an effective immune response against antigens and any such foreign matters in the body (Kirschner 1996) and consequently, the individual becomes susceptible to opportunistic infections and lymphomas. Thus, the T4 cell count can be considered a marker of disease progression in an

infected individual and the loss of T4 cells accounts for a major part of the immunosuppressive effect of HIV. As such, a stochastic catastrophe model is developed to obtain the mean, variance and covariance of the uninfected, infected and lysed T4 cells. Also obtained are the amount of toxin produced in a HIV infected person from the time of infection to the present time. Numerical illustration of the correlation structure between uninfected and infected T4 cells, and infected and lysed T4 cells is portrayed.

To combat the persistent death of humans before any cure can be obtained, antiretrioviral drugs were introduced to suppress the havoc done by these viruses in the human body. Treatment with single drug failed due to the fact that HIV evolved rapidly because of its high replication rate of an average of 10^{10} viral particles per day. Thus drug resistance to single therapeutic treatment in HIV infected individuals has promoted the research into combined treatments. Hence, in the sixth chapter a stochastic model under combined therapeutic treatment by extending the model of HIV pathogenesis under treatment by anti-viral drugs given by Perelson et al. (1996) is derived. Mean numbers of free HIV, infectious free HIV and non-infectious free HIV are obtained. Variance and co-variance structures of our parameters were obtained unlike in previous work of Perelson et al. (1996) and Tan and Xiang (1999). Comparison of simulated data for before and after treatment indicates the efficacy of our model in combined treatment.

CHAPTER TWO

PATHOGENESIS OF HIV

2.1 INTRODUCTION

The human immunodeficiency virus (HIV) is the early stage of the acquired immunodeficiency syndrome (AIDS) in which within 24 hours of contact, the virus replicates its RNA into the victim's DNA and as such the protein (gp120) on the virus binds to the protein on the $CD4^{+}$T cell thus affecting the immune response of the victim (Kirschner 1996). New virus particles then bud from the host cell after the duplication process. Thus the HIV virus replicates, mutate, recombine and bud off the host cell and it is the budding and maturity that determines both the duration (of transition from HIV to AIDS) and stage of infection either as the human immunodeficiency virus (HIV) or the acquired immunodeficiency syndrome (AIDS). This is because the HIV infection could be asymptomatic for years and only develops to AIDS when the $CD4^{+}$T cells fall so low due to increase in the viral load of the host cell. Holmes (1998) stated that mutation, recombination and natural selection produced a multitude of different genomes which allow the virus to continually evade immune response and to infect a variety of cell types, and the potential of HIV to evolve at a rate of about 1 million times faster than human nuclear DNA have undermined attempts to produce effective vaccines and allowed the development of resistance to some antiviral treatments within a matter of months. Thus, medicine, science and engineering have continually researched the pathogenesis of the human immunodeficiency virus (HIV) infection and mechanisms of genetic variations of HIV.

To understand HIV pathogenesis, the unique nature of the causative microbe was studied and compared with lentivirus infections of animals (because it shared features with other members of the non-transforming and cytopathic lentivirus family of retroviruses) to raise further questions regarding human disease such as (Weiss, 1993): Why do some horses permanently recover from equine infectious anemia when the virus evolves immune escape

variants as readily as HIV? Can the wasting syndrome and brain disease of sheep infected with visna-maedi virus be equated to human AIDS without CD4 depletion? And hypotheses such as AIDS being the end-stage disease of HIV, HIV mutating to produce different types of HIV, have been postulated to explain the relationship between HIV and AIDS. However, research is still done on why AIDS finally develop, if it is the HIV alone that brings about AIDS or maybe there are other viruses, why it takes a variable long time for HIV to develop to AIDS, and also the cofactors that influence the rate at which AIDS develop and so on.

Recent research by scientists such as Smith (2006), Sodora and Silvestri (2008), Levy (2009) showed that new data especially from non-human primate studies have raised doubts about the 1990's hypothesized theory that HIV-1 causes CD4+T cell depletion by direct cytopathic effect. Rather it has been shown that the immune activation of the virus causes the cell depletion. Thus shedding light on the research to see if HIV alone brings about AIDS or maybe there are other viruses. Hence they have strongly advocated a full understanding of HIV/AIDS pathogenesis which may lead to novel therapies (partially quoting Smith 2008). Also according to Hoffmann et al. (2007), an understanding of the immunopathogenesis of HIV-1 infection is a major prerequisite for rationally improving therapeutic strategies, developing immuno-therapeutics and prophylatic vaccines. Hence the delving into pathogenesis of the human immunodeficiency virus in this chapter.

2.2 HIV PATHOGENESIS

The pathogenic mechanisms of HIV disease are extremely complex and multifactorial (Fauci 1993, 2003). And in cases of the acquired immune deficiency syndrome (AIDS), marked depletion of $CD4^+$ T cells was recognized as a hallmark of disease early on (Gottlieb et al. 1981, Maseur et al. 1981, Fauci 2003), even before the classic demonstration in 1984 that the

CD4 molecule was the primary receptor for the virus on a subset of T cells and monocytes (Dalgleish et al. 1984, Klatzmann et al. 1984, Fauci 2003). Also much evidence has suggested that other factors were necessary for HIV fusion and entry, but these factors such as the co-receptors and chemokines remained elusive for several years (D'Souza and Harden 1996). According to Fauci (1996), D'Souza and Harden (1996) in the mid-1990s, a number of diverse areas of investigation elucidated the roles of the chemokine receptors CXCR4 and CCR5 in the efficient binding and entry of two different strains of HIV-1 called X4 and R5, respectively. The discovery that HIV could use different co-receptors also helped to explain the occurrence of syncytial (CXCR4-using) and nonsyncytial (CCR5-using) variants of HIV (Fauci 1996). The importance of the CCR5 co-receptor in the pathogenesis of HIV infection was proven by the finding that cells from individuals homozygous for a deletion of 32 base pairs in the CCR5 gene could not be infected in vivo with R5 viruses and that such individuals (who comprise about 5% of white populations) were thought to be extremely resistant to HIV infection even when repetitively exposed to virus until recent research proved otherwise and hence they can be termed as long-time progressors (O'Brien and Moore 2000, Fauci 2003, Hoffmann et al. 2007, Levy 2009).

The ability to measure plasma viremia precisely led to the classic viral dynamics studies of HIV. HIV research by mathematical scientists have tremendously helped in understanding the relationship between virus production and T cell dynamics (Ho et al. 1995, Wei et al. 1995, Fauci 2003). These studies led to a better insight of the HIV pathogenesis, hence making therapeutic treatments better and less toxic. Studies have shown that even in individuals in whom plasma viremia is driven by antiretroviral therapy to levels of less than 50 copies of RNA per ml ('undetectable') for up to 3 years, the viral reservoir persists and the virus rebounds from this reservoir within weeks of discontinuing therapy (Blackson et al. 2002,

Fauci 2003). Hence one may paradoxically say that studies of the immune response to HIV have been both productive and frustrating. Although individuals in whom HIV infection has been established cannot eliminate the virus from their bodies, continual research into better prophylaxic vaccines through the better understanding of the pathogenesis of these viruses still continues (Chun and Fauci 1999, Blackson et al. 2002, Fauci 2003). (Excerpts from Fauci 1993, 2003)

2.2.1 HIV Structure

HIV has a dense cylindrical core. It is around 120nm in diameter (120 billionths of a meter; around 60 times smaller than a red blood cell) and 10kb in length and roughly spherical. It is composed of two copies of single-stranded RNA enclosed by a conical capsid comprising the viral protein p24 (figure 2.1). This conical capsid can be described in layman's language as being bullet shaped. The RNA component is 9749 nucleotides long and it is surrounded by a plasma membrane of host-cell origin. The RNA is part of a protein-nucleic acid complex which is composed of the nucleo-protein p7 and the reverse transcriptase (RT) p66. The single-strand RNA is tightly bound to the nucleocapsid proteins p7 and enzymes such as reverse transcriptase (RT) i.e. p66, protease (PR) i.e. p11 and integrase (IT) i.e. p32 that are indispensable for the replication, proliferation and development of the viron. The nucleocapsid (p7 and p6) associates with the genomic RNA (one molecule per hexamer) and protects the RNA from digestion by nucleases. The ends of each strand of HIV RNA has an RNA sequence called the long terminal repeat (LRT). The LRT has regions which act as switches to control production of new viruses.

Surrounding this capsid is the matrix layer which is made up of the protein p17 and this ensures the integrity of the viron particle. Also enclosed within the viron particle are genes

such as Vpr, Nef, Vif, p7 and viral protease. These are genes that code the proteins used in controling the ability of the virus to infect a cell and produce new copies of virus and/or cause disease. The outer viral envelope which is formed when the capsid buds from the host cell, taking some of the host-cell membrane with it is a coat of lipoprotein membrane fat. Projecting from this viral envelop/membrane are 72 little spikes formed from the glycoproteins gp120 and gp 41 (HIV Wikipedia 2008, Hoffmann et al. 2007 and Smith 2008).

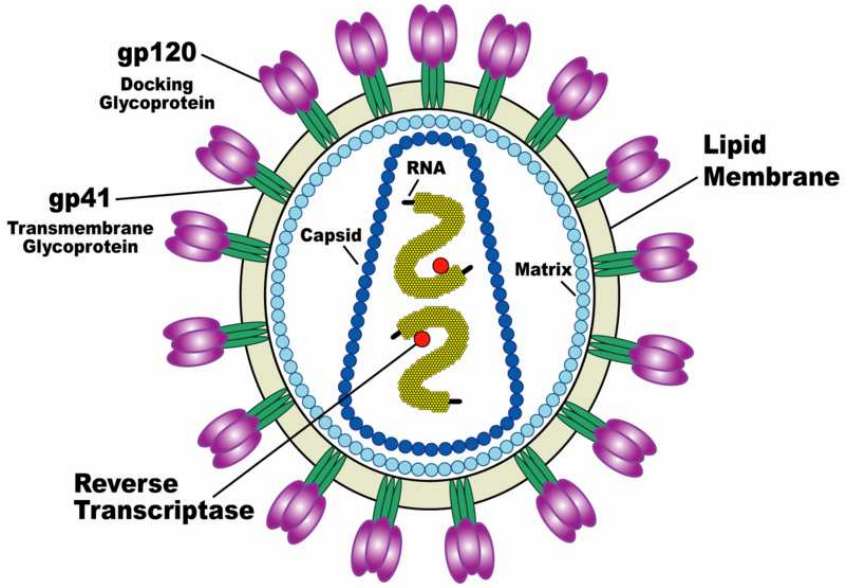

Figure 2.1 HIV genome showing the proteins involved in RNA coding and replication (Excerpt from HIV Wikipedia 2008)

2.2.2 Genes and Enzymes in HIV Entry and Replication

In HIV-1 there are 9 primary genes that encode within the RNA genome, namely: gag, env, pol, tat, rev, nef, vpr, vpu and vif. These genes and certain enzymes play different crucial roles in the entry and replication of the virus in the host cell. According to Fauci (2003), the identification of their relationship to the complex mechanism of HIV replication have been crucial in understanding HIV replication and its relationship to the pathogenic mechanism of the disease. Recent developments in controlling the destroying effects of the virus in the human body via development of effective antiretroviral drugs have also concentrated on some of these genes and enzymes (see section 2.3). These genes and enzymes and their functions are listed below.

i. Gag:

This encodes for the nucleocapsid and the glycoproteins gp 120 and gp 41 of the viral membrane.

ii. Env:

This codes for the glycoprotein gp 160 that is then broken down by a viral enzyme to form gp 120 and gp 41.

iii. Pol:

This codes for the reverse transcriptase (RT) and other enzymes.

iv. Tat:

This is a regulatory protein that accumulates within the nucleus and binds to the TAR found in the LRT of the viral RNA. It is a potent transcriptional activator of the LRT and its importance is in the *in vivo* culture system viral replication.

v. Cyclin TI:

It is a necessary cellular cofactor for tat.

vi. Rev:

This gene regulates splicing. It is also nuclear export factor which is important for switching from the early expression of regulatory protein to the structural proteins that are synthesized later. Both tat and rev stimulate the transcription of proviral HIV-1 DNA into RNA, promote RNA elongation, enhance the transportation of HIV RNA from the nucleus to the cytoplasm.

vii. Nef:

This codes for virus efficient replication. It may induce down-regulation of CD4 and HLA class I molecules from the surface of the infected cells. Thus the virus avoid recognition by CD4+T cells and hence evades any attack mediated by cytotoxic CD8+T cells. It is also essential for the high rate of virus production and progression of disease. It sometimes interfere with T cell activation by binding to various proteins that are involved in intracellular signal transduction pathways, thus helping in the disease progression.

viii. Vpr:

It is used in viral replication in non-dividing cells. it also stimulates the HIV LTR, promotes cellular and viral responses and its important for the transport of the viral pre-integration complex to the nucleus.

ix. Vpu:

This encoded protein influences the formation of new virons by allowing the recycling of gp 160. It also influences the release of new virus particles from infected cells by getting

involved in the degradation of CD4-gp 160 complexes within the endoplasmic reticulum. Thus it is important for the virus budding process.

x. Vif:

It supports viral replication.

xi. APOBEC3G:

Is an enzyme of the intracellular enzymes family. Its function is to deaminate cytosine to uracil in mRNA or DNA. APOBEC3G is expressed in lymphocytes and macrophages which are the primary target cells of HIV infection. In the presence of vif gene, it is complexed, degraded and not incorporated in newly formed virons.

xii. HLA class I:

xiii. HLA class II:

xiv. Others:

These are cellular binding proteins which have been found in the last 10 years (Levy 2009) to be associated with the HIV infection. They include C type lectings – DC-SIGN, Leukocyte function-associated antigens (LFA), Intercellular dhension molecules (ICAMs), $\alpha 4\beta 7$ integrin which acts as an HIV binding site particularly on $CD4^+$ memory T cells.

2.2.3 HIV-1 Strains

HIV-1 strains are classified by the cells they infect. Some of the HIV-1 strains are listed below.

i. Macrophage (M- tropic) strains

They are also known as the Non-syncitia-inducing strains (NSI). They gain entry through the β-chemokine receptor CCR5. Replication of this strain occur in the macrophages and the $CD4^{+}$T cells.

ii. T-tropic isolates strains

They are also known as the syncitia-inducing strains (SI). They gain entry through the α-chemokine receptor and CXCR5. Replication of this strain occur mainly in the $CD4^{+}$T cells and some in the macrophages.

iii Dual-tropic strains

They are also known as the transitional strains of the HIV-1. They use both the CCR5 and CXCR5 for co-receptors. Replication of this strain occur mainly in the $CD4^{+}$T cells and some in the macrophages.

2.2.4 HIV Co-receptors

According to Hoffmann et al. (2007), experiments using non-human cell lines transfected with human CD4 showed that expression of human CD4 on the cell surface of a non-human cell line was not sufficient to allow entry of HIV. Hence the existence of human co-receptors necessary for viral entry was postulated. Co-receptors are chemokines of the cytokine super-family. The chemokines are group of small proteins that mediate leukocyte traffic through specific receptors. They are involved in several human reproductive events such as sperm chemotaxis (i.e. carrying around of sperms), ovulation, implantation of embryo during conception, menstruation e.t.c. Also HIV-1 uses the chemokines as entry into the individual cell(s). There two types of chemokines namely the α-chemokines (these use the α- receptors) and the β-chemokines (these use the β- receptors). In layman's language, co-receptors are

elements that receive the virus or help the virus to gain entry into the targeted cells. Table 2.1 shows the strains of HIV-1 and their chemokines and co-receptors.

Table 2.1 HIV-1 Strains and their Chemokines and Co-receptors.

Strain of HIV-1	Type of chemokine receptor	Type of Co-receptor for entry	Cells tropism
Macrophage	β	CCR5	Macrophages, CD4+T cells
T-tropic	α	CXCR4	CD4+T cells, Macrophages
Dual-tropic		CCR5, CXCR4	
Others		CCR3, CCR2, CCR8, CCR9, STRL33 (Bonzo), Gpr 15 (Bob), Gpr 1	

2.2.5 HIV-1 Subgroup, Recombination and Epidemiological Structure

Although once an individual becomes infected, eradication of the virus still remains impossible despite all the therapeutic advantages achieved during the last decade, knowledge of the epidemiological prevalence can still help to contain the disease to a certain degree (Hoffmann et al. 2007). There are three subtypes of HIV-1 namely: M group or the “major” group, O group or the “outlier” group and N group or the “new” group. Each group is divided into subtypes and their recombined subtype known as the circulating recombinant forms (CRFs). Given below are the HIV-1 subgroups and their epidemiological prevalence.

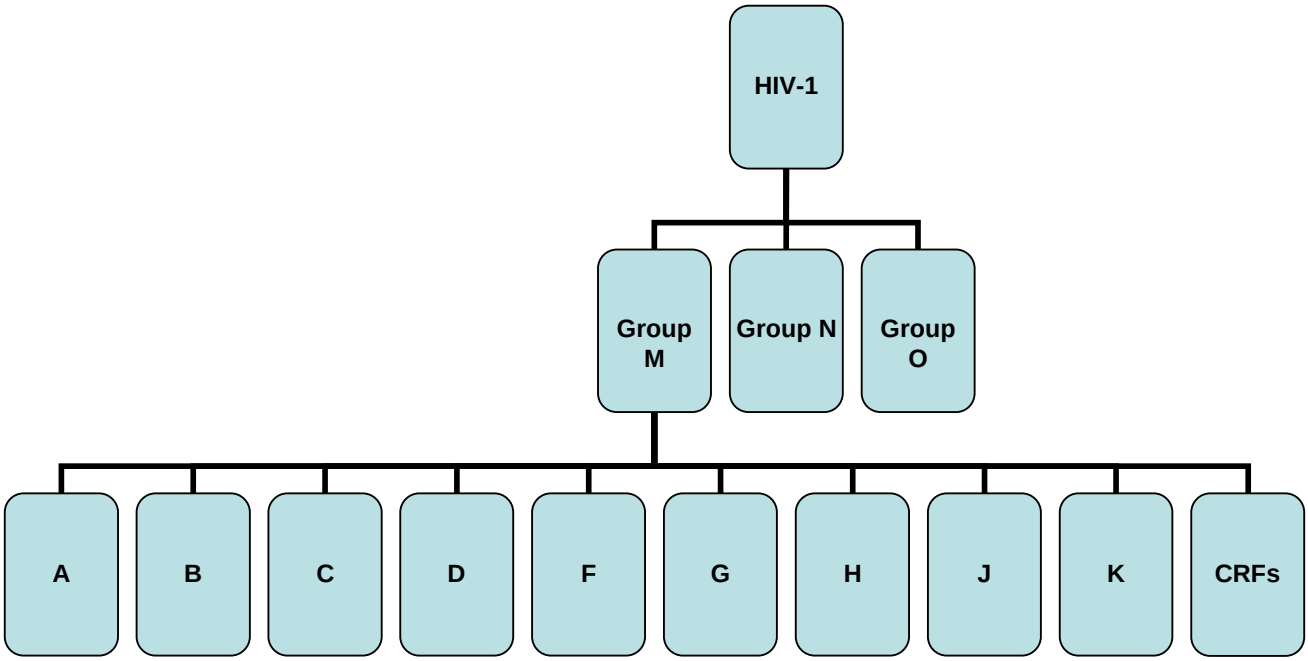

Figure 2.2 HIV-1 Group and Subtypes

Table 2.2 HIV-1 Subtypes and Regional Prevalence

HIV-1 Subtype	Region
A	West Africa, Central Africa, Russia
Crf A/G	West Africa, East Africa, Central Europe
Crf A/E	South-East Asia but originated from Central Africa
B	Europe, America, Japan, Australia
C	Southern Africa, East Africa, India, Nepal
D	East Africa, Central Africa
F	Central Africa, South America, Eastern Europe
G	West Africa, East Africa, Central Europe
H	Central Africa
J	Central Africa
K	Democratic Republic of Congo (DRC), Cameroon

2.3 RECENT DEVELOPMENTS AND PROBLEMS

In recent times scientists have come up with a new way of combating both the human immunodeficiency syndrome (HIV) and acquired immunodeficiency syndrome (AIDS) despite the absence of a cure for them. This recent discovery is still in the pipeline, but it involves the attack of reservoirs of dormant HIV. There are two reservoirs namely macrophages and memory T cells. The macrophages which are antigen scavengers usually engulf antigens in the body and afterwards the macrophages die while the memory T cells retain the whole process of attacking and building forces against antigens in the body so that a reoccurrence of such attack does not come into play (Kirschner 1996).

In the presence of HIV the macrophages still live long past their survival time and hence become a hideout for the virus. The inability of macrophages to die after being infected by the virus is caused by enzyme called Akt which is a protein produced by a cell-survival pathway of the virus. To combat the infected macrophages which is one of the habouring stations of the virus, drugs such as miltefosine and perifosine were used and these two rapidly killed the infected macrophages. Although perifosine is currently being studied as a possible cancer drug, miltefosine on the other hand is known to be safe in leishmaniasis patients, hence further research on the possible effects of using these two drugs to destroy infected macrophages.

Although recombinant viruses forming between HIV clades and groups have occurred due to co-infection and super-infection of cells by two or more virus strains/types usually prior to the establishment of a chronic infection. Recombination between HIV-1 and HIV-2 is impossible because of the differences in the location of the RNA dimmer hairpin sites (Dirac et al. 2002, Levy 2009). Hence recombinant viruses have posed a big problem in controlling the infection by administering antiretroviral drugs for too long because most times resistance to the drugs and poor immune response usually occur (Fultz 2004, Levy 2009).

Eradication of the virus in an infected human body has become impossible because the virus infects not only cells in the body, but also cells in the cellular and immune system. Also the virus is evident not only in the blood, but also in cells and different compartments of the body (Levy 2009).

With the emergence of new antiviral therapies especially the combined treatment, great hope to those at risk of advancing to AIDS have been brought. However long-term therapy

treatments may not be feasible because of toxic drug side effects such as liver damage and drug resistance due to fast mutation of the virus and/or recombination of different types of the virus (Khalili and Armaou 2008, Levy 2009, Hoffmann et al. 2007).

Other avenues explored in eradicating the virus or slowing down cell activation include: Using antibodies that attach to virus-infected cells via gp 120 or gp 41 to directly kill infected cells through antibody-directed cellular cytotocity (ADCC). Targeting intracellular protein needed for HIV replication by using anti-HIV therapy; for example Vpu was shown to reduce the activities of the human cellular membrane protein called tetherin with the help of a calcium-modulating cyclophilin ligand, thus blocking the budding of the virus from the cell surface. Also deficiency of Vif has shown in studies in Australia to help in delaying onset of AIDS whence such individuals have been able to stay as long-term AIDS progressors.

While these researches are in pipeline, work still continue in the detailed understanding of these two deadly viruses that have sacrilegiously and despicably invaded and destroyed the peace of the human race in the last thirty years.

CHAPTER THREE

A STOCHASTIC POINT PROCESS MODEL OF THE INCUBATION PERIOD OF A HIV INFECTED INDIVIDUAL

3.1 INTRODUCTION

Acquired Immune Deficiency Syndrome (AIDS) is a sure fatal but containable disease caused by the retrovirus HIV. It is found that there is a risk of contracting HIV infection from exposure to infected persons. The exposure can be through sharing of intravenous hypodermic needle with infected persons, transfusion of HIV infected blood, mother-to-child transmission at birth or performing a sexual act with HIV infected persons. As sex plays a major important role in human life, the virus has the vulnerability of being quickly transmitted from one infected individual to either an infected or non-infected individual by the pattern of their intimate behaviour. Since the behaviour is highly stochastic, the time for a susceptible to become an infective is unpredictable. Whence, the dynamics of the spread of HIV presents several perplexing difficulties in its comprehension even in the case of a specific community such as a population of transfusion related cases of AIDS (Medley et al. 1988). The foremost difficulty that is baffling the model builders is the incubation period of HIV. The incubation period (**IT**) of HIV in an infected individual is the period from the time of infection to the time of the first diagnosis of an opportunistic disease associated with AIDS. And according to Medley et al. (1988), one of the striking features of acquired immunodeficiency syndrome (AIDS) is that the incubation period appears to be both long and very variable. Usually, the time of infection is not known in several cases. However, the seroconversion time (**ST**) (i.e., the time at which an infected individual becomes HIV positive) may be known in many cases. The latent period, namely, the interval between the time of infection and the time of seroconversion is small (in weeks) compared to the incubation period (in years) of HIV. Hence, the time of infection is taken to be the time of seroconversion.

Studies on HIV incubation period have been carried out. For instance, Medley et al. (1988) in their study observed that the data on the time of infection was incomplete and estimated mean incubation period to be 4.5 years to 15 years.

Chevret et al. 1992 developed a new approach for estimating the incubation period of acquired immunodeficiency syndrome (AIDS) based on age distributions. They expressed the Incubation period as the difference between age at time of diagnosis and age at time of contamination. By assuming independence between age at time of infection and incubation period, the age distribution of newly diagnosed AIDS cases was given as the convolution product between the distributions of the age of freshly infected patients and of the incubation times. Hence, AIDS incubation time could therefore be estimated from the age distribution of newly HIV infected subjects and newly diagnosed AIDS cases.

Lee (1999) estimated the maturity of the HIV infection and the incubation period of AIDS by using data from 363 seroprevalent (i.e. those who were AIDS free at entry) Korean AIDS patients (including 59 seroincident cases). He proposed two methods for imputing the unknown times since seroconversion which were, firstly fitting Weibull regression with the marker of matured CD4+T cell count for seroincident cohorts, and secondly, using a random effects model with CD4+T cell count as a response for repeated measures from which the times since seroconversion can inversely be extracted.

Rao and Kakehashi (2005) estimated HIV incidence density from prevalence data and also the incubation time distribution by using the deconvolution technique and maximum likelihood method to estimate parameters. The difference was that their data was not based on homosexual men/women.

Several mathematical and statistical analyses have been proposed in the recent past to assimilate the data and provide information about the dynamics of the epidemic (Anderson and May 1991). In the statistical analyses of the data, the gamma, Gompertz, Lognormal, Normal and Weibull distributrions were used to model the distribution function F(t) of the incubation period (Brookmeyer and Gail 1994, Anbupalam et al. 2002). The advantages and disadvantages of using each of these models are outlined in Brookmeyer and Gail (1994). In particular, the Weibull model is used in situations where it is hypothesized that the hazard function λ(t) increases indefinitely and is proportional to a power of time from infection (Brookmeyer and Gail 1994). The hazard function quantifies how the risk of AIDS evolves with time from infection and is given by

$$\lambda(t) = \frac{\mathrm{f(t)}}{\mathrm{S(t)}}$$

where $f(t) = \mathrm{F}'(\mathrm{t})$ and S(t) = 1 – F(t) are the probability density function (p.d.f) and the survival function (s.f) of the incubation period respectively. However, as Brookmeyer and Gail (1994) have pointed out, the hazard function λ(t) should be consistent with epidemiological data and with theoretical considerations of the pathogenesis of HIV infection. Not much attention has been paid to the formulation of the distribution functions (hence the hazard functions) of the latent and the incubation periods by considering the stochastic behavioural aspects of the members of the population under study.

In this chapter, two stochastic models are presented namely:

i. Model I which is devoted to the determination of the distribution function of the gay-life (i.e. the time period from the entry of a susceptible in the specified community till he/she tested HIV positive) of a susceptible.

ii. Model II which determines the distribution function for the incubation period (i.e., the period from the time of seroconversion till the onset of overt symptom of AIDS).

Essentially, a two-parameter family distribution function for the gay-life and a one-parameter family of distribution for the incubation period are obtained. It is observed that the distribution function of the incubation period serves as a good fit for the data provided by Lui et al. (1988). Further, the distribution function is used to project AIDS incidence by back-calculation (Brookmeyer and Gail 1994).

The lay-out of this chapter is as follows: In section 3.2, a stochastic model for the determination of the p.d.f q(t) of the time interval ST between the time of entry of an individual into a population of homosexuals and the time of his/her seroconversion (becoming HIV positive) is proposed. In section 3.2.1 a two-parameter family of the probability distribution function of ST is obtained. The moments of ST are obtained in section 3.2.3 and the problem of estimation of the parameters of q(t) is considered in section 3.2.4. In section 3.3, a stochastic model for the determination of the probability function p_n of the incubation period (IT) is proposed. A one-parameter family of the probability function p_n of IT is obtained in section 3.3.1 while the moments of IT are obtained in section 3.3.2. The problem of estimation of the parameter of p_n is considered in section 3.3.3 and illustrated by a numerical example in section 3.3.4. The method of back-calculation is used in section 3.4 to obtain AIDS projection for a sample data.

3.2 A STOCHASTIC MODEL OF THE PERIOD OF THE GAY-LIFE

Consider a population of homosexuals consisting of susceptibles and infectives. Assume that at time t = 0, a new member who is tested HIV negative enters into the population and makes sexual contacts with members of the population. Assume further that his/her contacts occur at random time points which follow a Poisson process with parameter λ, λ > 0. Let the probability that the individual who has already had n contacts up to time t when he/she tested HIV positive for the first time in the interval (t, t+Δ) be given by

$$n\mu\Delta + o(\Delta),\ \mu > 0.$$

Let the gay life period of the individual be represented by the random variable ST. in the next section, we obtain the probability density function (p.d.f) of ST.

3.2.1 The Probability Distribution Function of the Gay-life

We define the p.d.f of ST by

$$q(t) = \lim_{\Delta \to 0} \frac{\Pr\{t < \mathrm{ST} < \mathrm{t} + \Delta\}}{\Delta}$$

Then q(t)Δ represents the probability that the individual tests HIV positive for the first time in the interval (t, t+Δ). At least one contact is needed to get infected with HIV, and also using probabilistic rules, we obtain

$$q(t) = \mathrm{e}^{-\lambda \mathrm{t}}\lambda \otimes e^{-(\lambda+\mu)t}\mu + \mathrm{e}^{-\lambda \mathrm{t}}\lambda \otimes \times \sum_{\mathrm{n}=2}^{\infty} \mathrm{e}^{-(\lambda+\mu)\mathrm{t}}\lambda \otimes \ldots \otimes e^{-(\lambda+(\mathrm{n}-1)\mu)t}\lambda \otimes e^{-(\lambda+n\mu)t} n\lambda \qquad (3.2.1.1)$$

Taking Laplace transform on both sides of 3.2.1.1 we get

$$q^*(s) = \frac{\lambda}{s+\lambda} \sum_{\mathrm{n}=1}^{\infty} \frac{n\lambda^{n-1}\mu}{(s+\lambda+\mu)\ldots(\mathrm{s}+\lambda+\mathrm{n}\mu)} \qquad (3.2.1.2)$$

Splitting into partial fractions, equation 3.2.1.1 yields

$$q^*(s) = \lambda \sum_{n=1}^{\infty} \frac{1}{(\mathrm{n}-1)!} \left(\frac{\lambda}{\mu}\right)^{(n-1)} \left\{ \sum_{j=0}^{\mathrm{n}} \binom{n}{j} (-1)^j \frac{1}{(s+\lambda+\mathrm{j}\mu)} \right\} \qquad (3.2.1.3)$$

Inverting 3.2.1.3, we obtain explicitly the p.d.f of ST given by

$$q(t) = \lambda e^{-\lambda t}(1 - e^{-\mu t})e^{\lambda \frac{(1 - e^{\mu t})}{\mu}} \tag{3.2.1.4}$$

The frequency curve for ST for various values of λ and μ can be obtained by using

$$t_{mode} = \frac{1}{\mu}\log\left(\frac{2\lambda}{2\lambda + \mu - \sqrt{\mu^2 + 4\lambda\mu}}\right) \tag{3.2.1.5}$$

The distribution function Q(t) is given by

$$Q(t) = \frac{\lambda}{\mu}\int_0^{1-e^{-\mu t}} u(1-u)^{\frac{\lambda}{\mu}-1} e^{\frac{\lambda}{\mu}u}\,du \tag{3.2.1.6}$$

If λ = μ = λ, then

$$Q(t) = 1 - e^{-\lambda t}e^{1-e^{-\lambda t}}$$

In this case, the hazard function λ(t) is given by

$$\lambda(t) = \lambda(1 - e^{-\lambda t})$$

It can be observed that the hazard rate is increasing monotonically, which agrees with Brookmeyer and Gail (1994). In the next section, the moments of ST are obtained using equation 3.2.1.3.

3.2.2 The Moments of ST

The k-th moment of ST is given by

$$E[ST^k] = (-1)^k\left[\frac{d^k}{ds^k}\{q^*(s)\}\right]_{s=0}$$

Consequently, from 3.2.1.3, we obtain

$$E[ST^k] = k!e^{\frac{\lambda}{\mu}}\sum_{j=0}^{\infty}\frac{(-1)^j}{j!(\lambda + j\mu)^k}\left(\frac{\lambda}{\mu}\right)^j \tag{3.2.2.1}$$

For the particular case $\lambda = \mu = \lambda$, the mean and variance of ST obtained from equation 3.2.2.1 are given by

$$E[ST] = \frac{e-1}{\lambda} \tag{3.2.2.2}$$

$$Var[ST] = \frac{2e}{\lambda^2}\sum_{n=0}^{\infty}\frac{(-1)^j}{(j+1)(j+1)!} - \left(\frac{e-1}{\lambda}\right)^2 \tag{3.2.2.3}$$

The parameters of q(t) are obtained in the next section by using the method of maximum likelihood.

3.2.3 Estimation of the Parameters of q(t)

The likelihood function $L(\lambda,\mu)$ for a sample of size n is given by

$$L(\lambda,\mu) = \lambda^n \exp\left(-\lambda\sum_{i=1}^{n} t_i\right)\prod_{j=1}^{n}(1-e^{-\mu t_j})\exp\left\{\frac{\lambda}{\mu}\left(n - \sum_{k=1}^{n} e^{-\mu t_k}\right)\right\}$$

The logarithm of L is given by

$$\log_e L = n\log\lambda - \lambda\sum_{i=1}^{n} t_i + \sum_{j=1}^{n}\log(1-e^{-\mu t_j}) + \frac{\lambda}{\mu}\left(n - \sum_{k=1}^{n} e^{-\mu t_k}\right) \tag{3.2.3.1}$$

When $\log_e L$ reaches its maximum value, the values of λ and μ satisfy the following simultaneous equations:

$$n(\lambda+\mu) - \lambda\mu\sum_{i=1}^{n} t_i - \lambda\sum_{k=1}^{n} e^{-\mu t_k} = 0 \tag{3.2.3.2}$$

$$\mu^2\sum_{j=1}^{n}\frac{t_j e^{-\mu t_j}}{1-e^{-\mu t_j}} + \lambda\mu\sum_{k=1}^{n} t_k e^{-\mu t_k} - n\lambda + \lambda\sum_{k=1}^{n} e^{-\mu t_k} = 0 \tag{3.2.3.3}$$

From equation 3.2.3.2, we obtain

$$\lambda = \frac{n\mu}{\mu\sum_{j=1}^{n} t_j + \sum_{k=1}^{n} e^{-\mu t_k} - n} \tag{3.2.3.4}$$

Substituting 3.2.3.4 into 3.2.3.3, we obtain the following transcendental equations for μ:

$$\mu\left(\sum_{j=1}^{n}\frac{t_j e^{-\mu t_j}}{1-e^{-\mu t_j}}\right)\mu\sum_{j=1}^{n}t_j+\sum_{k=1}^{n}e^{-\mu t_k}-n+n\left(\mu\sum_{k=1}^{n}t_k e^{-\mu t_k}-n+\sum_{k=1}^{n}e^{-\mu t_k}\right)=0 \qquad (3.2.3.5)$$

Equation 3.2.3.5 can be solved using Newton-Raphson algorithm (Sastry 1994). Accordingly, we put

$$\psi(\mu)=\mu\left(\sum_{j=1}^{n}\frac{t_j e^{-\mu t_j}}{1-e^{-\mu t_j}}\right)\left(\mu\sum_{j=1}^{n}t_j+\sum_{k=1}^{n}e^{-\mu t_k}-n\right)+n\left(\mu\sum_{k=1}^{n}t_k e^{-\mu t_k}-n+\sum_{k=1}^{n}e^{-\mu t_k}\right)=0 \quad (3.2.3.6)$$

Then if $\mu^{(0)}$ is an initial approximate value of μ, then the $(l+1)$th iterate of μ is given by the equation

$$\mu^{(l+1)}=\mu^{(l)}-\frac{\phi(\mu^{(l)})}{\phi'(\mu^{(l)})},\ l=0,1,\ldots \qquad (3.2.3.7)$$

The iterative scheme given by equation 3.2.3.7 is the Newton-Raphson algorithm.

3.3 A STOCHASTIC MODEL OF THE HIV INCUBATION PERIOD

Assume that an individual has tested HIV positive for the first time at time t = 0. Let the conditional probability that he/she shows the first identifiable symptoms of AIDS during the n-th year given that he/she has not shown any symptoms of AIDS in the previous years be given by

$$1-e^{-n\mu},\ n=1,2,\ldots,\ \mu>0$$

Let IT be the random variable representing the incubation period. In the next section, a one-parameter family of distribution functions of IT is obtained.

3.3.1 The Probability Distribution of the Incubation Period

Let the probability function of IT be defined by

$$p_n = \Pr\{IT = n\}$$

Then p_n represents the probability that the individual shows the first symptom of AIDS in the n-th year. By using probabilistic rules, we obtain

$$p_n = e^{-\mu} e^{-2\mu} \ldots e^{-(n-1)\mu}(1 - e^{-n\mu}), n = 1, 2, \ldots \quad (3.3.1.1)$$

Simplifying equation 3.3.1.1 yields

$$p_n = e^{-\frac{(n-1)n}{2}\mu} - e^{-\frac{n(n+1)}{2}\mu}, n = 1, 2, \ldots \quad (3.3.1.2)$$

The mode l of the distribution is given by

$$e^{-\frac{(l-2)(l-1)}{2}\mu}(1 - e^{-(l-1)\mu}) \le e^{-\frac{l(l-1)}{2}\mu}(1 - e^{-l\mu}) \le e^{-\frac{l(l+1)}{2}\mu}(1 - e^{-(l+1)\mu}) \quad (3.3.1.3)$$

The median θ of the distribution is given by

$$1 - e^{-\frac{\theta(\theta+1)}{2}\mu} = \frac{1}{2} \quad (3.3.1.4)$$

From equation 3.3.1.4, we have

$$\mu\theta(\theta+1) - 2\log 2 = 0 \quad (3.3.1.5)$$

Solving equation 3.3.1.5, the median is given by

$$\theta = \frac{\sqrt{\mu^2 + 8\log 2} - \mu}{2\mu} \quad (3.3.1.6)$$

3.3.2 The Moments of Incubation Period

The mean of IT is given by

$$\begin{aligned} E[IT] &= \sum_{n=1}^{\infty} np_n \\ &= \sum_{n=1}^{\infty} n\{e^{-\frac{(n-1)n}{2}\mu} - e^{-\frac{n(n+1)}{2}\mu}\} \\ &= \sum_{n=0}^{\infty} e^{-\frac{n(n+1)}{2}\mu} \end{aligned} \quad (3.3.1.7)$$

The second moment of IT is given by

$$E[IT^2] = \sum_{n=1}^{\infty} n^2 p_n$$
$$= \sum_{n=1}^{\infty} n^2 \{e^{-\frac{(n-1)n}{2}\mu} - e^{-\frac{n(n+1)}{2}\mu}\} \qquad (3.3.1.8)$$
$$= \sum_{n=0}^{\infty} (2n+1) e^{-\frac{n(n+1)}{2}\mu}$$

3.3.3 Estimation of the Parameter of p_n

Equation 3.3.1.2 represents a one-parameter family of probability distributions and for estimation of the parameter, either the method of moments or the method of maximum likelihood can be used.

3.3.3.1 The Method of Moments

Let $t_1, t_2, \ldots, t_m$ be a random sample of size n drawn from a population of incubation times of HIV infected individuals. Then the sample mean is given by

$$\bar{t} = \frac{1}{n} \sum_{n=1}^{m} t_n$$

Replacing E[T] by $\bar{t}$ in 3.3.1.7, we have

$$\bar{t} = \sum_{n=0}^{\infty} e^{-\frac{n(n+1)}{2}\mu} \qquad (3.3.3.1.1)$$

As the incubation time of an HIV-infected individual can never be greater than 100 years, equation 3.3.3.1.1 can be truncated in the following manner:

$$\bar{t} = \sum_{n=0}^{100} e^{-\frac{n(n+1)}{2}\mu} \qquad (3.3.3.1.2)$$

An approximate value $\bar{\mu}$ of μ can be obtained from equation 3.3.3.1.1 by using the Newton-Raphson algorithm.

3.3.3.2 The Method of Maximum Likelihood

The likelihood function L(μ) for a sample $\{n_1, n_2, \ldots, n_m\}$ of size m is given by

$$L(\mu) = \prod_{j=1}^{m} e^{-\frac{(n_j - 1)n_j}{2}} (1 - e^{-\mu n_j})$$

The logarithm of L(μ) is given by

$$\log_e L(\mu) = -\frac{\mu}{2} \sum_{i=1}^{m} (n_i - 1)n_i + \sum_{j=1}^{m} \log(1 - e^{-\mu n_j})$$

When $\log_e$ L(μ) reaches its maximum value, the value of μ satisfies the following equation:

$$\frac{\partial L}{\partial \mu} = 0 \qquad (3.3.3.2.1)$$

From equation 3.3.3.2.1, we obtain

$$\sum_{i=1}^{m} n_i \frac{e^{-n_i \mu}}{1 - e^{-n_i \mu}} = \frac{1}{2} \sum_{i=1}^{m} m(n_i^2 - n_i) \qquad (3.3.3.2.2)$$

By applying the Newton-Raphson algorithm to equation 3.3.3.2.2, an approximate value $\bar{\mu}$ for μ can be obtained.

3.3.3.3 The Method of Median

The value of μ can be estimated from equation 3.3.1.5. for a sample of incubation times, we obtain the sample median θ* and then replacing θ in equation 3.3.1.5 by θ*, we have the following equation for a crude estimation μ* of μ:

$$\mu^* = \frac{2\log 2}{\theta^*(\theta^* + 1)} \qquad (3.3.3.3.1)$$

A numerical example to compare the three methods is provided in the next section.

3.3.4 A Numerical Example

The data of 84 homosexuals and bisexual men analysed in Lui et al. (1988) is used to obtain the incubation periods of twenty one individuals who developed AIDS prior to the year 1988 (Table 3.1). Estimates for the value of μ by the three methods are obtained and corresponding expected values and standard deviations are determined. The estimates are then used to test the goodness of fit of the distribution obtained.

Table 3.1 HIV Incidence data of 84 homosexuals

Year of HIV Infection	Year of diagnosis									
	1979	1980	1981	1982	1983	1984	1985	1986	Censored	Total
1978	0	0	0	1	0	1	1	0	3	6
1979		0	0	0	0	0	0	1	7	8
1980			0	0	0	1	1	1	9	12
1981				0	2	2	1	5	19	29
1982					1	0	3	0	19	23
1983						0	0	0	2	2
1984							0	0	4	4

From this table, the following incubation times (in years) of 21 persons were obtained as:

4, 6, 7, 7,4, 5, 6, 2, 2, 3, 3, 4, 5, 5, 5, 5, 5, 1, 3, 3, 3.

The sample mean is 4.19 years and the sample median is 4 years. By using Newton-Raphson algorithm in equation 3.3.3.1.2, with table 3.2, we have the optimal value $\hat{\mu} = 0.09$ so that the expected value of IT is 4.19 years with a standard deviation of 2.15 years. On the other hand,

for the same data of 21 persons, by adopting Newton-Raphson algorithm in equation 3.3.3.2.2, we get $\tilde{\mu}=1.01$ so that the expected value of IT is 1.41 years with a standard deviation of 0.59 year. Also, using equation 3.3.3.3.1, we get μ* = 0.07 so that the expected value of IT is 4.80 years with a standard deviation of 2.48 years. The three values of the parameter μ are listed in table 3.2.

Table 3.2 Values of the Parameters of μ

Method	μ	Mean	Standard Deviation
Moments	$\hat{\mu}=0.09$	4.19	2.15
Maximum Likelihood	$\tilde{\mu}=1.01$	1.41	0.59
Median	μ* = 0.07	4.80	2.48

Further, by applying χ^2 test, it was observed that the value of μ obtained by the method of moments fits closely to the observed data. Hence in what follows, we assume μ = 0.09 and proceed to project AIDS incidence by the Back-Calculation Method with a sample data (Bacchetti 1990)

3.4 THE BACK-CALCULATION AND THE INFECTION RATE

One of the methods used in estimating and projecting the infection rate from AIDS incidence data is the back-calculation method (Brookmeyer and Gail 1994). It is an important method of constructing rates of HIV infection and estimating current prevalence of HIV infection and future incidence of AIDS (Bacchetti et al. 1993). This method has been used by many mathematical scientists to obtain and predict the AIDS incidence of different populations. Amongst the work done are those of Verdecchia and Mariotto (1995) who modelled past HIV infections in Italy considering the interaction between age and calendar time. Anbupalam et

al. (2002) also used the Back calculation method to project future AIDS cases in Tamil Nadu by assuming that the incubation distribution was Weibul and Log-logistic. Ong and Soo (2006) estimated the HIV infection rates and projection in Malaysia while Lopman and Gregson (2008) used the Back-calculation method to reconstruct the historical trends in HIV incidence in Harare, Zimbabwe by using mortality data. They also attempted to determine the amount of peakness of HIV incidence and when the peakness occurred in Harare, Zimbabwe.

The method in continuous time is based on the convolution equation

$$A(t) = \int_0^t g(s)F(t-s)ds \qquad (3.4.1)$$

where A(t) represents the expected cumulative number of AIDS cases diagnosed by calendar time t, g(s) is the infection-rate at calendar time s and F(t) is the distribution of the incubation period. Equation 3.4.1 is a Volterra integral equation for g(s) and has been obtained by noting that an individual can be diagnosed to have AIDS before calendar time t, provided he/she has been infected at some time s < t and has an incubation period less than t-s. For a given AIDS incidence data, A(t) can be fitted and a model used for F(t) in 3.4.1 so that the rate g(s) can be computed by de-convolving equation 3.4.1. Taking Laplace transform on both sides of 3.4.1, we have

$$A^*(u) = \frac{g^*(u)f^*(u)}{u}$$

so that

$$g^*(u) = \frac{uA^*(u)}{f^*(u)} \qquad (3.4.2)$$

By inverting 3.4.2, we obtain the infection rate g(s).

On the other hand, the back-calculation in discrete time is based on the equation

$$E(Y_j) = \sum_{i=1}^{j} g_i \, p_{j-i+1} \qquad (3.4.3)$$

where Yj is the number of AIDS cases diagnosed in the j-th year [j-1,j], g_j is the number infected in the beginning of the j-th year and p_j is the probability that a person who is infected at the beginning of the 1st year is diagnosed with AIDS in the j-th year. If A_n denotes the expected cumulative number of AIDS cases diagnosed up to the end of the n-th year, then using equation 3.4.3, we have

$$A_n = \sum_{j=1}^{n} E(Y_j) = \sum_{j=1}^{n} \sum_{i=1}^{j} g_i \, p_{j-i+1} \qquad (3.4.4)$$

Equation 3.4.4 is analogous to equation 3.4.1.

We proceed to illustrate the back-calculation in discrete time with the data used in Bacchetti (1990) where the monthly infection rate and monthly AIDS incidence among gay men in San Fransisco in the cohort born from October 1929 through September 1959 were estimated. Taking t = 0 to correspond to January 1978 and the time unit as year, the data is given in table 3.3 below.

Table 3.3 Data on AIDS incidence among gay men in San Fransisco

j	1	2	3	4	5	6	7	8	9	10	11
Y_j	0	0	1	26	93	278	560	840	1264	1464	1455

Table 3.4 Probability distribution of the Incubation Time

n	1	2	3	4	5	6	7	8	9	10
p_n	0.09	0.15	0.18	0.18	0.15	0.11	0.07	0.04	0.02	0.01

For μ = 0.09, the probability distribution of the incubation time is given in table 3.4. Following Brookmeyer and Gail (1994), we proceed to obtain the discrete time infection curve. We assume for simplicity that infections occurring in a calendar year are accounted at a single time point, for example, January 1 of the year and

$$g(2n-1) = g(2n) = \beta_n, \; n = 1, 2, \ldots \tag{3.4.5}$$

Equation 3.4.5 provides a simple smoothness assumption on the annual infection rate. Consequently, equation 3.4.3 leads to the following matrix equation:

$$\begin{pmatrix} E(Y_1) \\ E(Y_2) \\ E(Y_3) \\ E(Y_4) \\ E(Y_5) \\ E(Y_6) \\ E(Y_7) \\ E(Y_8) \\ E(Y_9) \\ E(Y_{10}) \\ E(Y_{11}) \end{pmatrix} = \begin{pmatrix} 0.09 & 0.00 & 0.00 & 0.00 & 0.00 & 0.00 \\ 0.24 & 0.00 & 0.00 & 0.00 & 0.00 & 0.00 \\ 0.34 & 0.09 & 0.00 & 0.00 & 0.00 & 0.00 \\ 0.36 & 0.24 & 0.00 & 0.00 & 0.00 & 0.00 \\ 0.32 & 0.34 & 0.09 & 0.00 & 0.00 & 0.00 \\ 0.25 & 0.36 & 0.24 & 0.00 & 0.00 & 0.00 \\ 0.18 & 0.32 & 0.34 & 0.09 & 0.00 & 0.00 \\ 0.11 & 0.25 & 0.36 & 0.24 & 0.00 & 0.00 \\ 0.06 & 0.18 & 0.32 & 0.34 & 0.09 & 0.00 \\ 0.03 & 0.11 & 0.25 & 0.36 & 0.24 & 0.00 \\ 0.01 & 0.06 & 0.18 & 0.32 & 0.34 & 0.09 \end{pmatrix} \begin{pmatrix} \beta_1 \\ \beta_2 \\ \beta_3 \\ \beta_4 \\ \beta_5 \\ \beta_6 \end{pmatrix} \tag{3.4.6}$$

Using the Poisson Regression Analysis (PRA) (Koch et al. 1986, McCillagh and Nelder 1989), the values of β_j for j = 1, 2, …, 6 are estimated. The method is based on the assumption that the random variable Y_j has a Poisson distribution. Setting $\mu_j = E(Y_j)$, the likelihood function corresponding to the sample $\{n_1, n_2, \ldots, n_{11}\}$ of $\{ Y_1, Y_2, \ldots, Y_{11}\}$ is given by

$$\varphi(\mu_1, \mu_2, \ldots \mu_{11}) = \prod_{i=1}^{11} e^{\mu_i} \frac{\mu_i^{N_i}}{n_i!} \tag{3.4.7}$$

But from equation 3.4.6, we have

$$\mu_1 = 0.09\beta_1$$
$$\mu_2 = 0.24\beta_1$$
$$\mu_3 = 0.34\beta_1 + 0.09\beta_2$$
$$\mu_4 = 0.36\beta_1 + 0.24\beta_2$$
$$\mu_5 = 0.32\beta_1 + 0.34\beta_2 + 0.09\beta_3$$
$$\mu_6 = 0.25\beta_1 + 0.36\beta_2 + 0.24\beta_3$$
$$\mu_7 = 0.18\beta_1 + 0.32\beta_2 + 0.34\beta_3 + 0.09\beta_4$$
$$\mu_8 = 0.11\beta_1 + 0.25\beta_2 + 0.36\beta_3 + 0.24\beta_4$$
$$\mu_9 = 0.06\beta_1 + 0.18\beta_2 + 0.32\beta_3 + 0.34\beta_4 + 0.09\beta_5$$
$$\mu_{10} = 0.03\beta_1 + 0.11\beta_2 + 0.25\beta_3 + 0.36\beta_4 + 0.24\beta_5$$
$$\mu_{11} = 0.01\beta_1 + 0.06\beta_2 + 0.18\beta_3 + 0.32\beta_4 + 0.34\beta_5 + 0.09\beta_6$$

and hence on substitution of these equations in 3.4.7, φ becomes a function of $\beta_1, \beta_2, \ldots, \beta_6$. Differentiating $\log_e \varphi$ with respect to β_j and equating the results to 0, the following system of equations is obtained:

$$\sum_{i=1}^{11}\left(\frac{\mu_i - n_i}{\mu_i}\right)\frac{\partial \mu_i}{\partial \beta_j} = 0,\ j = 1, 2, 3, 4, 5, 6. \qquad (3.4.8)$$

Equations 3.4.8 do not yield an explicit solution and so an iterative method is used to obtain an approximate solution for $(\beta_1, \beta_2, \ldots, \beta_6)$ as given below:

$$\hat{\beta}_1 = 6, \hat{\beta}_2 = 33, \hat{\beta}_3 = 1041, \hat{\beta}_4 = 2583, \hat{\beta}_5 = 3416, \hat{\beta}_6 = 5172.$$

The above values can be used to forecast AIDS incidence on short term. For example, the predicted AIDS incidence in the 12^{th} year is obtained as 6523 by using the following extended equation

$$\hat{Y}_{12} = \hat{\beta}_1(p_{11} + p_{10}) + \hat{\beta}_2(p_9 + p_8) + \ldots + \hat{\beta}_6(p_3 + p_2)$$

3.5 CONCLUSION

In this chapter a two-parameter family distribution function for the gay-life and a one-parameter family of distribution for the incubation period have been modelled. For the model, it was observed that the distribution function of the incubation period using the method of moments serves as a good fit for the data provided by Lui et al. (1988). The only setback of the Back-calculation method in projecting AIDS incidence is the inability to project for a very long time.

CHAPTER FOUR

STOCHASTIC MODEL OF THE GROWTH OF HIV IN AN INFECTED INDIVIDUAL

4.1 INTRODUCTION

In the discussion about the progression of the human immunodeficiency virus (HIV) infection, it is often seen that there is a variation in the viral genome. Studies (Kaye et al. 1992 and Loveday 1996) have shown that HIV may make 1 to 40 base errors per replication cycle with no genetic mechanisms for correction resulting in the production of genetically diverse viral species or quasi species with 20 – 25% variability. Feinberg (1996) also observed that HIV has an inherent tendency to evolve at a rate (about 1 million times faster than the human DNA) which is believed to be responsible for the development of resistance to antiviral treatments within a matter of months thereby undermining the attempts to produce effective vaccines. Holmes (1998) observed that even in the course of a single infection, a multitude of different genomes are produced through mutation, recombination and natural selection, which allow the virus to continually evade immune responses and infect a variety of cell types. Further, Musey et al. (1997), Phillips et al. (1997) and Barker et al. (1998) observed that there is a correlation between the antigen receptors of T-cells and HIV replication. Consequently, the pathogenesis of the infection can be understood only when the genetic variation in HIV and the receptor-specific HIV infection are given their due importance in the formulation of any model of the dynamics of HIV in an infected individual.

Stilianakis et al. (1997) analysed a model for the pathogenesis of AIDS in which the effect of the ongoing generation and selection of HIV mutants are considered. However, the nature of evolution of the resistant forms in a virus that is continually mutating in response to environmental pressures, and the impact of the location of the antigen receptor through which the virus has entered the cell body on the variable nature of viral replication through mutation have not been analysed so far in the literature. Accordingly, in this chapter, we propose and analyse two stochastic models:

(i) Model I which describes the dynamics of the viral load in a HIV infected person taking into consideration the fact that genetically diverse viral species are produced even in the course of a single infection and that the infection is receptor-specific.

(ii) Model II which describes the multiplication process of the virons inside an infected T4 cell under the assumption that genetically diverse viral species are produced at every lysis that occurs in a T4 cell population.

The organization of this chapter is as follows. Section 4.2 describes model I as a multi-type branching process. In Section 4.2.1, an infinite system of inter-connected integral equations for the probability generating functions of the various viral type populations is obtained. Explicit expressions for the means and co-variances of the viral populations are derived in Section 4.2.2 for a particular case where the virus exist in two forms only. In Section 4.3, model II which describes the dynamics of the growth of HIV inside an infected cell is analysed by a binary splitting process. Also provided in this section is a numerical illustration that brings out the impact of the genetic diversity in viral production.

4.2 MODEL I: THE MUTATION MODEL

We assume that at time t = 0, one HIV of type 0 is introduced into the blood stream (medium of T4 cells). Since each of the T4 cells has an infinite number of CD4+ receptors on its cell wall, we assume that the virus bonds with probability $\pi(j|0)$, j = 1, 2, … to the j-th CD4+ receptor on the cell membrane of one of the T4 helper cells and injects its RNA into the cell medium. The virus arrests the growth of the infected cell but utilises the cell medium to multiply itself into random numbers z_0 and z_j of virons of type 0 and type j respectively after which the cell undergoes a lysis releasing the virons whose numbers are governed by the probability generating function

$$f^{(0j)}(u,v) = \mathrm{E}[u^{z_0} v^{z_j}] = \sum_{m,n=0}^{\infty} p_{mn}^{(0j)} u^m v^n,\ j = 1,2,...$$

These virons in turn go to infect other T4 cells and the process continues indefinitely. We assume that a virus of type i, $i \neq 0$ anchors to the j-th CD4+ receptor on the cell membrane of a T4 cell with probability $\pi(j|i)$, j = 1, 2, … but generates virons of type i only according to the probability generating function defined by

$$f^{(i)}(s) = \sum_{j=0}^{\infty} p_j^{(i)} s^j,\ i = 1, 2, ...$$

where $\pi(j \mid i) = p_j^i$.

We also assume that, for each of the virons of type $\ell, \ell = 0, 1, 2, ...,$ the time from its release to the time of lysis it generates is a random variable T_ℓ whose distribution function is given by

$$f_\ell^{(t)} = \Pr\{T_\ell \leq t\},\ t \geq 0.$$

Let $X_\ell(t)$ denote the number of virons of type ℓ, ℓ = 0, 1, 2, … at time t and

$$X(t) = (X_0(t), X_1(t), ..., X_\ell(t), X_{\ell+1}(t), ...).$$

Then the process X(t) is identified as a multi-type branching process with state-space Z_+^∞, where Z_+ is the set of all non-negative integers. To study the process X(t), we investigate its probability generating function in the next section.

4.2.1 The Probability Generating Functions

Denoting $s = (s_0, s_1, ...)$, we define the following probability generating functions:

$$G^{(i)}(t,s) = \mathrm{E}[s_0^{x_0(t)} s_1^{x_1(t)} ... \mid X(0) = (\delta_{i0}, \delta_{i1}, \delta_{i2}, ...)],\ i = 0, 1, 2, ...$$

Using probabilistic arguments, it is easily seen that

$$G^{(0)}(t,s)=[1-\mathrm{F}_0(t)]s_0+\sum_{\ell=1}^{\infty}\pi(\ell\mid 0)\int_0^t f^{(0\ell)}(G^{(0)}(t-u,s),G^{(\ell)}(t-u,s))dF_0(u) \qquad (4.2.1.1)$$

$$G^{(i)}(t,s)=[1-\mathrm{F}_i(t)]s_i+\int_0^t f^{(i)}(G^{(i)}(t-u,s))dF_i(u),\mathrm{i}=1,2,... \qquad (4.2.1.2)$$

The moments of $X_j(t)$, j = 0, 1, 2, … can be derived from the equations (4.2.1.1) and (4.2.1.2).

We define

$$M_j(t\mid i)=\mathrm{E}[\mathrm{X}_j(t)\mid \mathrm{X}(0)=(\delta_{i0},\delta_{i1},\delta_{i2},...)],\mathrm{i}=0,1,2,...$$

Differentiating (4.2.1.1) partially with respect to s_j and setting s_k =1, k = 0, 1, 2, …, we obtain

$$M_j(t\mid 0)=[1-\mathrm{F}_0(t)]\delta_{0j}+\sum_{\ell=1}^{\infty}\pi(\ell\mid 0)\int_0^t\{\mathrm{m}_1^{(0\ell)}M_j(t-u\mid 0)+\mathrm{m}_2^{(0\ell)}M_j(t-u\mid \ell)\}dF_0(u) \qquad (4.2.1.3)$$

where j = 0, 1, 2, … and

$$m_1^{(0i)}=\left\{\frac{\partial}{\partial \mathrm{u}}f^{(0i)}(u,v)\right\}_{u=1,v=1},\quad m_2^{(0i)}=\left\{\frac{\partial}{\partial v}f^{(0i)}(u,v)\right\}_{u=1,v=1}$$

Differentiating (4.2.1.2) partially with respect to s_j and setting s_k =1, k = 0, 1, 2, …, we obtain

$$M_j(t\mid i)=[1-\mathrm{F}_i(t)]\delta_{ij}+\mathrm{m}^{(i)}\int_0^t M_j(t-u\mid i)dF_i(u) \qquad (4.2.1.4)$$

where i = 1, 2, …, j = 0, 1, 2, … and

$$m_1^{(i)}=\left\{\frac{\partial}{\partial \mathrm{u}}f^{(i)}(u)\right\}_{u=1}$$

If we assume $F_j(u)=1-\mathrm{e}^{-\lambda_1 u}$, then taking Laplace transform on both sides of (4.2.1.3) and (4.2.1.4), we obtain

$$M_j^*(\theta\mid 0)=\frac{\delta_{0\mathrm{j}}}{(\theta+\lambda_0)}+\sum_{\ell=1}^{\infty}\pi(\ell\mid 0)\frac{\lambda_0}{(\theta+\lambda_0)}\{m_1^{(0\ell)}M_j^*(\theta\mid 0)+m_2^{(0\ell)}M_j^*(\theta\mid \ell)\} \qquad (4.2.1.5)$$

$$M_j^*(\theta\mid i)=\frac{\delta_{\mathrm{ij}}}{(\theta+\lambda_{\mathrm{i}})}+\frac{\lambda_{\mathrm{i}}}{(\theta+\lambda_{\mathrm{i}})}m_1^{(i)}M_j^*(\theta\mid i) \qquad (4.2.1.6)$$

where i = 1, 2, …, and j = 0, 1,2 , …. Solving the equation (4.2.1.6), we get

$$M_j^*(\theta \mid i) = \frac{\delta_{ij}}{\theta + \lambda_i(1 - m_1^{(i)})}, \text{ i, j} = 1, 2, \ldots \qquad (4.2.1.7)$$

Substituting (4.2.1.7) in (4.2.1.5) and simplifying, we get

$$M_j^*(\theta \mid 0) = \frac{\delta_{0j}}{\theta + \lambda_0(1 - m_1^{(0)})} + \frac{\lambda_0}{(\theta + \lambda_0(1 - m_1^{(0)}))} \sum_{\ell=1}^{\infty} \pi(\ell \mid 0) \frac{\delta_{\ell j} m_2^{(0\ell)}}{\theta + \lambda_\ell(1 - m_1^{(\ell)})} \qquad (4.2.1.8)$$

where $m_1^{(0)} = \sum_{\ell=1}^{\infty} \pi(\ell \mid 0) m_1^{(0\ell)}$

Inverting the equations (4.2.1.7) and (4.2.1.8), we obtain

$$M_j(t \mid i) = \delta_{ij} e^{-\alpha_i t} \qquad (4.2.1.9)$$

$$M_j(t|0) = \delta_{0j} e^{-\alpha_0 t} + (1 - \delta_{0j}) \frac{\lambda_0 m_2^{(0j)} \pi(j|0)}{(\alpha_0 - \alpha_j)} (e^{-\alpha_j t} - e^{-\alpha_0 t}), \qquad (4.2.1.10)$$

$$M_j(t \mid 0) = \delta_{ij} e^{-\alpha_i t}$$

where $\alpha_0 = \lambda_0(1 - m_1^{(0)})$; $\alpha_i = \lambda_i(1 - m_1^{(i)})$; i = 1, 2, …; j = 0, 1,2 , ….

To obtain the covariance structure of $X_j(t)$ and $X_k(t)$ where j, k = 0, 1, 2, …, we define

$$M_{jk}(t|i) = E[X_j(t)X_k(t)|X(0) = (\delta_{i0}, \delta_{i1}, \delta_{i2}, \ldots)], \quad i = 0, 1, 2, \ldots. \qquad (4.2.1.11)$$

Differentiating (4.2.1.1) with respect to s_j and s_k and setting $s_0 = 1$, $s_1 = 1$, $s_2 = 1$, …, we obtain

$$M_{jk}(t|0) = \sum_{\ell=1}^{\infty} \pi(\ell|0) \int_0^t [m_1^{(0\ell)} M_{jk}(t - u|0) + m_2^{(0\ell)} M_{jk}(t - u|\ell)$$

$$+ m_{11}^{(0\ell)} M_j(t - u|0) M_k(t - u|0) + m_{22}^{(0\ell)} M_j(t - u|\ell) M_k(t - u|\ell)$$

$$+ m_{12}^{(0\ell)} \{M_j(t - u|0) M_k(t - u|\ell) + M_j(t - u|\ell) M_k(t - u|0)\}] dF_0(u), \qquad (4.2.1.12)$$

where

$$m_{11}^{(0\ell)} = \left\{ \frac{\partial^2 f^{(0\ell)}(u, v)}{\partial u^2} \right\}_{u=1, v=1}$$

$$m_{12}^{(0\ell)} = \left\{\frac{\partial^2 f^{(0\ell)}(u, v)}{\partial u \partial v}\right\}_{u=1,v=1}$$

$$m_{22}^{(0\ell)} = \left\{\frac{\partial^2 f^{(0\ell)}(u, v)}{\partial v^2}\right\}_{u=1,v=1}$$

Differentiating (4.2.1.2) with respect to s_j and s_k and setting $s_0 = 1$, $s_1 = 1$, $s_2 = 1$, …, we obtain

$$M_{jk}(t|i) = \int_0^t \{m_1^{(i)} M_{jk}(t - u|i) + m_{11}^{(i)} M_j(t - u|i) M_k(t - u|i)\} dF_i(u), \qquad (4.2.1.13)$$

where

$$m_{11}^{(i)} = \left\{\frac{\partial^2 f^{(i)}(u)}{\partial u^2}\right\}_{u=1}, \quad i = 1, 2, \ldots.$$

Taking Laplace transform on both sides of (3.2.1.13), we get

$$M_{jk}^*(\theta|i) = \frac{\lambda_i}{\theta + \lambda_i}\left\{m_1^{(i)} M_{jk}^*(\theta|i) + \frac{m_{11}^{(i)} \delta_{ij} \delta_{ik}}{\theta + 2\alpha_i}\right\}.$$

Which on simplification gives

$$M_{jk}^*(\theta|i) = \frac{\lambda_i m_{11}^{(i)} \delta_{ij} \delta_{ik}}{(\theta + \alpha_i)(\theta + 2\alpha_i)}. \qquad (4.2.1.14)$$

Inverting (4.2.1.14), we get

$$M_{jk}(t|i) = \frac{\lambda_i m_{11}^{(i)} \delta_{ij} \delta_{ik}}{\alpha_i}(e^{-\alpha_i t} - e^{-2\alpha_i t}). \qquad (4.2.1.15)$$

Now, taking Laplace transform on both sides of (4.2.1.12), we get

$$M_{jk}^*(\theta|0) = \frac{\lambda_0}{\theta + \lambda_0} \sum_{\ell=1}^{\infty} \pi(\ell|0)[m_1^{(0\ell)} M_{jk}^*(\theta|0) + m_2^{(0\ell)} M_{jk}^*(\theta|\ell)$$

$$+ m_{11}^{(0\ell)} L\{M_j(t|0) M_k(t|0)\} + m_{22}^{(0\ell)} L(M_j(t|\ell) M_k(t|\ell))$$

$$+ m_{12}^{(0\ell)} L\{M_j(t|0) M_k(t|\ell) + M_j(t|\ell) M_k(t|0)\}]. \qquad (4.2.1.16)$$

Substituting (4.2.1.7), (4.2.1.8) and (4.2.1.14) in (4.2.1.16) and simplifying, we get

$$M^{*}_{jk}(\theta|0) = \lambda_0^2(1 - \delta_{0j})(1 - \delta_{0k})\delta_{jk}\frac{\pi(\mathrm{j}|0)\mathrm{m}_2^{(0\mathrm{j})}\mathrm{m}_{11}^{(j)}}{(\theta + \alpha_0)(\theta + \alpha_{\mathrm{j}})(\theta + 2\alpha_{\mathrm{j}})}$$

$$+ \lambda_0\mathrm{m}_{11}^{(0)}\Bigg\{\delta_{0j}\delta_{0k} + (1 - \delta_{0j})\delta_{0k}\frac{\lambda_0\mathrm{m}_2^{(0)}\pi(\mathrm{j}|0)}{\alpha_{\mathrm{j}} - \alpha_0} + \delta_{0j}(1 - \delta_{0k})\frac{\lambda_0\mathrm{m}_2^{(0)}\pi(\mathrm{k}|0)}{\alpha_{\mathrm{k}} - \alpha_0}$$

$$+ (1 - \delta_{0j})(1 - \delta_{0k})\frac{\lambda_0^2(\mathrm{m}_2^{(0)})\pi(\mathrm{j}|0)\pi(\mathrm{k}|0)}{(\alpha_{\mathrm{j}} - \alpha_0)(\alpha_{\mathrm{k}} - \alpha_0)}\Bigg\}\frac{1}{(\theta + \alpha_0)(\theta + 2\alpha_0)}$$

$$- \lambda_0\mathrm{m}_{11}^{(0)}\{\delta_{0j}(1 - \delta_{0k})\frac{\lambda_0\mathrm{m}_2^{(0)}\pi(\mathrm{k}|0)}{\alpha_{\mathrm{k}} - \alpha_0}$$

$$+ (1 - \delta_{0j})(1 - \delta_{0k})\frac{\lambda_0^2(\mathrm{m}_2^{(0)})^2\pi(\mathrm{j}|0)\pi(\mathrm{k}|0)}{(\alpha_{\mathrm{j}} - \alpha_0)(\alpha_{\mathrm{k}} - \alpha_0)}\}\frac{1}{(\theta + \alpha_0)(\theta + \alpha_0 + \alpha_{\mathrm{k}})}$$

$$+ \lambda_0\mathrm{m}_{11}^{(0)}(1 - \delta_{0j})(1 - \delta_{0k})\frac{\lambda_0^2(\mathrm{m}_2^{(0)})^2\pi(\mathrm{j}|0)\pi(\mathrm{k}|0)}{(\alpha_{\mathrm{j}} - \alpha_0)(\alpha_{\mathrm{k}} - \alpha_0)}\frac{1}{(\theta + \alpha_0)(\theta + \alpha_{\mathrm{j}} + \alpha_{\mathrm{k}})}$$

$$+ \lambda_0\sum_{\ell=1}^{\infty}\pi(\ell|0)\mathrm{m}_{22}^{(0\ell)}\delta_{\ell j}\delta_{\ell k}\frac{1}{(\theta + \alpha_0)(\theta + 2\alpha_\ell)}$$

$$+ \lambda_0\sum_{\ell=1}^{\infty}\pi(\ell|0)\mathrm{m}_{12}^{(0\ell)}\frac{(\delta_{0j}\delta_{\ell k} - \delta_{\ell j}\delta_{0k})}{(\theta + \alpha_0)(\theta + \alpha_0 + \alpha_\ell)}$$

$$+ \lambda_0\sum_{\ell=1}^{\infty}\pi(\ell|0)\mathrm{m}_{12}^{(0\ell)}\{(1 - \delta_{0j})\delta_{\ell k}\frac{\lambda_0\mathrm{m}_2^{(0)}\pi(j|0)}{\alpha_{\mathrm{j}} - \alpha_0}$$

$$+ (1 - \delta_{0k})\delta_{\ell j}\frac{\lambda_0\mathrm{m}_2^{(0)}\pi(k|0)}{\alpha_{\mathrm{k}} - \alpha_0}\Bigg\}\frac{1}{(\theta + \alpha_0)(\theta + \alpha_0 + \alpha_\ell)}$$

$$- \lambda_0\sum_{\ell=1}^{\infty}\pi(\ell|0)\mathrm{m}_{12}^{(0\ell)}(1 - \delta_{0j})\delta_{\ell k}\frac{\lambda_0\mathrm{m}_2^{(0)}\pi(j|0)}{\alpha_{\mathrm{j}} - \alpha_0}\frac{1}{(\theta + \alpha_0)(\theta + \alpha_{\mathrm{j}} + \alpha_\ell)}$$

$$- \lambda_0\sum_{\ell=1}^{\infty}\pi(\ell|0)\mathrm{m}_{12}^{(0\ell)}(1 - \delta_{0k})\delta_{\ell j}\frac{\lambda_0\mathrm{m}_2^{(0)}\pi(k|0)}{\alpha_{\mathrm{k}} - \alpha_0}\frac{1}{(\theta + \alpha_0)(\theta + \alpha_{\mathrm{k}} + \alpha_\ell)}. \quad (4.2.1.17)$$

Inverting (4.2.1.17), we get explicitly the covariance structure of the viral population.

4.2.2 A Particular Case

For simplicity, we assume that there are two genetically different virons only, called type 0 and type 1. Precisely, on bonding to a T4 cell, a type 0 HIV produces type 0 virons and type 1 virons, while type 1 HIV produces type 1 virons only. Following the same notation as in 4.2.1, we obtain the mean population sizes of the two types of virons as given below:

$$M_0(t|1) = 0, \quad M_1(t|1) = e^{-\alpha_1 t};$$

$$M_0(t|0) = e^{-\alpha_0 t}, \quad M_1(t|0) = \frac{\lambda_0 m_2^{(01)}}{\alpha_1 - \alpha_0}\{e^{-\alpha_0 t} - e^{-\alpha_1 t}\}.$$

The co-variances of the population sizes of the virons are obtained in the following form:

$$M_{00}(t|1) = 0, \quad M_{01}(t|1) = 0,$$

$$M_{11}(t|1) = \frac{\lambda_1 m_{11}^{(11)}}{\alpha_1}\{e^{-\alpha_1 t} - e^{-2\alpha_1 t}\};$$

$$M_{00}(t|0) = \frac{\lambda_0 m_{11}^{(01)}}{\alpha_0}\{e^{-\alpha_0 t} - e^{-2\alpha_0 t}\};$$

$$M_{01}(t|0) = \lambda_0\left[\frac{\lambda_0 m_{11}^{(01)} m_2^{(01)}}{\alpha_0(\alpha_1 - \alpha_0)}(e^{-\alpha_0 t} - e^{-2\alpha_0 t})\right.$$

$$\left. + \left\{\frac{m_{12}^{(01)}}{\alpha_1} - \frac{\lambda_0 m_{11}^{(01)} m_2^{(01)}}{\alpha_1(\alpha_1 - \alpha_0)}\right\}(e^{-\alpha_0 t} - e^{-(\alpha_0 + \alpha_1)t})\right]$$

$$M_{11}(t|0) = \lambda_0\left[\lambda_1 m_2^{(01)} m_{11}^{(1)}\left\{\frac{e^{-\alpha_0 t} - e^{-\alpha_1 t}}{\alpha_1(\alpha_1 - \alpha_0)} - \frac{e^{-\alpha_0 t} - e^{-2\alpha_1 t}}{\alpha_1(2\alpha_1 - \alpha_0)}\right\}\right.$$

$$\left. + \frac{C_{12}}{(\alpha_1 - \alpha_0)^2}\lambda_0^2 (m_2^{(01)})^2\left\{\frac{e^{-\alpha_0 t} - e^{-2\alpha_0 t}}{\alpha_0} - 2\frac{e^{-\alpha_0 t} - e^{-(\alpha_0+\alpha_1)t}}{\alpha_1} + \frac{e^{-\alpha_0 t} - e^{-2\alpha_1 t}}{(2\alpha_1 - \alpha_0)}\right\}\right]$$

where $C_{12} = m_{11}^{(01)} + 2m_{12}^{(01)} + m_{22}^{(01)}$.

If $\alpha_0 = \alpha_1 = \alpha \neq 0$, then

$$M_0(t|0) = M_1(t|1) = e^{-\alpha t}, \; M_0(t|1) = 0, \; M_1(t|0) = \lambda_0 m_2^{(01)} t e^{-\alpha t};$$

$$M_{00}(t|1) = M_{01}(t|1) = 0,\ M_{11}(t|1) = \frac{\lambda_1 m_{11}^{(1)}}{\alpha}\{e^{-\alpha t} - e^{-2\alpha t}\},$$

$$M_{00}(t|0) = \frac{\lambda_0 m_{11}^{(01)}}{\alpha}\{e^{-\alpha t} - e^{-2\alpha t}\},$$

$$M_{11}(t|0) = \{m_{11}^{(01)} + 2m_{12}^{(01)} + m_{22}^{(01)}\}(m_2^{(01)})^2 \frac{(\lambda_0 t)^3}{3},$$

$$M_{01}(t|0) = \left\{\frac{\lambda_0}{\alpha}\right\}^2 m_{11}^{(01)} m_2^{(01)} e^{-\alpha t}\{1 - (1 + \alpha t)e^{-\alpha t}\} + \left\{\frac{\lambda_0}{\alpha}\right\} m_{12}^{(01)} e^{-\alpha t}(1 - e^{-\alpha t}).$$

4.3 MODEL II: THE MULTIPLICATION PROCESS INSIDE A T4 CELL

Before describing model II, we briefly outline the life-cycle of HIV and the events that occur between the time of an infection of HIV with a T4 cell and the lysis of the host cell (for a more detailed account, see Fauci (1988), Shaw et al. (1988), Haseltine (1990) and Greene (1991)).

4.3.1 The Life Cycle of HIV

The HIV is a retrovirus and its RNA carries the genetic information. The HIV has a dense cylindrical core encasing two molecules of the viral genome. Virus-encoded enzymes required for efficient multiplication, such as reverse transcriptase and integrase, are also incorporated into the virus particle. After attaching itself to the cell wall of the host T4 cell, the virus injects its RNA together with the enzymes reverse transcriptase and integrase into the cytoplasm of the host cell. The viral reverse transcriptase enzyme first synthesises a single complementary, negative-sense DNA copy to the HIV RNA; next the RNA is denatured; and then a complementary positive-sense DNA copy is synthesised to create double-stranded proviral DNA.

The proviral DNA may either reside in episomal form or enter the cell nucleus and become integrated into host DNA under the action of the viral integrase enzyme. Within the cell, the proviral DNA (also called provirus) can remain latent, giving no sign of its presence for several months or years. In this stage, every time the infected cell divides, the provirus is duplicated with the cell's DNA. On the other hand, once the cell activation occurs due to antigen or mitogen, the proviral DNA transcribes viral genomic RNA and messenger RNA (mRNA). The messenger RNA translates the regulatory proteins tat and rev. Tat protein promotes transcription of more messenger RNA. Rev protein causes multiple spliced segments of messenger RNA to form singly spliced segments that are translated into structural proteins, envelope proteins and viral enzymes. The assembly of proteins and enzymes, together with the viral genomic RNA are assembled to form mature HIV virus which buds on the cell wall. The ongoing process of budding of mature virons on the cell wall takes place until the infected cell is unable to withstand the burden of the viral production when the cell undergoes the lysis releasing the mature virons ready to attack other T4 cells.

Loveday et al. (1995) observed that the replication process has limited efficiency as incomplete, RNA-deficient and damaged virons may be released from the host cell and viral proteins may be produced in excess during the life-cycle and can be detected while the host cell undergoes lysis. The population of defective virons may inhibit the production of fully mature virons. Accordingly, we proceed to formulate a stochastic model of viral production in a host cell by taking into consideration the fact that along with fully mature HIV virons, damaged virons are also produced at the time of lysis.

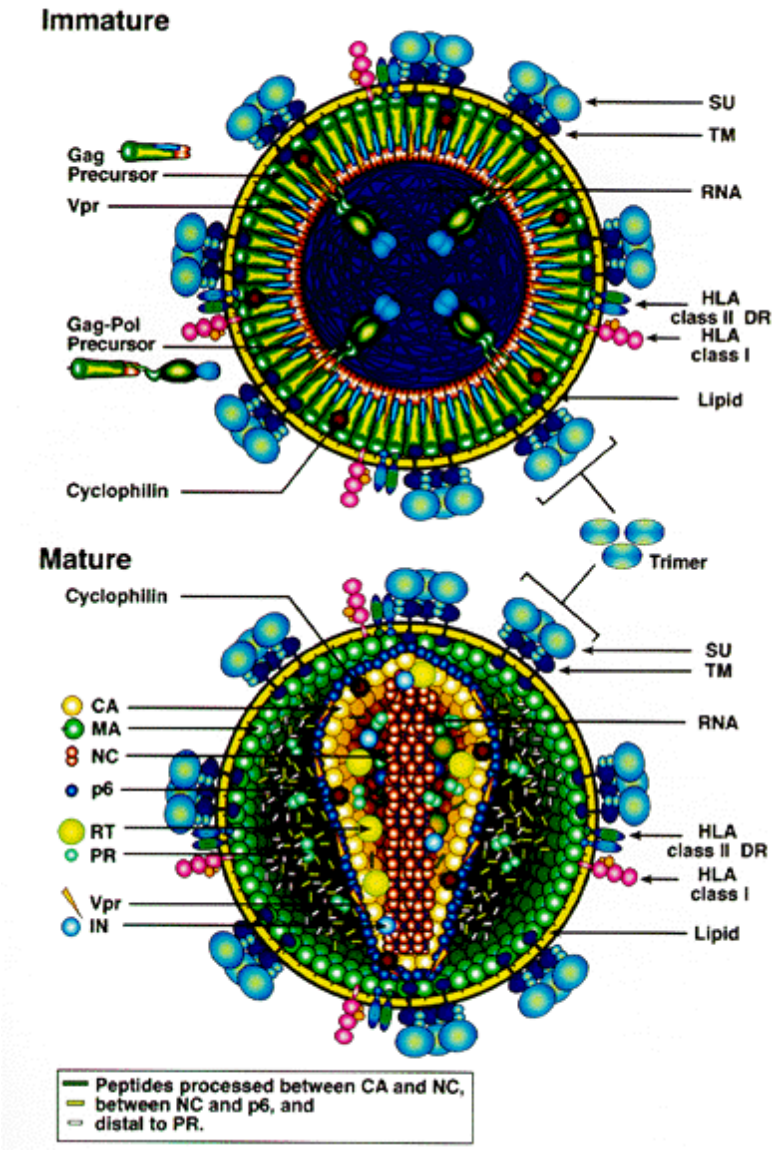

Figure 4.1 The immature and the mature HIV-1 viron
(Excerpt from http://msl.cs.uiuc.edu/~yershova/bcb495/bcbProjects-3.htm)

4.3.2 The Model Formulation

We assume that at time t = 0, a HIV attaches to the cell wall of a T4 cell and injects its RNA instantaneously into the cytoplasm of the host cell. Let T be the time at which the viral DNA gets integrated with the host DNA. Let the probability distribution function of T be given by

$$\Pr\{T \leq \tau\} = 1 - e^{-\alpha\tau},\ \alpha > 0,\ \tau > 0.$$

We assume that viral RNAs are replicated according to a Poisson process with rate λ, λ > 0. Let N(t) be the number of viral RNAs that are present inside the cell at time t. We assume that at any time t, the budding of HIV takes place with a rate proportional to N(t). Let X(t) be the number of HIV buds that are present on the cell wall at time t. Then the vector process (X(t), N(t)) is Markov and its structure is analysed in the following section. For brevity, we denote Z(t) = (X(t), N(t)).

4.3.3 The Probability Generating Function for (X(t), N(t))

The probability generating function of the vector process (X(t), N(t)) defined by $G(u, v; t) = E[u^{X(t)}u^{N(t)}]$. We proceed to obtain a differential equation for $G(u, v; t)$. First, we define the probability function

$$p(n, m; t) = \Pr\{Z(t) = (n, m)\}. \qquad (4.3.3.1)$$

Then, we see that

$$p(0, 0; t) = e^{-\alpha t} + \alpha e^{-\alpha t} \otimes e^{-\lambda t}$$

$$= \frac{\lambda e^{-\alpha t} - \alpha e^{-\lambda t}}{(\lambda - \alpha)}; \qquad (4.3.3.2)$$

$$p(0, 1; t) = \alpha e^{-\alpha t} \otimes \lambda e^{-\lambda t} \otimes e^{-(\lambda+\mu)t}$$

$$= \frac{\lambda\alpha}{\mu(\lambda - \alpha)(\lambda + \mu - \alpha)}\{\mu e^{-\alpha t} - (\lambda + \mu - \alpha)e^{-\lambda t} + (\lambda - \alpha)e^{-(\lambda+\mu)t}\}. \qquad (4.3.3.3)$$

The infinitesimal transition probabilities are given by

$$\Pr\{Z(t + \Delta) = (n, m+1) | Z(t) = (n, m)\} = \lambda\Delta, \; n \geq 0, \; m \geq 1;$$

$$\Pr\{Z(t + \Delta) = (n + 1, m-1) | Z(t) = (n, m)\} = \mu m\Delta, \; n \geq 0, \; m \geq 1;$$

Then, by using probabilistic laws, we obtain

$$\frac{\partial p(n, m; t)}{\partial t} = -(\lambda + m\mu)p(n, m; t) + \lambda p(n, m - 1; t) + \mu(m + 1)p(n - 1, m + 1; t), \; n \geq 1, \; m \geq 1, \tag{4.3.3.4}$$

$$\frac{\partial p(0, m; t)}{\partial t} = -(\lambda + m\mu)p(0, m; t) + \lambda p(0, m - 1; t), \; m \geq 2, \tag{4.3.3.5}$$

$$\frac{\partial p(n, 0; t)}{\partial t} = -\lambda p(n, 0; t) + \mu p(n - 1, 1; t), \; n \geq 1. \tag{4.3.3.6}$$

Equations (4.3.3.4) to (4.3.3.6) can be recursively solved starting with (4.3.3.2) and (4.3.3.3) to give the state probabilities $p(n, m; t)$, $n \geq 0$, $m \geq 0$. However, the expressions are quite unwieldy and hence, we proceed to obtain the differential equation satisfied by probability generating function $G(u, v; t)$.

We note that

$$G(u, v; t) = \sum_{n=0}^{\infty}\sum_{m=0}^{\infty} p(n, m; t)u^n v^m$$

and hence, by using the equations (4.3.3.2) to (4.3.3.6), we obtain the following partial differential equation:

$$\frac{\partial G}{\partial t} + \mu(v - u)\frac{\partial G}{\partial v} = \lambda(v - 1)(G - e^{-\alpha t}), \tag{4.3.3.7}$$

with the initial condition $G(u, v; 0) = 1$. When $\alpha \to \infty$, equation (4.3.3.7) becomes

$$\frac{\partial G}{\partial t} + \mu(v - u)\frac{\partial G}{\partial v} = \lambda(v - 1)G. \tag{4.3.3.8}$$

Equation (4.3.3.8) is readily solved to yield

$$G(u, v; t) = e^{\frac{\lambda}{\mu}\{(v - u)(1 - e^{-\mu t}) + (\mu - 1)\mu t\}}$$

from which all the moments of X(t) and N(t) can be easily obtained. However, for the nontrivial case $\alpha < \infty$, equation (4.3.3.7) appears to be intractable and as such, we content ourselves in obtaining the moments of X(t) and N(t) in the next section.

4.3.4 The Moment of (X(t), N(t))

Differentiating (4.3.3.7) with respect to u at u = 1, v = 1, we get the differential equation

$$\frac{\partial E[X(t)]}{\partial t} - \mu E[N(t)] = 0. \qquad (4.3.4.1)$$

Differentiating (4.3.3.7) with respect to v at u = 1, v = 1, we get the differential equation

$$\frac{\partial E[N(t)]}{\partial t} + \mu E[N(t)] = \lambda(1 - e^{-\alpha t}). \qquad (4.3.4.2)$$

Differentiating (4.3.3.7) twice with respect to u at u = 1, v = 1, we get

$$\frac{\partial E[X(t)\{X(t) - 1\}]}{\partial t} = 2\mu E[X(t)N(t)]. \qquad (4.3.4.3)$$

Differentiating (4.3.3.7) twice with respect to v at u = 1, v = 1, we get

$$\frac{\partial E[N(t)\{N(t) - 1\}]}{\partial t} + 2\mu E[N(t)\{N(t) - 1\}] = \lambda E[N(t)]. \qquad (4.3.4.4)$$

Differentiating (4.3.3.7) with respect to u and v at u = 1, v = 1, we get

$$\frac{\partial E[X(t)N(t)]}{\partial t} + \mu E[X(t)N(t)] = \mu E[N(t)\{N(t) - 1\}] + \lambda E[X(t)]. \qquad (4.3.4.5)$$

Using Laplace transform method, the system of equations (4.3.4.1) to (4.3.4.5) yields the Laplace transforms:

$$L\{E[N(t)]\} = \frac{\lambda\alpha}{\theta(\theta + \alpha)(\theta + \mu)}; \qquad (4.3.4.6)$$

$$L\{E[X(t)]\} = \frac{\lambda\mu\alpha}{\theta^2(\theta + \alpha)(\theta + \mu)}; \qquad (4.3.4.7)$$

$$L\{E[X(t)N(t)]\} = \frac{2\lambda^2\mu\alpha}{\theta^2(\theta + \alpha)(\theta + \mu)(\theta + 2\mu)}; \qquad (4.3.4.8)$$

$$L\{E[N(t)\{N(t)\ -1\}]\} = \frac{\lambda^2\alpha}{\theta(\theta + \alpha)(\theta + \mu)(\theta + 2\mu)}; \qquad (4.3.4.9)$$

$$L\{E[X(t)\{X(t)\ -1\}]\} = \frac{4\lambda^2\mu^2\alpha}{\theta^3(\theta + \alpha)(\theta + \mu)(\theta + 2\mu)}. \qquad (4.3.4.10)$$

Inverting equations (4.3.4.6) to (4.3.4.10), we get

$$E[N(t)] = \frac{\lambda}{\mu}\left\{1 - \frac{\mu e^{-\alpha t} - \alpha e^{-\mu t}}{\mu - \alpha}\right\}; \qquad (4.3.4.11)$$

$$E[X(t)] = \lambda t - \frac{\lambda}{\mu - \alpha}\left\{\frac{\mu}{\alpha}(1 - e^{-\alpha t}) - \frac{\alpha}{\mu}(1 - e^{-\mu t})\right\}; \qquad (4.3.4.12)$$

$$E[X(t)N(t)] = \frac{\lambda^2}{\mu}t - \frac{2\lambda^2\mu}{\alpha(\mu - \alpha)(2\mu - \alpha)}(1 - e^{-\alpha t})$$

$$+ \frac{2\lambda^2\alpha}{\mu^2(\mu - \alpha)}(1 - e^{-\mu t}) - \frac{\lambda^2\alpha}{2\mu^2(2\mu - \alpha)}(1 - e^{-2\mu t}); \qquad (4.3.4.13)$$

$$E[N(t)\{N(t) - 1\}] = \frac{\lambda^2}{2\mu^2}\left\{1 - \frac{2\mu^2}{(\mu - \alpha)(2\mu - \alpha)}e^{-\alpha t} + \frac{2\alpha}{\mu - \alpha}e^{-\mu t} - \frac{\alpha}{2\mu - \alpha}e^{2\mu t}\right\}$$

(4.3.4.14)

$$E[X(t)\{X(t) - 1\}] = \lambda^2t^2 - \frac{4\lambda^2\mu^2}{\alpha(\mu - \alpha)(2\mu - \alpha)}t + \frac{4\lambda^2\alpha}{\mu(\mu - \alpha)}t - \frac{\lambda^2\alpha}{\mu(2\mu - \alpha)}t$$

$$+ \frac{4\lambda^2\mu^2}{\alpha^2(\mu - \alpha)(2\mu - \alpha)}(1 - e^{-\alpha t}) - \frac{4\lambda^2\alpha}{\mu^2(\mu - \alpha)}(1 - e^{-\mu t}) + \frac{\lambda^2\alpha}{2\mu(2\mu - \alpha)}(1 - e^{-2\mu t})$$

(4.3.4.15)

Using the expressions (4.3.4.11) to (4.3.4.15), we can obtain explicitly the correlation coefficient ρ between X(t) and N(t). However, we present in the following section a numerical illustration to highlight the impact of the parameters α, λ and μ on ρ.

4.3.5 A Numerical Illustration

For the purpose of illustration we assume $\alpha = 100.0$, $\lambda = 200.0$, $\mu = 300.0$ and obtain the first two moments of X(t) and N(t), the ratio between their means and the correlation coefficient (ρ) between them. The results are highlighted in Tables 4.1 to 4.3.

Since $\alpha = 100$, the mean time for the viral RNA to get integrated and start releasing the HIV buds is 0.01. Hence for increasing values of $t > 0.01$ both E[X(t)] and E[N(t)] can be expected to increase. Table 4.1 shows this trend. We also observe that the released viral RNAs rapidly become buds since the ratio E[X(t)]/E[N(t)] is increasing (Table 4.1). As the viral RNAs become buds, the number of buds will increase and the number of viral RNAs will increase which is indicated as negative correlation between X(t) and N(t) in Table 4.1.

As μ increases E[X(t)] increases but E[N(t)] decreases and hence the ratio between E[X(t)] and E[N(t)] increases (Table 4.2) and the correlation between X(t) and N(t) remains negative (Table 4.2). As the rate of releasing viral RNAs increases, both the mean number of buds and the viral RNAs should increase. However, since the rate of buds is a constant, we find that the ratio remains a constant even though the value of λ increases (Table 4.3). In this case also the correlation between X(t) and N(t) remains negative (Table 4.3).

4.4 CONCLUSION

In this chapter, the mean of X(t) i.e. the number of HIV buds that are present on the cell wall at time t and N(t) i.e. the number of viral RNAs that are present inside the cell at time t have been obtained. Contribution of the stochastic models to statistical work is the ability to obtain the covariance structure of which is very difficult to obtain.

Table 4.1 E[X(t)], **E**(N(t)], **E**[X(t)]/ **E**(N(t)], ρ **versus** t

for α = 100.0, λ = 200.0, μ = 300.0

t	**E**[X(t)]	**E**(N(t)]	**E**[X(t)]/ **E**(N(t)]	ρ
0.0500	7.3535	0.6599	11.1429	-0.5067
0.0600	9.3408	0.6642	14.0634	-0.5406
0.0700	11.3361	0.6658	17.0274	-0.5366
0.0800	13.3343	0.6663	20.0116	-0.5184
0.0900	15.3337	0.6665	23.0048	-0.4963
0.1000	17.3335	0.6666	26.0020	-0.4746
0.1100	19.3334	0.6666	29.0008	-0.4545
0.1200	21.3334	0.6667	32.0003	-0.4364
0.1300	23.3333	0.6667	35.0001	-0.4202
0.1400	25.3333	0.6667	38.0000	-0.4055
0.1500	27.3333	0.6667	41.0000	-0.3923

Table 4.2 E[X(t)], **E**(N(t)], **E**[X(t)]/ **E**(N(t)], ρ **versus** μ

for α = 100.0, λ = 200.0, t = 0.05

μ	**E**[X(t)]	**E**(N(t)]	**E**[X(t)]/ **E**(N(t)]	ρ
300.00	7.3535	0.6599	11.1429	-0.5067
310.00	7.3747	0.6387	11.5457	-0.4631
320.00	7.3946	0.6189	11.9485	-0.4241
330.00	7.4133	0.6002	12.3513	-0.3890
340.00	7.4309	0.5826	12.7542	-0.3575
350.00	7.4474	0.5660	13.1571	-0.3291
360.00	7.4631	0.5504	13.5601	-0.3034
370.00	7.4779	0.5355	13.9631	-0.2802
380.00	7.4920	0.5215	14.3661	-0.2592
390.00	7.5053	0.5082	14.7692	-0.2400
400.00	7.5180	0.4955	15.1722	-0.2260
410.00	7.5300	0.4835	15.5753	-0.2067
420.00	7.5415	0.4720	15.9784	-0.1922
430.00	7.5524	0.4610	16.3816	-0.1790
440.00	7.5629	0.4506	16.7847	-0.1668
450.00	7.5729	0.4406	17.1879	-0.1557
460.00	7.5824	0.4310	17.5911	-0.1454
470.00	7.5916	0.4219	17.9942	-0.1360
480.00	7.6004	0.4131	18.3974	-0.1273
490.00	7.6088	0.4047	18.8006	-0.1193
500.00	7.6168	0.3966	19.2039	-0.1119

Table 4.3 E[X(t)], **E**(N(t)], **E**[X(t)]/ **E**(N(t)], ρ **versus** λ

for α = 100.0, μ = 300.0, t = 0.05

λ	**E**[X(t)]	**E**(N(t)]	**E**[X(t)]/ **E**(N(t)]	ρ
200.00	7.3535	0.6599	11.1429	-0.5067
210.00	7.7212	0.6929	11.1429	-0.5027
220.00	8.0889	0.7259	11.1429	-0.4995
230.00	8.4566	0.7589	11.1429	-0.4967
240.00	8.8243	0.7919	11.1429	-0.4944
250.00	9.1919	0.8249	11.1429	-0.4924
260.00	9.5596	0.8579	11.1429	-0.4907
270.00	9.9273	0.8909	11.1429	-0.4892
280.00	10.2950	0.9239	11.1429	-0.4879
290.00	10.6626	0.9569	11.1429	-0.4868
300.00	11.0303	0.9899	11.1429	-0.4858
310.00	11.3980	1.0229	11.1429	-0.4849
320.00	11.7657	1.0559	11.1429	-0.4841
330.00	12.1334	1.0889	11.1429	-0.4834
340.00	12.5010	1.1219	11.1429	-0.4828
350.00	12.8687	1.1549	11.1429	-0.4823
360.00	13.2364	1.1879	11.1429	-0.4818
370.00	13.6041	1.2209	11.1429	-0.4813
380.00	13.9717	1.2539	11.1429	-0.4810
390.00	14.3394	1.2869	11.1429	-0.4806
400.00	14.7071	1.3299	11.1429	-0.4803

CHAPTER FIVE

THE T4 CELL COUNT AS A MARKER OF HIV PROGRESSION IN THE ABSENCE OF ANY DEFENSE MECHANISM

5.1 INTRODUCTION

T4 cells which originate in the bone marrow and mature in the thymus gland play a dominant role in the immune system of the human body. Infact, these cells amplify immune responses through the release of various cytokine mediators. It has been observed in HIV infected individuals that as a consequence of HIV infection, selective depletion of T4 cells occurs. When the T4 cell count in such an individual drops, these cells are unable to mount an effective immune response and consequently, the individual becomes susceptible to opportunistic infections and lymphomas. Accordingly, the T4 cell count can be considered a marker of disease progression in an infected individual and the loss of T4 cells accounts for a major part of the immunosuppressive effect of HIV (Stein et al. 1992, Phillips et al. 1992, Feinberg 1996 and Sabin et al.1998).

In the recent past, several researchers have developed various stochastic and deterministic models to describe the temporal progression of the T4 cell count in a HIV infected individual and its relationship to the survival time of the individual (Longini et al. 1991, Perelson et al.1993, De Gruttola and Tu 1994, Philips et al. 1994, Cozzi-Lepri et al. 1997 and Wick 1999). Longini et al. (1991) modelled the decline of T4 cells in HIV infected individuals with a continuous-time Markov process in which the state space consists of seven states. These states are the end points of six progression T4 cell count intervals and the beginning of the first interval corresponds to the time of HIV infection and the end of the last interval synchronizes with the time of AIDS diagnosis. Perelson et al. (1993) developed a model for the interaction of HIV with T4 cells by considering four populations namely, uninfected T4 cells, latently infected T4 cells, actively infected T4 cells, and free HIV; and using the model, they examined several features of HIV infection and in particular the process of T4 cell depletion.

De Gruttola and Tu (1994) proposed a model to study the progression of the T4 cell count and the relationship between different features of this progression and survival time. In their model, they observed the T4 cell count only at certain fixed time points and using random effects estimated the T4 trajectory.

Philips et al. (1994) developed an extrapolation model based upon T4 cell counts measured at discrete points, and using the model estimated the probability of remaining free of AIDS for up to 25 years after infection with HIV. Cozzi Lepri et al. (1997) used multilevel modelling techniques to asses the rate of T4 cell decline in HIV infected individuals and predicted that the rate of T4 cell decline is actually slower at the later stage of the disease.

In the work of Wick (1999), the T4 cell loss in a HIV infected individual has been analysed by proposing a model in which the rates of proliferation and programmed cell death (apoptosis) control the rise and fall of the T4 cell count. In all these works, the stochastic mechanism of HIV production has not been given its due importance in understanding the decline of the T4 cell count and the status of HIV progression in infected individuals. Further, no work appears to be available in literature incorporating the correlation structure between uninfected and infected T4 cell populations.

Also, in HIV related models, there appears to be no work which quantifies the amount of toxins produced during the progression of HIV in infected individuals and its correlation with the loss of T4 cells. In this chapter, an attempt is made to fill the gap by building a more realistic stochastic model of HIV production/progression leading to the decline of the T4 cell count in an infected individual.

The organization of this chapter is as follows: In Section 5.2, we develop a catastrophe model of HIV production. The probability generating function for X(t), the number of uninfected cells, Y(t), the number of infected cells at any time t and Z(t), the number of lysed cells up to time t is obtained in Section 5.3. The means and variances of X(t), Y(t), and Z(t) are explicitly found in Section 5.4. We also obtain explicit expressions for the co-variances between X(t) and Y(t), Y(t) and Z(t), and Z(t) and X(t) in section 5.4. The total amount of toxins produced up to time t since the time of HIV infection is quantified and analysed in Section 5.5. In Section 5.6, a numerical illustration is provided to drive home a satisfactory picture of what happens during the progression of HIV in an infected individual up to the onset of AIDS.

5.2 THE CATASTROPHE MODEL

At time t = 0, one HIV infects a cell population of size N of uninfected T4 cells. The infected cell either splits into two infected cells or undergoes a lysis releasing a random number K of HIV's which instantaneously infect an equal number of uninfected T4 cells; and the process continues. Further, there is an independent Poisson arrival of uninfected T4 cells with rate α into the population of T4 cells. The process of splitting of an infected cell into two infected cells can be viewed as a birth of an infected cell with the parent survival; and the event of a lysis of an infected cell can be considered as the death of an infected cell. The death of an infected cell is a disaster to the population of uninfected cells. This observation enables us to make the assumption that the population of infected cells undergoes a linear birth and death process, with λ and μ as the birth and death rates respectively; and the population of uninfected cells is subject to disasters occurring at the event of the death of an infected cell. Let X(t) and Y(t) denote respectively the number of uninfected and infected cells at time t.

Then, by the initial condition, we have X(0) = N – 1 and Y(0) = 1, where N is sufficiently large and fixed. Let Z(t) represents the number of cells that have undergone lysis up to time t. Then, it is easy to note that

$$X(t) + Y(t) + Z(t) \geq N.$$

We assume that K has a discrete distribution defined by

$$\Pr(K = r) = \pi_r, \quad r = 0, 1, 2, \ldots$$

The vector process (X(t), Y(t), Z(t)) is clearly Markov and we proceed to obtain its probability generating function in the next section.

5.3 THE PROBABILITY GENERATING FUNCTION

We define the probability generating function of (X(t), Y(t), Z(t)).

$$G(u, v, w; t) = E[u^{X(t)}v^{Y(t)}w^{Z(t)}].$$

Then it is easy to note that $G(u, v, w; 0) = u^{N-1}v$. To derive an expression for $G(u, v, w; t)$, we first define the probability function

$$p(i, j, k; t) = \Pr\{X(t) = i, Y(t) = j, Z(t) = k\}$$

Then, using probabilistic laws, we obtain

$$\frac{\partial p(i, j, k: t)}{\partial t} = -\{j(\lambda + \mu) + \alpha\}p(i, j, k; t) + \alpha p(i - 1, j, k; t)$$

$$+ (j - 1)\lambda p(i, j - 1, k; t) + \sum_{r=0}^{j+1}(j + 1 - r)\mu p(i + r, j + 1 - r, k - 1; t)\pi_r \qquad (5.3.1)$$

From (5.3.1), following the lines of Bailey (1975), it can be shown that the probability generating function $G(u, v, w; t)$ satisfies the partial differential equation

$$\frac{\partial G}{\partial t} = -(\lambda + \mu)v\frac{\partial G}{\partial v} - \alpha(1 - u)G + \lambda v^2\frac{\partial G}{\partial v} + \mu w\sum_{r=0}^{\infty}\pi_r u^{-r}v^r\frac{\partial G}{\partial v}, \qquad (5.3.2)$$

with the initial condition $G(u, v, w; 0) = u^{N-1}v$.

On simplification, the equation (5.3.2) becomes

$$\frac{\partial G}{\partial t} = -\alpha(1 - u)G + \{-(\lambda + \mu)v + \lambda v^2 + \mu w h(\frac{v}{u})\}\frac{\partial G}{\partial v}, \tag{5.3.3}$$

with the initial condition $G(u, v, w; 0) = u^{N-1}v$.

The equation (5.3.3) is not easily solvable even for any simple form of the generating function h(.). However, we can obtain from the equation (5.3.3) the various moments of X(t), Y(t) and Z(t). Accordingly, in the next section, we study the moment structure of the process (X(t), Y(t), Z(t)). We also study the covariance structure of X(t), Y(t) and Z(t).

5.4 THE MOMENT STRUCTURE (X(t), Y(t), Z(t))

We have the following notations:

$M_X(t) = E[X(t)]$, $M_Y(t) = E[Y(t)]$, $M_Z(t) = E[Z(t)]$,
$M_X^{(2)}(t) = E[X(t)\{X(t) - 1\}]$, $M_Y^{(2)}(t) = E[Y(t)\{Y(t) - 1\}]$, $M_Z^{(2)}(t) = E[Z(t)\{Z(t) - 1\}]$,
$M_{XY}(t) = E[X(t)Y(t)]$, $M_{YZ}(t) = E[Y(t)Z(t)]$, $M_{ZX}(t) = E[Z(t)X(t)]$.

Then, from the equation (5.3.3), we obtain the following system of equations:

$$\frac{\partial M_X(t)}{\partial t} = \alpha - \mu h'(1) M_Y(t) \tag{5.4.1}$$

$$\frac{\partial M_Y(t)}{\partial t} = a M_Y(t) \tag{5.4.2}$$

$$\frac{\partial M_z(t)}{\partial t} = \mu M_Y(t) \tag{5.4.3}$$

$$\frac{\partial M_X^{(2)}(t)}{\partial t} = -2\mu h'(1) M_{XY}(t) + 2\alpha M_X(t) + d M_Y(t) \tag{5.4.4}$$

$$\frac{\partial M_Y^{(2)}(t)}{\partial t} = 2a M_Y^{(2)}(t) + c M_Y(t) \tag{5.4.5}$$

$$\frac{\partial M_Z^{(2)}(t)}{\partial t} = 2\mu M_{YZ}(t) \tag{5.4.6}$$

$$\frac{\partial M_{XY}(t)}{\partial t} = aM_{XY}(t) + bM_Y(t) - \mu h'(1) M_Y^{(2)}(t) \tag{5.4.7}$$

$$\frac{\partial M_{YZ}(t)}{\partial t} = aM_{YZ}(t) + \mu M_Y^{(2)}(t) + \mu h'(1) M_Y(t) \tag{5.4.8}$$

$$\frac{\partial M_{ZX}(t)}{\partial t} = \alpha M_Z(t) + \mu M_{XY}(t) - \mu h'(1) M_Y(t) - \mu h'(1) M_{YZ}(t) \tag{5.4.9}$$

where

$a = \lambda - \mu + \mu h'(1)$, $b = \alpha - \mu h'(1) - \mu h''(1)$, $c = 2\lambda + \mu h''(1)$, $d = 2\mu h'(1) + \mu h''(1)$.

Noting the fact that

$$M_X(0) = N - 1,\ M_Y(0) = 1,\ M_Z(0) = 0,$$
$$M_X^{(2)}(0) = (N - 1)(N - 2),\ M_Y^{(2)}(0) = 0,\ M_Z^{(2)}(0) = 0,$$
$$M_{XY}(0) = N - 1,\ M_{YZ}(0) = 0,\ M_{ZX}(0) = 0$$

And using Laplace transformation, the equations (5.4.1) to (5.4.9) yield

$$M_X^*(s) = \frac{N - 1}{s} + \frac{\alpha}{s^2} - \frac{\mu h'(1)}{s(s - a)} \tag{5.4.10}$$

$$M_Y^*(s) = \frac{1}{s - a} \tag{5.4.11}$$

$$M_Z^*(s) = \frac{\mu}{s(s - a)} \tag{5.4.12}$$

$$M_X^{(2)*}(s) = \frac{(N - 1)(N - 2)}{s} + \frac{d}{s(s - a)} - 2\mu h'(1)\left\{\frac{N - 1}{s(s - a)} + \frac{b(s - 2a) - \mu h'(1)c}{s(s - a)^2(s - 2a)}\right\}$$
$$+ 2\alpha\left\{\frac{N - 1}{s^2} + \frac{\alpha}{s^3} - \frac{\mu h'(1)}{s^2(s - a)}\right\} \tag{5.4.13}$$

$$M_Y^{(2)*}(s) = \frac{c}{(s - a)(s - 2a)} \tag{5.4.14}$$

$$M_Z^{(2)}(s) = 2\mu^2\left\{\frac{c + h'(1)(s - 2a)}{s(s - a)^2(s - 2a)}\right\} \tag{5.4.15}$$

$$M^{*}_{XY}(s) = \frac{N - 1}{s - a} + \frac{b(s - 2a) - \mu h'(1)c}{(s - a)^2(s - 2a)} \tag{5.4.16}$$

$$M^{*}_{YZ}(s) = \mu\left\{\frac{c + h'(1)(s - 2a)}{(s - a)^2(s - 2a)}\right\} \tag{5.4.17}$$

$$M^{*}_{ZX}(s) = \mu\left\{\frac{N - 1}{s(s - a)}\frac{h'(1)}{s(s - a)} + \frac{(b - \mu\{h'(1)\}^2)(s - 2a) - 2\mu h'(1)c}{s(s - a)^2(s - 2a)} + \frac{\alpha}{s^2(s - a)}\right\} \tag{5.4.18}$$

Inverting the equations (5.4.10) and (5.4.11), we obtain

$$M_X(t) = N - 1 + \alpha t - \frac{\mu h'(t)}{a}(e^{at} - 1) \tag{5.4.19}$$

$$M_Y(t) = e^{at} \tag{5.4.20}$$

$$M_Z(t) = \frac{\mu}{a}(e^{at} - 1) \tag{5.4.21}$$

$$M^{(2)}_X(t) = (N - 1)(N - 2)\frac{d}{a}(e^{at} - 1) + \frac{\alpha}{a^2}\{2(N - 1)a^2t + \alpha(at)^2 - 2\mu h'(1)(e^{at} - at - 1)\}$$

$$- 2\mu h'(1)\left\{\frac{N - 1}{a}(e^{at} - 1) - \frac{\mu h'(1)c}{2a^2(e^{2at} - 2ate^{at} - 1)} - \frac{b}{a^2}(e^{at} - ate^{at} - 1)\right\} \tag{5.4.22}$$

$$M^{(2)}_Y(t) = \frac{c}{a}(e^{2at} - e^{at}) \tag{5.4.23}$$

$$M^{(2)}_Z(t) = \frac{\mu^2}{a^2}\left\{\frac{c}{a}(e^{2at} - 2ate^{at} - 1) - 2h'(1)(e^{at} - ate^{at} - 1)\right\} \tag{5.4.24}$$

$$M_{XY}(t) = (N - 1 + bt)e^{at} - \frac{\mu h'(1)c}{a^2}(e^{2at} - ate^{at} - e^{at}) \tag{5.4.25}$$

$$M_{YZ}(t) = \mu\left\{\frac{c}{a^2}(e^{2at} - ate^{at} - e^{at}) + h'(1)te^{at}\right\} \tag{5.4.26}$$

$$M_{ZX}(t) = \frac{\mu}{a}\left\{(N - 1 - h'(1))(e^{at} - 1) - \frac{(b - \mu)\{h'(1)\}^2)}{a}(e^{at} - ate^{at} - 1)\right.$$

$$+ \frac{\alpha}{a}(e^{at} - at - 1) - \frac{\mu h'(1)c}{a^2}(e^{2at} - 2ate^{at} - 1)\Big\} \qquad (5.4.27)$$

5.5 THE AMOUNT OF TOXIN PRODUCED

Whenever an infected cell appears, a quantity of toxic substance is produced in the blood. The estimation of the total amount of toxins produced by the infected cells since the beginning of the HIV infection up to any time is useful in knowing the level of HIV infection. In this section, we quantify the total amount of the toxins and obtain its mean and variance. Since the amount of toxins produced at time t is proportional to the number of infected cells present at time t, it is evident that the total amount of toxins produced up to time t since the beginning of the HIV infection is given by the stochastic integral

$$W(t) = \int_0^t Y(u)du \qquad (5.5.1)$$

The stochastic integral in (5.5.1) exists almost surely and has been studied very extensively in several biological applications by several researchers (Puri 1966, Jagers 1967, Pakes 1975 and Udayabaskaran and Sudalaiyandi 1986).

We proceed to obtain the joint moment generating function of Y(t) and W(t) defined by

$$H(u, v; t) = E[u^{Y(t)}e^{-vW(t)}|Y(0) = 1] \qquad (5.5.2)$$

Fixing the occurrence of the first event since time t = 0 and using probabilistic arguments, we obtain the following integral equation:

$$H(u, v; t) = ue^{-(\lambda+\mu+\varepsilon)t} + \lambda\int_0^t e^{-(\lambda+\mu+\varepsilon)\tau}\{H(u, v; t - \tau)\}^2 d\tau$$

$$+ \mu\int_0^t e^{-(\lambda+\mu+\varepsilon)\tau}h(H(u, v; t - \tau))d\tau \qquad (5.5.3)$$

where $h(s) = \sum_{0}^{\infty} P_r^{s^r}$ is the generating function of the number of HIV's produced at the time of a lysis. From the equation (5.5.3), we can obtain the mean and variance of W(t) and the correlation structure of W(t) with Y(t).

Differentiating (5.5.3) with respect to v at (u = 1, v = 0), we get

$$M_W(t) = te^{-(\lambda+\mu)t} + \lambda\int_0^t e^{-(\lambda+\mu)\tau}[2M_W(t-\tau) + \tau]d\tau$$

$$+ \mu\int_0^t e^{-(\lambda+\mu)\tau}[h'(1)M_W(t-\tau) + \tau]d\tau \qquad (5.5.4)$$

Differentiating (5.5.3) twice with respect to v at (u = 1, v = 0), we get

$$M_{WW}(t) = t^2e^{-(\lambda+\mu)t} + (\lambda+\mu)\int_0^t e^{-(\lambda+\mu)\tau}\tau^2 d\tau$$

$$+ [2\lambda + \mu h'(1)]\int_0^t e^{-(\lambda+\mu)\tau}M_{WW}(t-\tau)d\tau$$

$$+ [2\lambda + \mu h''(1)]\int_0^t e^{-(\lambda+\mu)\tau}\{M_W(t-\tau)\}^2 d\tau$$

$$+ 2[2\lambda + \mu h'(1)]\int_0^t e^{-(\lambda+\mu)\tau}\tau M_W(t-\tau)d\tau \qquad (5.5.5)$$

Differentiating (5.5.3) with respect to u and v at (u = 1, v = 0), we get

$$M_{YW}(t) = te^{-(\lambda+\mu)t} + [2\lambda + \mu h'(1)]\int_0^t e^{-(\lambda+\mu)\tau}M_{YW}(t-\tau)d\tau$$

$$+ [2\lambda + \mu h''(1)]\int_0^t e^{-(\lambda+\mu)\tau}M_Y(t-\tau)M_W(t-\tau)d\tau$$

$$+ [2\lambda + \mu h'(1)]\int_0^t e^{-(\lambda+\mu)\tau}\tau M_Y(t-\tau)d\tau \qquad (5.5.6)$$

On applying Laplace transform to equations (5.5.4), (5.5.5) and (5.5.6) we get

$$M_W^*(s) = \frac{1}{s(s-a)} \qquad (5.5.7)$$

$$M_{WW}^*(s) = \frac{2}{s(s-a)(s+\lambda+\mu)} + \frac{2\lambda+\mu h''(1)}{a^2}\left\{\frac{1}{s-2a} - \frac{2a}{(s-a)^2} - \frac{1}{s}\right\}$$

$$+ \frac{2[2\lambda + \mu h'(1)]}{a^2}\left\{\frac{a}{(s - a)^2} - \frac{1}{s - a} + \frac{1}{s}\right\} \qquad (5.5.8)$$

$$M^*_{YW}(s) = \frac{1}{(s - a)^2} + \frac{2\lambda + \mu h''(1)}{a^2}\frac{1}{(s - 2a)} - \frac{a}{(s - a)^2} + \frac{1}{s - a} \qquad (5.5.9)$$

On inversion, the equations (5.5.7), (5.5.8) and (5.5.9) yield

$$M_W(t) = \frac{1}{a}(e^{at} - 1) \qquad (5.5.10)$$

$$M_{WW}(t) = 2\left\{\frac{1}{a(\lambda + \mu + a)}e^{at} + \frac{1}{(\lambda + \mu)(\lambda + \mu + a)}e^{-(\lambda+\mu)t} - \frac{1}{a(\lambda + \mu)}\right\}$$

$$+ \frac{2\lambda + \mu h''(1)}{a^3}\{e^{2at} - 2ate^{at} - 1\} - \frac{2[2\lambda + \mu h'(1)]}{a^2}(e^{at} - ate^{at} - 1) \qquad (5.5.11)$$

$$M_{YW}(t) = te^{at} + \frac{2\lambda + \mu h''(1)}{a^2}(e^{2at} - ate^{at} - e^{at}) \qquad (5.5.12)$$

5.6 NUMERICAL ILLUSTRATION

The behaviour of the means of X(t), Y(t) and Z(t) and the correlation coefficient (ρ) between X(t) and Y(t) (R_{XY}) and that between Y(t) and Z(t) (R_{YZ}) with respect to time is studied. For this, we assume α = 100.0, λ = 0.20, μ = 0.10, and vary t from 0.5 to 0.8 in steps of 0.5. The results are highlighted in Tables 5.1 to 5.4.

The number of uninfected T4 cells present at any instant of time decreases (Table 5.1) and that of the infected cells (Table 5.2) increases with time as can be expected. This implies that the mean of the cumulative quantity of toxin produced should also increase with time and Table 5.1 confirms this result. Also we observe that the correlation between X(t) and Y(t) remains negative (Table 5.2) whereas correlation between Y(t) and Z(t) is positive throughout the period under consideration (Table 5.2).

As the rate of arrival of uninfected T4 cells increases (α = 100), the mean number of uninfected T4 cells present at the time of instant 0.5 increases. However, the means of the number of infected cells and that of the cumulative quantity of toxin produced remain the same irrespective of the values of α (Table 5.3). Also, there is a negative correlation between X(t) and Y(t) (Table 5.4). Correlation between Y(t) and Z(t) exists but nothing can be said about the nature of its variation (Table 5.4) with respect to α.

5.6 CONCLUSION

In this chapter, we have obtained the mean number of uninfected, infected and lysed T cells in a HIV infected individual. Unlike other models proposed by some mathematical scientist (see Longini et al. 1991, Perelson et al.1993, De Gruttola and Tu 1994, Philips et al. 1994, Cozzi-Lepri et al. 1997 and Wick 1999), our model not only gave moment structure of our variables, but also the co-variance relationship between them. Hence we have been able to build on previous models establish in the line of the T4 cell count as marker of the disease progression. Also we were able to model the quantity of toxin produced at time t in a HIV infected individual.

Table 5.1 E[X(t)], E[Y(t)], E[Z(t)] versus t

for α = 100.0, λ = 0.20, μ = 0.10

t	E[X(t)]	E[Y(t)]	E[Z(t)]
0.50	10.0483	0.0017	0.0007
1.00	10.0972	0.0030	0.0018
1.50	10.1452	0.0052	0.0038
2.00	10.1917	0.0090	0.0073
2.50	10.2357	0.0156	0.0133
3.00	10.2753	0.0156	0.0133
3.50	10.2753	0.0271	0.0237
4.00	10.3259	0.0815	0.0731
4.50	10.3216	0.1412	0.1274
5.00	10.2775	0.2447	0.2215
5.50	10.1644	0.4241	0.3846
6.00	9.9316	1.2741	1.1574
6.50	9.4916	0.7351	0.6674
7.00	8.6923	2.2083	2.0067
7.50	7.2702	3.8276	3.4788
8.00	4.7688	6.6342	6.0302

Table 5.2 R_{XY} , R_{YZ} versus t

for α = 100.0, λ = 0.20, μ = 0.10

t	R_{XY}	R_{YZ}
0.50	-0.8770	0.8406
1.00	-0.9226	0.9130
1.50	-0.9616	0.9446
2.00	-0.9829	0.9641
2.50	-0.9934	0.9769
3.00	-0.9970	0.9854
3.50	-0.9989	0.9909
4.00	-0.9995	0.9944
4.50	-0.9998	0.9966
5.00	-0.9999	0.9980
5.50	-1.0000	0.9988
6.00	-1.0000	0.9993
6.50	-1.0000	0.9996
7.00	-1.0000	0.9998
7.50	-1.0000	0.9999
8.00	-1.0000	0.9999

Table 5.3 E[X(t)], E[Y(t)], E[Z(t)] versus α

for t = 0.50, λ = 0.20, μ = 0.01

α	E[X(t)]	E[Y(t)]	E[Z(t)]
100.00	10.0483	0.0017	0.0007
200.00	10.0983	0.0017	0.0007
300.00	10.1483	0.0017	0.0007
400.00	10.1983	0.0017	0.0007
500.00	10.2483	0.0017	0.0007
600.00	10.2983	0.0017	0.0007
700.00	10.3483	0.0017	0.0007
800.00	10.3983	0.0017	0.0007
900.00	10.4483	0.0017	0.0007
1000.00	10.4983	0.0017	0.0007

Table 5.4 R_{XY} , R_{YZ} versus α for

t = 0.50, λ = 0.20, μ = 0.01

α	R_{XY}	R_{YZ}
100.00	-0.8770	0.8406
200.00	-0.7595	0.8406
300.00	-0.6578	0.8406
400.00	-0.6036	0.8406
500.00	-0.5674	0.8406
600.00	-0.5262	0.8406
700.00	-0.4929	0.8406
800.00	-0.4688	0.8406
900.00	-0.4479	0.8406
1000.00	-0.4297	0.8406

CHAPTER SIX

A STOCHASTIC MODEL OF THE DYNAMICS OF HIV UNDER A COMBINATION THERAPEUTIC INTERVENTION

6.1 INTRODUCTION

In HIV infected individuals, the infection exhibits a long asymptomatic phase (after the initial high infectious phase), on average about 10 years before the onset of AIDS. During this incubation period which some call the clinical latency period, the individuals appear to be well and may contribute significantly to the spread of the epidemic in a community. Some clinical markers such as the CD4 cell count and the RNA viral load (viraemia) provide information about the progression of the disease in infected individuals. Also, the clinical latency period of the disease may provide a sufficiently long period to try for an effective suppressive therapeutic intervention in HIV infections.

The knowledge of principal mechanisms of viral pathogenesis, namely the binding of the retrovirus to the gp120 protein on the CD4 cell, the entry of the viral RNA into the target cell, the reverse transaction of viral RNA to viral DNA, the integration of the viral DNA with that of the host, the viral regulatory processes mediated through regulatory proteins such as tat and rev and the action of viral protease in cleaving viral proteins into mature products, led to the design of drugs (chemotherapeutic agents) to control the production of HIV. Two principal directions along which drugs (such as AZT and Ritonavir (Shafer et al. 2001) are attempted are inhibition of the reverse transcriptase of HIV and inhibition of the protease of HIV. The inhibition of the function of either the reverse transcriptase or the protease of HIV reduces the production of infectious free HIV thereby the onset of AIDS can be delayed in HIV-infected individuals (Brookmeyer and Gail 1994).

A cure for HIV is yet to be discovered but progress is being made in obtaining effective vaccine and/or eradicating the virus from the human body. For example, in recent months result from a bone marrow transplant of a then HIV infected individual to be saved from leukaemia showed no known virus in his system (neither in the blood nor the reservoirs); is

this not a cure at hand? It was stated that this is not a recommended way of tackling HIV infection as it is very expensive and it takes time for the individual to have immunity because at the stage of transplant the individual has no immunity due to the new stem cells that are yet to grow and replicate (http://www.welt.de/english-news/article2715739/HIV-patient-cured-by-marrow-transplant.html). With the widespread of the epidemic and also in the absence of an "effective" vaccine or cure, therapeutic interventions still have to be heavily relied on. Several research studies have been made in the recent past both theoretically and experimentally to analyse the impact of therapy on the viral load in HIV infected persons to test the effectiveness of the treatment (Nelson and Perelson 1995, Wei et al. 1995, Perelson et al. 1996, Mellors et al. 1997, Nijhuis et al. 1998, Tan and Xiang 1999 and Bangsberg et al. 2004).

Nelson and Perelson (1995) proposed a mathematical model of therapeutic intervention to delay the onset of AIDS by the stimulated production of genetically engineered defective interfering virus (DIVs) that interferes with the HIV replication process. A DIV is a deletion mutant and it is incapable of replicating by itself in a host cell (CD4 cell), but may replicate if the host cell is co-infected with HIV. Assuming that DIV depends on HIV to multiply, Nelson and Perelson (1995) constructed a mathematical model describing the interaction among HIV, DIV and uninfected CD4 cells and they analysed the co-evolution of DIV and HIV in a single compartment. Their model is essentially given by a system of ordinary differential equations involving eight variables and several parameters representing the activities of DIV and HIV. By considering a higher level of DIV activity in the production of co-infected CD4 cells, they investigated the possibility of blocking the production of HIV so that the burden of HIV on the population of CD4 cells is reduced.

In the paper of Wei et al. (1995), based upon the results of several experimental studies of the dynamics of HIV replication in the presence of antiretroviral agents, it was reported that HIV had enormous potential in showing resistance to drugs and undergoing several mutations and a rapid and virtually complete replacement of wild-type HIV by drug resistant virus occurred when anti-viral drugs were administered. Nijhuis et al. (1998) noticed high drug resistance and unique combination of mutation in individuals when they proposed a stochastic model to test the resistance to protease inhibitors, although there was reduced effective free HIV population (500 – 15000).

Perelson et al. (1996) presented a mathematical model which was used to analyse the kinetic picture of HIV pathogenesis subject to the administration of a drug called Ritonavir to inhibit potently the protease of HIV. In their paper, they represented the dynamics of cell infection and viral production after treatment with ritonavir, by a set of ordinary differential equations using deterministic model and, assumed that the viral inhibition of ritonavir was 100% so that all newly produced virons after the treatment with ritonavir were non-infectious. Hence by using the mathematical model and non-linear least squares fitting of the viral load data of five HIV-1 infected patients, they were able to obtain estimates of the rate of viral clearance, the infected cell life-span and the average viral generation time.

Tan and Xiang (1999) had a state-space model of HIV pathogenesis in HIV infected individuals undergoing a combination-treatment (i.e. a treatment with a combination of anti-viral drugs such as AZT and Ritonavir which can inhibit either the reverse transcriptase or the protease of HIV). Their model gave way for the production of infectious free HIV and non-infectious free HIV, by extending the model of Perelson et al. (1996) and developing procedures for estimating and predicting the number of uninfected CD4 cells, infectious free

HIV, non-infectious free HIV and HIV infected CD4 cells. They not only extended Perelson et al. (1996) model into a stochastic model, but they also applied their model to data of some patients given by Perelson et al. (1996). Their model was discrete in time and was described by a system of stochastic difference equations which were derived based on the biological specifications of the HIV-replication cycle. However, the nature of the HIV-replication cycle indicated that a stochastic model approach of point events that are distributed over continuous infinity of states is very much appropriate to analyse the basic underlying process of generation of HIV and the interaction of defective HIV on the kinetics of HIV, so that an efficient therapeutic intervention may be devised to combat the production of HIV.

Since Perelson et al. (1996) had considered the deterministic model and Tan and Xiang (1999) had a state-space model, we considered a stochastic model of the growth of HIV population which carries over the principle of the virology of HIV and the life-cycle of HIV and allows the production of non-infectious (defective) free HIV to reduce the severity of HIV in a HIV-infected individual undergoing a combination-therapeutic treatment. Our aim in this paper is to use stochastic model obtained by extending the model of Perelson et al. (1996) to determine number of uninfected T4 cells, infected T4 cells and free HIV in an infected individual by examining the combined antiviral treatment of HIV. This is important because it helps in determining the efficacy of methods used in the research areas of pathogenesis, progression and combined treatment of HIV. By obtaining the variance and co-variance structures of the variables X(t), V(t) and D(t), we have contributed to the work afore done by Perelson et al. (1996) and Tan and Xiang (1999). Based upon the model, we obtain the expected numbers of HIV infected cells, infectious free HIV and non-infectious free HIV at any time t, and derive conclusions for the reduction or elimination of HIV in HIV-infected individuals.

The organisation of this chapter is as follows: In Section 6.2, we formulate a stochastic model to describe the production and the clearance of virus producing cells, infectious free HIV and non-infectious free HIV in a therapeutic environment. In Section 6.3, we derive a system of differential difference equations for the probability function associated with the process and also obtain a partial differential equation for the probability generating function of the numbers of HIV-infected CD4 cells, infectious free HIV and non-infectious free HIV at time t. The population measures are derived in Section 6.4. In Section 6.5, we provide a numerical illustration to show the impact of the usage of combination-therapy in controlling the progression of HIV and also obtained variance and co-variance structures of the variables. We have also compared equations we obtained with those obtained by Perelson et al. (1996) as our model is an extension of their model.

6.2 THE FORMULATION OF THE MODEL

Assume that at time t = 0, a combination-therapy treatment is initiated in an HIV-infected individual. We assume that the therapeutic intervention inhibits either the enzyme action of reverse transcriptase or that of the protease of an HIV in a HIV-infected cell. A HIV-infected cell with the inhibited HIV-transcriptase can be considered as a dead cell as it cannot participate in the production of the copies of any type of HIV. On the other, a HIV-infected cell in which the reverse transcription has already taken place and the viral DNA is fused with the DNA of the host but the enzyme activity of HIV-protease is inhibited, undergoes a lysis releasing infectious free HIV and non-infectious free HIV. A non-infectious free HIV cannot successfully infect a CD4 cell. Accordingly, at any time t, the blood of the infected person contains virus-producing HIV-infected cells, infectious free HIV and non-infectious free HIV.

A virus producing cell existing at time t in the therapeutic environment undergoes one of the following possibly in the interval $(t, t+\Delta)$:

(i) it splits into two HIV-infected cells with probability $\lambda_1\Delta + o(\Delta)$;

(ii) it undergoes a lysis with probability $\upsilon\Delta + o(\Delta)$, producing a random number K_1 of infectious free HIV and a random number K_2 of non-infectious free HIV;

(iii) it dies with probability $\mu\Delta + o(\Delta)$;

(iv) it remains as it is with probability $1 - (\lambda_1 + \upsilon + \mu)\Delta + o(\Delta)$;

We assume that K_1 and K_2 have the joint probability generating function $h(s_1, s_2)$ defined by

$$h(s_1, s_2) = \sum_{l=0}^{\infty} \sum_{m=0}^{\infty} \pi_{lm} s_1^l s_2^m$$

where π_{lm} represents the probability that l infections free HIV and m non-infectious free HIV are released at the lysis occurring at any time. An infectious free HIV existing at time t in the blood of the individual may undergo one of the following possibilities in the interval $(t, t+\Delta)$:

(i) it infects a T4 cell with probability $\lambda_2\Delta + o(\Delta)$ making the cell into a viruses producing cell;

(ii) it dies with probability $c\Delta + o(\Delta)$;

(iii) it remains as it is with probability $1 - (\lambda_2 + c)\Delta + o(\Delta)$;

The population of non-infectious free HIV does not grow by replication of its members but grows by admitting bulk immigrations which occur at the lysis of HIV-infected cells. A non-infectious HIV existing at time t dies in the interval $(t, t+\Delta)$ with probability $c\Delta + o(\Delta)$.

Let X(t) be the number of virus producing cells (these are cells that produce more virus to infect other cells) at time t. Let V(t) and D(t) be respectively the number of infectious free HIV (these are HIV in the body that infect cells in the body) and the number of non-

infectious free HIV (these are HIV in the body that do not infect cells in the body) at time t. For simplicity, we assume that X(0) = N, V(0) = n, D(0) = 0. We proceed to discuss the probability generating function of the vector process (X(t), V(t), D(t)) in the next section.

6.3 PROBABILITY GENERATING FUNCTION

The probability generating function of (X(t), V(t), D(t)) is defined by

$$G(u_1, u_2, u_3; t) = E[u_1^{X(t)} u_2^{V(t)} u_3^{D(t)}]$$

From the initial condition, it is easy to note that:

$$G(u_1, u_2, u_3; 0) = E[u_1^N u_2^n u_3^0] = E[u_1^N u_2^n]$$

To derive an equation for $G(u_1,u_2,u_3;t)$, we need the probability function which is defined for any time t by

$$p(i,j,k;t) = \Pr\{X(t) = i, V(t) = j, D(t) = k\},$$

where i, j, k = 0, 1, 2 …

Now, we proceed to derive a system of differential-difference equations for the function p(i, j, k; t). For this, we list below the exhaustive and mutually exclusive events that occur in (t, t+Δ) given that X (t) = i > 0, V (t) = j > 0 and D (t) = k > 0:

(i) one HIV infected cell splits into two HIV-infected cells in (t, t+Δ). The probability for this event to occur is $i\lambda_1\Delta + o(\Delta)$;

(ii) one HIV-infected cell undergoes a lysis in (t, t+Δ). The probability for this event to occur is $i\upsilon\Delta + o(\Delta)$;

(iii) one HIV-infected cell dies in (t, t+Δ). The probability for this event to occur is $i\mu\Delta + o(\Delta)$;

(iv) one infectious free HIV virus infects one CD4 cell making the CD4 cell an HIV-infected cell in (t, t+Δ). The probability for this event to occur is

$j\lambda_2\Delta + o(\Delta)$;

(v) one infectious free HIV virus dies in $(t, t+\Delta)$. The probability for this event to occur is $jc\Delta + o(\Delta)$;

(vi) one non-infectious free HIV virus dies in $(t, t+\Delta)$. The probability for this event to occur is $kc\Delta + o(\Delta)$;

(vii) none of the above occurs in $(t, t+\Delta)$.

Using probabilistic arguments, we obtain

$$p(i,j,k;t+\Delta) = p(i,j,k;t)\left[1-\{i(\lambda_1+\nu+\mu)+j(\lambda_2+c)+kc\}\Delta\right]+ p(i-1,j,k;t)(i-1)\lambda_1\Delta$$

$$+\sum_{l=0}^{j}\sum_{m=0}^{k}\pi_{lm}\,p(i+1,j-l,k-m;t)(i+1)\nu\Delta + p(i+1,j,k;t)(i+1)\mu\Delta + p(i-1,j+1,k;t)(j+1)\lambda_2\Delta$$

$$+ p(i,j+1,k;t)(j+1)c\Delta + p(i,j,k+1;t)(k+1)c\Delta \qquad (6.3.1)$$

From equation 6.3.1, we readily obtain the following equations:

$$p'(i,j,k;t) = -\{i(\lambda_1+\nu+\mu)+j(\lambda_2+c)+kc\}\,p(i,j,k;t) + (i-1)\lambda_1 p(i-1,j,k;t)$$

$$+(i+1)\nu\sum_{l=0}^{j}\sum_{m=0}^{k}\pi_{lm}\,p(i+1,j-l,k-m;t) + (i+1)\mu p(i+1,j,k;t) + (j+1)\lambda_2 p(i-1,j+1,k;t)$$

$$+(j+1)cp(i,j+1,k;t) + (k+1)cp(i,j,k+1;t),\ i>0 \qquad (6.3.2)$$

$$p'(0,j,k;t) = -\{j(\lambda_2+c)+kc\}\,p(0,j,k;t) + \nu\sum_{l=0}^{j}\sum_{m=0}^{k}\pi_{lm}\,p(1,j-l,k-m;t)$$

$$+\mu p(1,j,k;t) + (j+1)cp(0,j+1,k;t) + (k+1)cp(0,j,k+1;t) \qquad (6.3.3)$$

Now, we have

$$G(u_1,u_2,u_3;t)=\sum_{i=0}^{\infty}\sum_{j=0}^{\infty}\sum_{k=0}^{\infty}p(i,j,k;t)u_1^i u_2^j u_3^k,$$

And so, by using equations 6.3.2 and 6.3.3, we obtain

$$\frac{\partial G}{\partial t}=[(\mu-\lambda_1 u_1)(1-u_1)+\nu\{h(u_2,u_3;t)-u_1\}]\frac{\partial G}{\partial u_1}+[\lambda_2(u_1-u_2)+c(1-u_2)]\frac{\partial G}{\partial u_2}+c(1-u_3)\frac{\partial G}{\partial u_3} \quad (6.3.4)$$

Equation 6.3.4 is not solvable even for any simple form of $h(u_2,u_3;t)$. However, we can obtain the moment-structure of (X(t), V(t), D(t)). We do this in the next section.

6.4 THE MOMENT STRUCTURE OF (X(t), V(t), D(t))

We have the following notation:

$$M_{\xi}(t)=E[\xi(t)]$$

$$M_{\xi}^{(2)}(t)=E[\xi(t)(\xi(t)-1)]$$

$$M_{\xi\eta}(t)=E[\xi(t)\eta(t)]$$

$$Var(\xi(t))=E[\xi(t)^2]-(E[\xi(t)])^2$$

$$Cov(\xi(t),\eta(t))=E[\xi(t)\eta(t)]-E[\xi(t)]E[\eta(t)]$$

$$m_1=\left[\frac{\partial h(s_1,s_2)}{\partial s_1}\right]s_1=1,s_2=1,$$

$$m_2=\left[\frac{\partial h(s_1,s_2)}{\partial s_2}\right]s_1=1,s_2=1,$$

$$m_{11}=\left[\frac{\partial^2 h(s_1,s_2)}{\partial s_1^2}\right]s_1=1,s_2=1,$$

$$m_{22} = \left[\frac{\partial^2 h(s_1, s_2)}{\partial s_2^2}\right] s_1 = 1, s_2 = 1,$$

$$m_{12} = \left[\frac{\partial^2 h(s_1, s_2)}{\partial s_1 s_2}\right] s_1 = 1, s_2 = 1,$$

$$A = (u_1 = 1, u_2 = 1, u_3 = 1), \alpha = \mu - \lambda_1 + \nu, \beta = \lambda_2 + c.$$

Differentiating equation 6.3.4 with respect to u_1 at A, we obtain

$$\frac{\partial M_X(t)}{\partial t} + \alpha M_X(t) = \lambda_2 M_V(t) \tag{6.4.1}$$

Differentiating (6.3.4) with respect to u_2 at A, we obtain

$$\frac{\partial M_V(t)}{\partial t} + \beta M_V(t) = \nu m_1 M_X(t) \tag{6.4.2}$$

Differentiating (6.3.4) with respect to u_3 at A, we obtain

$$\frac{\partial M_D(t)}{\partial t} + cM_D(t) = \nu m_2 M_X(t) \tag{6.4.3}$$

Differentiating (6.3.4) with respect to u_1 twice at A, we get

$$\frac{\partial M_X^{(2)}(t)}{\partial t} + 2\alpha M_X^{(2)}(t) = 2\left[\lambda_1 M_X(t) + \lambda_2 M_{XV}(t)\right] \tag{6.4.4}$$

Differentiating (6.3.4) with respect to u_2 twice at A, we get

$$\frac{\partial M_V^{(2)}(t)}{\partial t} + 2\beta M_V^{(2)}(t) = \nu\left[m_{11} M_X(t) + m_1 M_{XV}(t)\right] \tag{6.4.5}$$

Differentiating (6.3.4) with respect to u_3 twice at A, we get

$$\frac{\partial M_D^{(2)}(t)}{\partial t} + 2cM_D^{(2)}(t) = \nu\left[2m_2 M_{XD}(t) + m_{22} M_X(t)\right] \tag{6.4.6}$$

Differentiating (6.3.4) with respect to u_1 and u_2 at A, we get

$$\frac{\partial M_{XV}(t)}{\partial t} + (\alpha+\beta)M_{XV}(t) = \nu m_1 M_X^{(2)}(t) + \lambda_2 M_V^{(2)}(t) \qquad (6.4.7)$$

Differentiating (6.3.4) with respect to u_2 and u_3 at A, we get

$$\frac{\partial M_{VD}(t)}{\partial t} + (\beta+c)M_{XD}(t) = \nu\left[m_1 M_{XD}(t) + m_{12} M_X(t) + m_2 M_{XV}(t)\right] \qquad (6.4.8)$$

Differentiating (6.3.4) with respect to u_1 and u_3 at A, we get

$$\frac{\partial M_{XD}(t)}{\partial t} + (\alpha+c)M_{XD}(t) = \nu m_2 M_X^{(2)}(t) + \lambda_2 M_{VD}(t) \qquad (6.4.9)$$

Although the differential equations 6.4.2 and 6.4.3 are similar to the equations in Perelson et al. (1996), equation 6.4.1 differs from the corresponding equation in Perelson et al. (1996). Equations 6.4.2 and 6.4.3 in Perelson et al. (1996) were given as $\frac{dV}{dt} = \mathrm{N}\delta\Gamma^* - \mathrm{cV}$ and $\frac{dV_{NI}}{dt} = \mathrm{N}\delta\Gamma^* - \mathrm{cV_{NI}}$ respectively and equation 6.4.1 as $\frac{dT^*}{dt} = \mathrm{kVT} - \delta\Gamma^*$ (where T is target cells, T^* is productively infected cells, V is the concentration of viral particles in plasma, δ is the rate of loss of virus producing cells, N is the number of new virons produced per infected cell during its lifetime, c is the rate constant for viron clearance and V_{NI} is the concentration of virons in the non-infectious pool).We proceed to solve the above equations to obtain the moments $M_X(t)$, $M_V(t)$ and $M_D(t)$ explicitly. Writing these equations in the matrix form, we obtain the following matrix differential equation:

$$\frac{\partial}{\partial t}\begin{pmatrix} M_X(t) \\ M_V(t) \\ M_D(t) \end{pmatrix} = R\begin{pmatrix} M_X(t) \\ M_V(t) \\ M_D(t) \end{pmatrix} \qquad (6.4.10)$$

Where R is the matrix given by

$$R = \begin{pmatrix} -\alpha & \lambda_2 & 0 \\ \nu m_1 & -\beta & 0 \\ \nu m_2 & 0 & -c \end{pmatrix}$$

The characteristic equation of the matrix R is given by

$$(c+\lambda)\left[(\alpha+\lambda)(\beta+\lambda) - \nu m_1 \lambda_2\right] = 0 \qquad (6.4.11)$$

Solving equation 6.4.11, we obtain the characteristic values of R which are real and distinct, and are given as

$$-c, \frac{-(\alpha+\beta) \pm \sqrt{(\alpha-\beta)^2 + 4\nu m_1 \lambda_2}}{2}$$

The corresponding characteristic vectors are respectively,

$$R_1 = \begin{pmatrix} 0 \\ 0 \\ 1 \end{pmatrix}, R_2 = \begin{pmatrix} \lambda_2(c+\theta_1) \\ (c+\theta_1)(\alpha+\theta_1) \\ \nu m_2 \lambda_2 \end{pmatrix}, R_3 = \begin{pmatrix} \lambda_2(c+\theta_2) \\ (\alpha+\theta_2)(c+\theta_2) \\ \nu m_2 \lambda_2 \end{pmatrix}$$

Where

$$\theta_1 = \frac{-(\alpha+\beta) + \sqrt{(\alpha-\beta)^2 + 4\nu m_1 \lambda_2}}{2}$$

and

$$\theta_2 = \frac{-(\alpha+\beta) - \sqrt{(\alpha-\beta)^2 + 4\nu m_1 \lambda_2}}{2}$$

Accordingly, the general solution of 6.4.10 is

$$\begin{pmatrix} M_X(t) \\ M_V(t) \\ M_D(t) \end{pmatrix} = C_1 R_1 e^{-ct} + C_2 R_2 e^{\theta_1 t} + C_3 R_3 e^{\theta_2 t},$$

where C_1, C_2 and C_3 are constants. In our model, we have assumed that X(0) = N, V(0) = n, D(0) = 0 and so we have the following initial conditions:

$M_X(0) = N$, $M_V(0) = n$, $M_D(0) = 0$.

Consequently, the constants C_1, C_2 and C_3 satisfy the following system of linear equations:

$$\begin{aligned} \lambda_2(c+\theta_1)C_2 + \lambda_2(c+\theta_2)C_3 &= N \\ (c+\theta_1)(\alpha+\theta_1)C_2 + (c+\theta_2)(\alpha+\theta_2)C_3 &= n \\ C_1 + \nu m_2 \lambda_2 C_2 + \nu m_2 \lambda_2 C_3 &= 0 \end{aligned} \qquad (6.4.12)$$

Solving the system (6.4.12), we obtain

$$C_1 = \frac{-\nu m_2 \{N(c+\alpha+\theta_1+\theta_2) - n\lambda_2\}}{(c+\theta_1)(c+\theta_2)}$$

$$C_2 = \frac{N(\alpha+\theta_2) - n\lambda_2}{\lambda_2(c+\theta_1)(\theta_2-\theta_1)}$$

$$C_3 = \frac{-N(\alpha+\theta_1) + n\lambda_2}{\lambda_2(c+\theta_2)(\theta_2-\theta_1)}$$

Hence, we obtain

$$\begin{aligned} M_X(t) = & \frac{N(c+\theta_2)(\alpha+\theta_2) - n\lambda_2(c+\theta_2)}{(c+\theta_2)(\theta_2-\theta_1)} e^{-\theta_1 t} \\ & + \frac{-N(c+\theta_1)(\alpha+\theta_1) + n\lambda_2(c+\theta_1)}{(c+\theta_1)(\theta_2-\theta_1)} e^{-\theta_2 t} \end{aligned} \qquad (6.4.13)$$

$$M_V(t) = \begin{aligned} &\frac{N(c+\theta_2)(\alpha+\theta_2)-n\lambda_2(c+\theta_2)}{\lambda_2(c+\theta_2)(\theta_2-\theta_1)}(\alpha+\theta_1)e^{\theta_1 t} \\ &+\frac{-N(c+\theta_1)(\alpha+\theta_1)+n\lambda_2(c+\theta_1)}{\lambda_2(c+\theta_1)(\theta_2-\theta_1)}(\alpha+\theta_2)e^{\theta_2 t} \end{aligned} \qquad (6.4.14)$$

$$M_D(t) = \begin{aligned} &\frac{vm_2\{n\lambda_2 - N(c+\alpha+\theta_1+\theta_2)\}}{(c+\theta_1)(c+\theta_2)}e^{-ct} \\ &+\frac{vm_2\{N(c+\theta_2)(\alpha+\theta_2)-n\lambda_2(c+\theta_2)\}}{(c+\theta_1)(c+\theta_2)(\theta_2-\theta_1)}e^{\theta_1 t} \\ &+\frac{vm_2\{n\lambda_2(c+\theta_1)-N(\alpha+\theta_1)(c+\theta_1)\}}{(c+\theta_1)(c+\theta_2)(\theta_2-\theta_1)}e^{\theta_2 t} \end{aligned} \qquad (6.4.15)$$

We have not obtained explict results for $M_X^{(2)}(t), M_D^{(2)}(t), M_{XV}(t), M_{VD}(t)$ and $M_{XD}(t)$.

However, we are able to solve completely the equations (6.4.1) to (6.4.9) in a special case where no infectious free virus is released at the lysis of every HIV-infected cell treated with combination therapy. We have for this special case, $m_1 = 0$, $m_{11} = 0$, $m_{12} = 0$.

Consequently, equations 6.4.1 to 6.4.9 yield

$$M_X(t) = Ne^{-\alpha t} - n\lambda_2\left(\frac{e^{-\alpha t} - e^{-\beta t}}{\alpha-\beta}\right) \qquad (6.4.16)$$

$$M_V(t) = ne^{-\beta t} \qquad (6.4.17)$$

$$M_D(t) = vm_2\left[\frac{n\lambda_2 - N(c-\beta)}{(c-\alpha)(c-\beta)}e^{-ct} - \frac{n\lambda_2 - N(\alpha-\beta)}{(c-\alpha)(\alpha-\beta)}e^{-\alpha t} + \frac{n\lambda_2}{(c-\beta)(\alpha-\beta)}e^{-\beta t}\right] \qquad (6.4.18)$$

$$M_V^{(2)}(t) = n(n-1)e^{-2\beta t} \qquad (6.4.19)$$

$$M_{XV}(t) = Nne^{-(\alpha+\beta)t} + \frac{\lambda_2 n(n-1)}{\alpha-\beta}\{e^{-2\beta t} - e^{-(\alpha+\beta)t}\} \tag{6.4.20}$$

$$M_{VD}(t) = \begin{aligned} &\frac{Nn\nu m_2}{c-\alpha}\{e^{-(\alpha+\beta)t} - e^{-(\beta+c)t} \\ &-\frac{\nu m_2 \lambda_2 n(n-1)}{(\alpha-\beta)(\beta-c)(c-\alpha)}\{(c-\alpha)e^{-2\beta t} \\ &+(\beta-c)e^{-(\alpha+\beta)t} + (\alpha-\beta)e^{-(\beta+c)t}\} \end{aligned} \tag{6.4.21}$$

$$M_X^{(2)}(t) = \begin{aligned} &\frac{2\lambda_1\{(\alpha-\beta)N-n\lambda_2\}}{\alpha(\alpha-\beta)}e^{-\alpha t} + \frac{2\lambda_1\lambda_2 n}{(\alpha-\beta)(2\alpha-\beta)}e^{-\beta t} \\ &+\frac{2\lambda_2\{Nn(\alpha-\beta)-\lambda_2 n(n-1)\}}{(\alpha-\beta)^2}e^{-(\alpha+\beta)t} \\ &+\left[\frac{N(N-1)\alpha(2\alpha-\beta)-2\lambda_1\{(2\alpha-\beta)N-n\lambda_2\}}{\alpha(2\alpha-\beta)} + \frac{\lambda_2\{\lambda_2 n(n-1)-2Nn(\alpha-\beta)\}}{(\alpha-\beta)^2}\right]e^{-2\alpha t} \\ &+\frac{\lambda_2^2 n(n-1)}{(\alpha-\beta)^2}e^{-2\beta t} \end{aligned} \tag{6.4.22}$$

$$M_{XD}(t) = A_1e^{-\alpha t} + A_2e^{-\beta t} + A_3e^{-2\alpha t} + A_4e^{-2\beta t} + A_5e^{-(\alpha+c)t} + A_6e^{-(\beta+c)t} + A_7e^{-(\alpha+\beta)t} \tag{6.4.23}$$

$$M_D^{(2)}(t) = 2\nu m_2 [\ A_1\left\{\frac{e^{-2ct}-e^{-\alpha t}}{\alpha-2c}\right\}+A_2\left\{\frac{e^{-2ct}-e^{-\beta t}}{\beta-2c}\right\}$$

$$+A_3\left\{\frac{e^{-2ct}-e^{-2\alpha t}}{2(\alpha-c)}\right\}+A_4\left\{\frac{e^{-2ct}-e^{-2\beta t}}{2(\beta-c)}\right\}$$

$$+A_5\left\{\frac{e^{-2ct}-e^{-(\alpha+c)t}}{\alpha-c}\right\}+A_6\left\{\frac{e^{-2ct}-e^{-(\beta+c)t}}{\beta-c}\right\}+A_7\left\{\frac{e^{-2ct}-e^{-(\alpha+\beta)t}}{\alpha+\beta-2c}\right\}\ ]$$

$$+\nu m_{22}\left[\left\{N-\frac{n\lambda_2}{\alpha-\beta}\right\}\left\{\frac{e^{-2ct}-e^{-\alpha t}}{\alpha-2c}\right\}+\frac{n\lambda_2}{\alpha-\beta}\left\{\frac{e^{-2ct}-e^{-\beta t}}{\beta-2c}\right\}\right] \quad (6.4.24)$$

where $A_1=\dfrac{2\lambda_1\{N(\alpha-\beta)-\lambda_2 n\}}{\alpha c(\alpha-\beta)}$

$$A_2=\frac{2\lambda_1\lambda_2 n}{(\alpha-\beta)(2\alpha-\beta)(\alpha-\beta+c)}$$

$$A_3=\frac{N(2\alpha-\beta)\{\nu m_2(N-1)\alpha-2\lambda_1\}+2\lambda_1\lambda_2 n}{\alpha(2\alpha-\beta)(c-\alpha)}+\frac{\nu m_2\lambda_2 n\{\lambda_2(n-1)-2N(\alpha-\beta)\}}{(\alpha-\beta)^2(c-\alpha)}$$

$$A_4=\frac{\nu m_2\lambda_2^2 n(n-1)}{(\alpha-\beta)^2(c-\beta)}$$

$$A_5=\frac{\nu m_2\lambda_2 n\{N(\alpha-2\beta-c)-\lambda_2(n-1)\}}{(c-\beta)(\alpha-\beta)(\alpha-2\beta-c)}+\frac{2\nu m_2\lambda_2 n\{N(\alpha-2\beta-c)-\lambda_2(n-1)\}}{(c-\beta)(c-\alpha)(\alpha-2\beta+c)}$$

$$+\frac{\{2\lambda_1-\nu m_2(N-1)c\}N(\alpha-\beta+c)-2\lambda_1\lambda_2 n}{c(c-\alpha)(\alpha-\beta)(\alpha-\beta+c)}$$

$$A_6=\frac{\nu m_2\lambda_2 n\{\lambda_2(n-1)-N(c-\beta)\}}{(c-\alpha)(c-\beta)(\alpha-\beta)}$$

$$A_7=\frac{2\nu m_2\lambda_2 n\{N(\alpha-\beta)-\lambda_2(n-1)\}}{(\alpha-\beta)^2(c-\beta)}+\frac{\nu m_2\lambda_2 n\{N(\alpha-\beta)-\lambda_2(n-1)\}}{(c-\alpha)(c-\beta)(\alpha-\beta)}$$

Although the above expressions for $M_{XD}(t)$ and $M_D^{(2)}(t)$ are quite laborious, we have presented them here for the sake of completeness. However, for the purpose of numerical illustration considered in the next section, we prefer the following integral expressions which are obtained from equations 6.4.18 to 6.4.24.

$$M_D(t) = \nu m_2 \int_0^t e^{-cu} M_X(t-u)du \tag{6.4.25}$$

$$M_{XV}(t) = Nn + \lambda_2 \int_0^t e^{-(\alpha+\beta)u} M_V^{(2)}(t-u)du \tag{6.4.26}$$

$$M_{VD}(t) = \nu m_2 \int_0^t e^{-(\beta+c)u} M_{XV}(t-u)du \tag{6.4.27}$$

$$M_X^{(2)}(t) = N(N-1) + 2\lambda_2 \int_0^t e^{-2\alpha u} M_{XV}(t-u)du + 2\lambda_1 \int_0^t e^{-2\alpha u} M_X(t-u)du \tag{6.4.28}$$

$$M_{XD}(t) = \nu m_2 \int_0^t e^{-(\alpha+c)u} M_X^{(2)}(t-u)du + \lambda_2 \int_0^t e^{-(\alpha+c)u} M_{VD}(t-u)du \tag{6.4.29}$$

$$M_D^{(2)}(t) = 2\nu m_2 \int_0^t e^{-2cu} M_{XD}(t-u)du + \nu m_{22} \int_0^t e^{-2cu} M_X(t-u)du \tag{6.4.30}$$

Where the expressions for $M_X(t)$, $M_V(t)$, $M_D(t)$ and $M_V^{(2)}(t)$ are given by equations 6.4.16, 6.4.17, 6.4.18 and 6.4.19 respectively.

6.5 NUMERICAL ILLUSTRATION OF MODEL

For the purpose of numerical illustration, we have extrapolated estimates from Perelson et al. (1996) and Tan and Xiang (1999) and considered three cases (we adopt Simpson's one-third rule for the computation of integrals (equations) 6.4.25 to 6.4.30).

Case (i): Both the mean numbers of the infectious free HIV m_1 and non-infectious free HIV m_2 produced by a virus producing cell at the time of its lysis are greater than zero.

Case (ii): $m_1 = 0$ and $m_2 \neq 0$ and obtain values of the means $M_X(t)$, $M_V(t)$, and $M_D(t)$ for the values of t ranging from 0.0 to 2.5 in steps of 0.5 for all the cases and the results are highlighted in Figure 6.1.

Case (iii): The second moments are evaluated by adopting Simpson's one-third rule for the evaluation of integrals. The assumed values of the parameters are given below in table 6.1 and the results are highlighted in Table 6.2 to 6.5 and figure 6.1. For simulated results, we take 1 hour as 0.5 time unit.

Table 6.1: Assumed values of parameters used in data simulation

Parameters Notation	Parameters	Assumed values
C	Rate of dying of a free HIV	3/day
N	Number of virus producing cells at time t = 0	412copies/ ml
n	Number of infectious free HIV at time t = 0	98000/mm^3
λ_1	Rate of splitting of a virus producing cell	5/day/mm^3 and 10/day/mm^3
λ_2	Rate with which a free HIV infects a CD4 cell	1/day/mm^3
ν	Rate of occurrence of lysis of virus producing cell	0.02/day
μ	Rate of death of virus producing cell	0.4/day
m_1	Expected number of infectious free HIV produced at the time of lysis of an infected cell	200/mm^3
m_2	Expected number of non-infectious free HIV produced at the time of lysis of an infected cell	100/mm^3
m_{22}	Second factorial moments of the number of non-infectious free HIV produced at the time of lysis of an infected cell	9900/mm^6

Case (i): From Figure 6.1 and table 6.2, it was easily noted that as t increases the values of $M_X(t), M_V(t), M_D(t)$ also increases for $\lambda_1 = 5.0$. When $\lambda_2 = 10.0$ (the rate at which HIV infected cell splits into two), the values of $M_X(t)$, $M_V(t), M_D(t)$ also increased with

increasing value of t (table 6.2). This shows that as the value of λ_1 increases, the values of $M_X(t)$, $M_V(t)$, $M_D(t)$ increases significantly with time before treatment.

Case (ii): Assume $m_1 = 0$, $m_2 = 100.0$, $m_{22} = 9900.0$. From Figure 6.1 that has the fitted curves for $M_X(t)$, $M_V(t)$, $M_D(t)$ before and after treatment, it is observed that there is a remarkable difference in the values obtained before and after treatment especially after t = 1.5. This shows the effectiveness of the treatment using the stochastic model. As such the expected number of virus producing cells and expected number of non-infectious free HIV decreased significantly after treatment (effect of reverse transcriptase drugs). And the expected numbers of infectious free HIV was reduced to almost nil at t = 2.5 which is the effect of protease inhibitor drugs as they reduce the generation of infectious free HIV at the death of actively infected T4 cells.

Case (iii): Assume $m_1 = 0$, $m_2 = 100.0$, $m_{22} = 9900.0$. The values of the second order moments namely: $M_X^{(2)}(t)$, $M_D^{(2)}(t)$, $M_V^{(2)}(t)$, $M_{XD}(t)$, $M_{XV}(t)$, and $M_{VD}(t)$ are provided in Table 6.4 and Table 6.5. The variances of virus producing cells and non-infectious free HIV are so large in comparison to those of infectious free HIV and their values increased significantly with t increasing. Unlike those of infectious free HIV that decreased significantly after treatment. The co-variance results shows that there is a positive relationship between virus producing cells and infectious free HIV.

Table 6.2 : $M_X(t)$, $M_V(t)$, $M_D(t)$ versus t (before treatment) with C = 3.0, N = 412.0, n = 98000.0, υ = 0.02, μ = 0.49, m_1 = 200.0, m_2 = 100.0, m_{22} = 9900.0, λ_2 = 1.0

	$\lambda_1 = 5.0$		
t	$M_X(t)*10^{-5}$	$M_V(t)*10^{5}$	$M_D(t)*10^{-4}$
0.50	1	1	3
1.00	15	7	38
1.50	178	80	449
2.00	2106	943	5307
2.50	24870	11131	62665

	$\lambda_1 = 10.0$		
t	$M_X(t)*10^{-5}$	$M_V(t)*10^{5}$	$M_D(t)*10^{-5}$
0.50	1	2	2
1.00	130	378	204
1.50	17324	50286	27111
2.00	2303609	6686681	3604945
2.50	306314300	889138100	479355000

Table 6.3: $M_X(t), M_V(t), M_D(t)$ versus t (after treatment) with C = 3.0, N = 412.0, n = 98000.0, $\upsilon = 0.02$, $\mu = 0.49$, $\lambda_2 = 1.0$, $m_2 = 100.0$, $m_{22} = 9900.0$

	$\lambda_1 = 5.0$		
t	$M_X(t) * 10^{-5}$	$M_V(t)$	$M_D(t) * 10^{-4}$
0.50	1	13263	3
1.00	11	1795	28
1.50	101	243	269
2.00	950	33	2535
2.50	8964	4	23936

Table 6.4: $M_X^{(2)}(t), M_D^{(2)}(t), M_V^{(2)}(t)$ versus t with C = 3.0, N = 412.0, n = 98000.0, $\upsilon = 0.02$, $\mu = 0.49$, $m_2 = 100.0$, $m_{22} = 9900.0$, $\lambda_1 = 2.5$, $\lambda_2 = 1.0$

t	$M_X^{(2)}(t) * 10^{-6}$	$M_D^{(2)}(t) * 10^{-6}$	$M_V^{(2)}(t)$
0.50	1893	195	175901600
1.00	15054	2349	3221750
1.50	105300	18217	59008
2.00	702573	134013	1081
2.50	4510266	969590	20

Table 6.5: $M_{XV}(t), M_{XD}(t), M_{VD}(t)$ versus t with C = 3.0, N = 412.0, n = 98000.0, $\upsilon = 0.02$, $\mu = 0.49$, $m_2 = 100.0$, $m_{22} = 9900.0$, $\lambda_1 = 2.5$, $\lambda_2 = 1.0$

t	$M_{XV}(t) * 10^{-6}$	$M_{XD}(t) * 10^{-6}$	$M_{VD}(t) * 10^{-6}$
0.50	598	605	186
1.00	255	5925	95
1.50	120	43175	43
2.00	70	295546	24
2.50	51	1948272	17

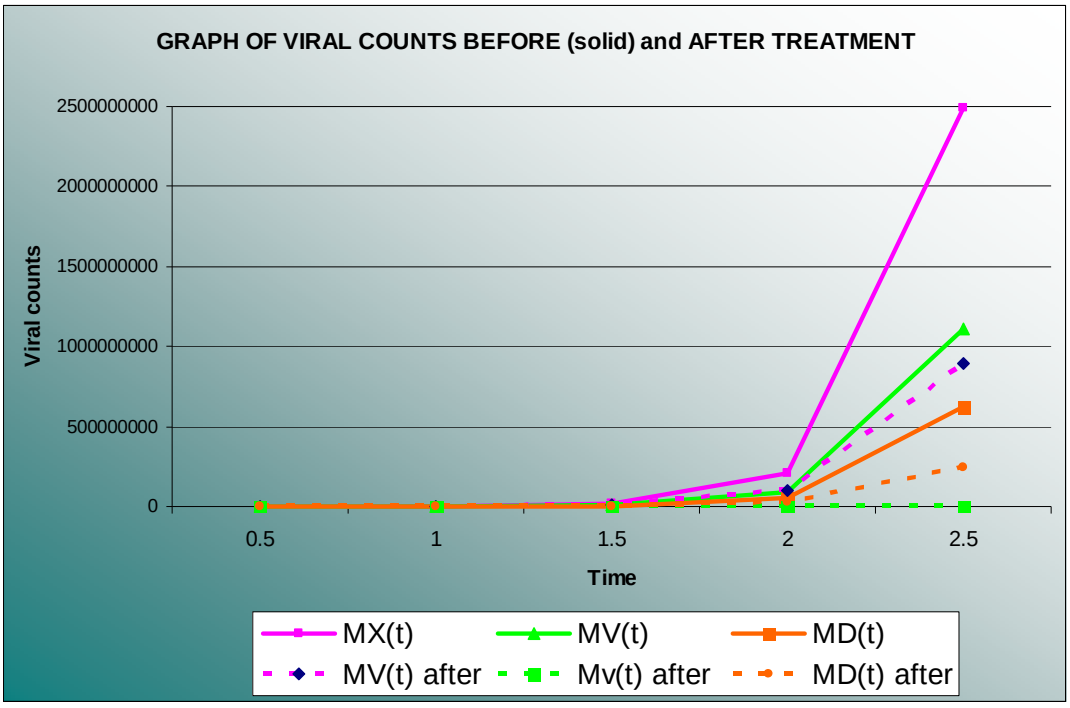

Figure 6.1: Graph of simulated mean number of free HIV, infectious free HIV and non-infectious free HIV before and after combined therapeutic treatment. (Units: on x-axis 0.5 is 1hour and viral counts on y-axis is copies/ml of blood)

6.6 CONCLUSION

In this chapter, we have shown the necessity of our stochastic model under combined treatment by obtaining the variance and co-variance structure of the number of virus producing cells at time t, the number of infectious free HIV and the number of non-infectious free HIV at time t. Compared with the models obtained by Perelson et al. (1996) and Tan and Xiang (1999), the variance and co-variance structures were not obtained, rather only the expected numbers of the variables and their estimates were obtained. Numerical simulation of results obtained in section 6.5 above has shown the efficacy of our model. We have not included t = 0 (after treatment) for the data simulation which is the time of pharmacokinetic delay which vary from person to person, and this is the time required for drug absorption, drug distribution and penetration into target cells (Perelson et al. 1996).

We have used estimates extrapolated from clinical data in Perelson et al. (1996) and Tan and Xiang (1999) to simulate our results. However a real life data for each time point are yet to be used because of limited resources to obtain RNA viral load of patients every 30 minutes to one hour interval. In a follow-up work, we intend to obtain such data as in Perelson et al. (1996) to test the efficacy of our model as we have done with simulated data.

REFERENCES

Anbupalam, T., Ravanan, R. and Venkatesan, P. (2002) Backcalculation of HIV nad AIDS in Tamil Nadu. *Biostatistical aspect of Health and Epidemiology*, pp. 232 – 243.

Ancelle, R., Bletry, O., Baglin, A.C., Bru-Vezinet, F., Rey, M.A. and Godeau, P. (1987) Long incubation period for HIV-2 infection. *Lancet*, Vol. 1, pp. 688 – 689.

Avert.org

Bacchetti, P. (1990) Estimating the incubation period of AIDS by comparing population infection and diagnosis patterns. *Journal of the American Statistical Association*, Vol. 85, No. 412, pp. 1002 – 1008.

Bacchetti, P., Segal, M.R., and Jewell, N.P. (1993) Back-calculation of HIV infection rates. *Statistical Sciences*, Vol. 8, No. 2, pp. 82 – 119.

Bangsberg, D.R., Porco, T.C., Kagay, C., Charlebois, E.D., Deeks, S.G., Guzman, D., Clark, R. and Moss, A. (2004) Modeling the HIV protease inhibitor adherence – resistance curve by use of empirically derived estimates. *The Journal of Infectious Diseases*, Vol. 190, pp. 162 – 165.

Barker, E., Mackerwicz, C.E., Reyes-Teran, G., Sato, A., Stranford, S.A., Fujimura, S.H., Christopherson, C., Chang, S.Y., and Levy, J.A. (1998) Virological and Immunological Features of Long-Term Human Immunodeficiency Virus Infected Individuals

Who Have Remained Asymptomatic Compared With Those Who Have Progressed to Acquired Immunodeficiency Syndrome. *Blood*, Vol. 92, No. 9, pp. 3105-3114.

Blankson, J.N., Persaud, D. and Siliciano, R.F. (2002) The challenge of viral reservoirs in HIV-1 infection. *Annual Review of Medicine*, Vol. 53, pp. 557-593.

Bortz, D.M. and Nelson, P.W. (2006) Model selection and Mixed-effects modelling of HIV infection dynamics. *Bulletin of Mathematical Biology*, Vol. 68, No. 8, pp. 2005 – 2025.

Brookmeyer, R and Gail, M.H. (1994) AIDS epidemiology: A quantitative approach. Oxford University Press, US.

Butler, S., Kirschner, D. and Lenhart, S. (1995) Optimal control of the chemotherapy affecting the infectivity of HIV. *Mathematical Biology*, Vol. 6, World Scientific.

Carvajal-Rodriguez, A., Crandall, K.A and Podada, D. (2007) Recombination favours the evolution of drug resistance in HIV-1 during antiretroviral therapy. *Infectious Genetic Evolution*, Vol. 7, No. 4, pp. 476 – 483.

Chevret, S., Costagliola, D., Lefrere, J.J. and Valleron, A.J. (1992) A new approach to estimating AIDS incubation times: results in homosexual infected men. *Journal of Epidemiology Community Health*, Vol. 46(6), pp. 582 – 586.

Chun, T.W. and Fauci, A.S. (1999) Latent reservoirs of HIV: obstacles to the eradication of virus. *Proceedings of National Academic Science, USA*, Vol. 96, pp. 10958-10961.

Cozzi-Lepri, A., Sabin, C.A, Pezzoti, P.D., Philips, A.N. and Rezza, G. (1997) Is there a general tendency for the CD4 lymphocyte decline to speed up during human immunodeficiency virus infection? Evidence from the Italian Seroconversion Study. *Journal of Infectious Diseases*, Vol. 175, pp. 775-780.

Dalgleish, A.G., Beverley, P.C, Clapham, P.R, Crawford, D.H, Greaves, M.F and Weiss R.A. (1984) The CD4 (T4) antigen is an essential component of the receptor for the AIDS retrovirus. *Nature*, Vol. 312, pp. 763-767.

De Gruttola, V., Lang, N. and Dafni, U. (1991) Modeling the progression of HIV infection. *Journal of the American Statistical Association*. Vol. 86, pp. 569-577.

De Gruttola, V. and Tu, X.M. (1994) Modeling progression of CD4-lymphocyte count and the relationship to survival time. *Biometrics*, Vol. 50, No. 4, pp. 1003 -1014.

Ding, A.A. and Wu, H. (1999) A comparison study of models and fitting procedures for biphasic viral dynamics in HIV-1 infected patients treated with antiviral therapies. *Biometrics*, Vol. 56, No. 1, pp. 293 – 300.

Douek, D. (2005) Making sense of HIV pathogenesis. Reprint from The PRN Notebook.

D'Souza, M.P. and Harden, V.A. (1996) Chemokines and HIV-1 second receptors. Confluence of two fields generates optimism in AIDS research. *Nature Medicine*, Vol., 2, pp. 1293-1300.

Fauci, A.S. (1993) Multifactorial nature of human immunodeficiency virus disease: implications for therapy. *Science*, Vol. 262, pp. 1011-1018.

Fauci, A.S. (1996) Host factors and the pathogenesis of HIV-induced disease. *Nature*, Vol. 384, pp. 529-534.

Fauci, A.S. (1988) The Human Immunodeficiency Virus: Infectivity and Mechanisms of Pathogenesis. *Science*, Vol. 239, pp. 617-622.

Fauci, A.S. (2003) HIV and AIDS: 20 years of science. *Nature Medicine*, Vol.9, No. 7, pp. 839 – 843.

Feinberg, M.B. (1996) Changing the Natural History of HIV Disease. *Lancet*, Vol. 348, pp. 239-246.

Fister, K.R., Lenhart, S and McNally, J.S. (1998) Optimizing chemotherapy in an HIV model. *Electronic Journal of Differential Equations*, Vol. 32, pp. 1 – 12.

Frost, S.D.W. (2001) Bayesian modelling of viral dynamics and evolution. *AIDS cyber Journal (Online)*, Vol. 4(2).

Gottlieb, M.S., Schroff , R., Schanker, H.M., Weisman, J.D., Fan, P.T., Wolf, R.A. and Saxon, A. (1981) Pneumocystis carinii pneumonia and mucosal candidiasis in previously healthy homosexual men: evidence of a new acquired cellular immunodeficiency. *The New England Journal of Medicine*, Vol. 305, pp. 1425-1431.

Greene, W.C. (1991) The Molecular Biology of Human Immunodeficiency Syndrome Type 1 Infection. *The New England Journal of Medicine*, Vol. 324, pp. 308 – 317.

Groot, F. (2006) Dendritic cell-mediated HIV-1 transmission. Ph.D Thesis. University of Amsterdam, The Netherlands.
http://www.feddegroot.org/publications/PhD-thesis_Fedde-Groot.pdf

Han, C., Chaloner, K and Perelson, A.S. (2002) Bayesian analysis of a population HIV dynamic model. *Case studies in Bayesian Statistics*, Vol. 6. Springer-Verlag, New York.

Hasentile, W.A. (1990) Molecular Biology of HIV-1 In: AIDS and new viruses. Dalgliesh, AG and Weiss RA (eds.) London: Academic Press, pp. 11-22.

HIV Wikipedia 2008
http://en.wikipedia.org/wiki/HIV

HIV
http://msl.cs.uiuc.edu/~yershova/bcb495/bcbProjects-3.htm

HIV pathogenesis – New Advances
http://www.ccspublishing.com/journal2a/hiv_pathogenesis.htm

Ho, D.D., Neumann, A.U., Perelson, A.S., Chen, W, Leonard, J.M. and Markowitz, M. (1995) Rapid turnover of plasma virons and CD4 lymphocytes in HIV-1 infection. *Nature*, Vol. 373, pp. 123-126.

Hoffmann, C., Rockstroh, J.K. and Kamps, B.S. (2007) HIV Medicine. 15th edition. Flying Publisher.

Holmes, E.C (1998) Human Immunodeficiency Virus, DNA and Statistics. *Journal of Royal Statistical Society. A*, Vol. 161, Part 2, pp. 199-208.

http://www.welt.de/english-news/article2715739/HIV-patient-cured-by-marrow-transplant.html

Huang, Y. and Wu, H. (2006) A Bayesian approach for estimating antiviral efficacy in HIV dynamic model. *Journal of Applied Statistics*, Vol. 33, pp. 155 – 174.

Hyman, J.M and Stanley, E.A. (1988) Using mathematical models to understand the AIDS epidemic. *Mathematical Biosciences*, Vol. 90, pp. 415 -474.

Jagers, P. (1967) Integrals of branching processes. *Biometrika*, Vol. 54, pp. 263 – 271.

Joshi, H.R, (2002) Optimal control of an HIV immunology model. *Optimal Control Applied Methods*, Vol. 23, pp. 199 – 213.

Kaye, S., Loveday, C. and Tedder, R.S. (1992) A Microtitre Format Point Mutation Assay: Application to the Detection of Drug Resistance in HIV-1 Infected Patients Treated with zidovudine. *Journal of Medical Virology*, Vol. 37, pp. 241- 246.

Khalili, S. and Armaou, A. (2008) Modeling intracellular dynamics of HIV infection and treatment. AIChE Annual Meeting, 160g, Philadelphia, PA.

Kirschner, D. (1996) Using mathematics to understand HIV immune dynamics. *AMS Notices*, pp. 191 – 202.

Kirschner, D., Lenhart, S. and Serbin, S. (1997) Optimal control of the chemotherapy of HIV. *Journal of Mathematical Biology*, Vol. 35, pp. 775 – 792.

Kirschner, D.E and Webb, G.F. (1998) Immunotherapy of HIV-1 infection. *Journal of Biological Systems*, Vol. 6, No. 1, pp. 71 – 83.

Klatzmann, D., Champagne, E., Chamaret, S., Gruest, J., Guetard, D., Hercend, T., Gluckman, J and Montagnier, L. (1984) T-lymphocyte T4 molecule behaves as the receptor for human retrovirus LAV. *Nature*, Vol. 312, pp. 767-768.

Kouyos, R.D, Althaus, C.L. and Bonhoeffer, S. (2006) Stochastic or deterministic: What is the effective population size of HIV-1? *Trends in Microbiology*, Vol. 14, pp. 507 – 511.

Lee, S (1999) Estimation of the maturity of HIV and the Incubation period of AIDS patients. http://www.tilastokeskus.fi/isi99/proceedings/arkisto/varasto/lee_0375.pdf

Levy, J.A. (2009) HIV Pathogenesis: 25 years of progress and persistent challenges. *AIDS*, Vol. 23, No. 2, pp. 147 – 160.

Longini, L.M. Jr., Clark, W.S., Gardener, L.I. and Brundage, J. (1991) The dynamic of CD4+T-lymphocyte decline in HIV-infected individual, A Markov Modelling approach. *Journal of Acquired Immune Deficiency Syndromes*, Vol. 4, pp. 1141-1147.

Lopman, B. and Gregson, S. (2008) When did HIV incidence peak in Harare, Zimbabwe? Back-Calculation from mortality statistics. *PLos ONE online journal*, Vol. 3(3): e1711 (http://www.plosone.org).

Louie, M., Hogan, C., Hurley, A., Simon, V., Chung, C., Padte, N., Lamy, P., Flaherty, J., Coakley, D., Mascio, M.D., Perelson, A.S. and Markowitz, M. (2003) Determining the antiviral activity of tenofovir disoproxil fumarate in treatment-naïve chronically HIV-1 infected individuals. *AIDS*, Vol.17, pp. 1151 – 1156.

Loveday, C. (1996) Virology of AIDS, AIDS: A Pocket Book of Diagnosis and Management. 2nd edition, edited by Adrian Mindel and Robert Miller, Co-published by Oxford University Press, Inc., New York, pp. 19 – 41.

Loveday, C., Kaye, S. and Tenant-Flowers, M. (1995) HIV-1, RNA Serum Load and Resistant Viral Genotypes During Early Zidovudine Therapy. *Lancet*, Vol. 345, pp. 820 – 824.

Lui, K.J, Darrow, W.W and Rutherford, G.W. (1988) A model-based estimate of the mean incubation period for AIDS in homosexual men. *Science*, Vol. 240, No. 4857, pp. 1333 – 1335.

Masur, H., Michelis, M.A., Greene, J.B., Onorato, I., Stouwe, R.A., Holzman, R.Z., Wormser, G., Brettman, L., Lange, M., Murray, H.W. and Cunningham-Rundle, S. (1981) An outbreak of community-acquired pneumocystis carinii pneumonia: initial manifestation of cellular immune dysfunction. *The New England Journal of Medicine*, Vol. 305, pp. 1431-1438.

Medley, G.F., Billard, L., Cox, D.R. and Anderson, R.M. (1988) The distribution of the incubation period for the acquired immunodeficiency syndrome (AIDS). *Proceedings of the Royal Society of London, Series B, Biological Sciences*, Vol. 233, No. 1272, pp. 367 – 377.

Mellors, J.W., Munoz, A., Giorgi, J.V., Margolick, J.B., Tassoni, C.J., Gupta, P., Kingsley, L.A., Todd, J.A., Saah, A.J., Detels, R., Phair, J.P. and Rinaldo, C.R. (1997) Plasma viral load and CD4+ lymphocytes as prognostic markers of HIV-1 infection. *Annals of Internal Medicine*, Vol. 126, pp. 946 – 954.

Mota-Miranda, A., Gomes, H., Marques, R., Serrao, R., Lourenco, H., Santos-Ferreira, O. and Lecour, H. (1995) HIV-2 infection with a long asymptomatic period. *Journal of Infection*, Vol. 31, pp. 163 – 164.

Musey, L., Hughes, J., Schacker, T., Shea, T., Correy, L. and McElrath, M.J. (1997) Cytotoxic T-cell Responses, Viral load and Disease Progression in Early Human Immunodeficiency Virus Type 1 Infection. *New England Journal of Medicine*, Vol. 337, pp. 1267 – 1274.

Nelson, P.W. and Perelson, A.S. (1995) Modeling defective interfering virus therapy for AIDS: Conditions for DIV survival. *Mathematical Biosciences*, Vol. 125, pp. 127 – 153.

Nelso,n P.W. and Perelson, A.S. (2002) Mathematical analysis of delay differential equation models of HIV-1 infection. *Mathematical Biosciences*, Vol. 179, pp. 73 – 94.

Nijhuis, M., Boucher, C.A.B., Schipper, P., Leitner, T., Schuurman, R. and Albert, J. (1998) Stochastic processes strongly influence HIV-1 evolution during suboptimal protease – inhibitor therapy. *Proceeding of National Academic of Science USA*, Vol. 95, pp. 14441 – 14446.

O'Brien, S.J. and Moore, J.P. (2000) The effect of genetic variation in chemokines and their receptors on HIV transmission and progression to AIDS. *Immunological Reviews*, Vol. 177, pp. 99-111.

Ong, H.C. and Soo, K.L. (2006) Backcalculation of HIV infection rates in Malaysia. *The Medical Journal of Malaysia*, Vol. 61(5), pp. 616 – 620.

Pakes, A.G. (1975) On Markov branching processes with immigration. *The Indian Journal of Statistics, Series A*, Vol. 37, No. 1, pp. 129 – 138.

Perelson, A.S, Essunger P., Cao, Y., Vesanen, M., Hurley, A., Saksela, K., Markowitz, M. and Ho, D.D. (1997) Decay characteristics of HIV-1-infected compartments during combination therapy. *Nature*, Vol. 387, pp. 188 – 191.

Perelson, A.S., Kirschner, D.E. and De Boer, R. (1993) The dynamics of HIV infection of CD4+T- cells. *Mathematical Biosciences*, Vol. 114, pp. 81-125.

Perelson, A.S. and Nelson, P.W. (1999) Mathematical analysis of HIV-1 dynamics in vivo. *Society for Industrial and Applied Mathematics (SIAM review)*, Vol. 41, pp. 3 – 44.

Perelson, A.S., Neumann, A.U., Markowitz, M., Leonard, J.M. and Ho, D.D. (1996) HIV-1 dynamics in vivo viron clearance rate, infected cell life span, and viral generation time. *Science New Series*, Vol. 271, pp. 1582 – 1586.

Philips, A.N., Lee, C.A. and Elford, J. (1992). The cumulative risk of AIDS as the CD$ lymphocyte count declines. *Journal of Acquired Immune Deficiency Syndromes*, Vol. 5, pp. 148-152.

Philips, A.N., Pezzotti, P., Cozzi Lepri, A. and Rezza, G.(1994) CD4 lymphocyte count as a determinant of the time from HIV seroconversion to AIDS and death from AIDS: evidence from the Italian Seroconversion Study. *AIDS*, Vol. 8, pp. 1299-1305.

Phipps, D.J., Yousefi, S. and Branch, D.R. (1997) Increased Enzymatic Activity of the T-cell Antigen Receptor=Associated Fyn Protein Tyrosine Kinase in Asymptomatic Patients Infected with the Human Immunodeficiency Virus. *Blood*, Vol. 90, No. 9, pp. 3603 – 3612.

Puri, P.S. (1966) On the homogeneous birth-and-death process and its integral. *Biometrika*, Vol. 53, pp. 61 – 71.

Putter, H., Heisterkamp, S.H., Lange, J.M.A. and Wolf, F. (2002) A Bayesian approach to parameter estimation in HIV dynamic models. *Statistics in Medicine*, Vol. 21, pp. 2199-2214.

Rao, A.S.R.S. and Kakehashi, M. (2005) Incubation – Time distribution in Back-calculation applied to HIV/AIDS data in India. *Mathematical Biosciences in Engineering*, Vol 2(2), pp. 263 – 277.

Sabin, C.A., Mocroft, A. and Lepri, A.C. (1998) Cofactors and markers of disease progression in human immunodeficiency virus infection. *Journal of Royal Statistical Society*, Vol. 161, Part 2, pp. 177-189.

Shafer, R.W., Dupnik, K., Winters, M.A. and Eshleman, S.H. (2001) A guide to HIV-1 reverse transcriptase and protease sequencing for drug resistance studies.

Shaw, G.M., Wong-Staal, F. and Gallo, R.C. (1988) Etiology of AIDS: Virology, Molecular Biology, and Evolution of Human Immunodeficiency Virus. In DeVita, V.T., Jr., Hellman, S., and Rosenberg, S.A (eds.), AIDS: Etiology, Diagnosis, Treatment and Prevention., Philadelphia: Lippincott, pp. 11 – 31.

Smith, S.S. (2006) The Pathogenesis of HIV infection: stupid may not be so dumb after all. *Retrovirology*, Vol. 3:60.

Sodora, D.L. and Silvestri, G. (2008) Immune Activation and AIDS pathogenesis. *AIDS*, Vol. 22, pp. 436 – 446.

Sridharah, V. and Jayashree, P.R. (1993) A population model of infected T-4 cells in AIDS. *Korean Journal of Computational and Applied Mathematics*, Vol. 6, No. 1, pp. 99 – 110.

Stein, D.S., Korvick, J.A. and Vermund, S.H. (1992). CD4+ lymphocyte cell enumeration for prediction of clinical course of human immunodeficiency virus disease: a review. *Journal of Infectious Diseases*, Vol. 165, pp. 352-363.

Stilianakis, N.I., Dietz, K. and Schenzle, D. (1997) Analysis of a Model for the Pathogenesis of AIDS. *Mathematical Biosciences*, Vol. 145, pp. 27 – 46.

Tan, W. (2000) Stochastic modelling of AIDS epidemiology and HIV pathogenesis. World Scientific.

Tan, W. and Wu, H. (1998) Stochastic modelling of the dynamics of $CD4^{+}$T cell infection by HIV and some Monte Carlo studies. *Mathematical Biosciences*, Vol. 147, pp. 173 – 205.

Tan, W. and Xiang, Z. (1999) Some state space models of HIV pathogenesis under treatment by anti-viral drugs in HIV – infected individuals. *Mathematical Biosciences*, Vol. 156, pp. 69 – 94.

Udayabaskaran, S. and Sudalaiyandi, G. (1986). On a stochastic integral of a branching process. *Journal of Mathematical Biology*, Vol. 24, pp. 467-472.

Utsumi, T., Nagakawa, H., Uenishi, R., Kusakawa, S. and Takebe, Y. (2007) An HIV-2-infected Japanese man who was a long-term nonprogressor for 36 years. *AIDS*, Vol. 21, No. 13, pp. 1834 – 1835.

Verdecchia, A. and Mariotto, A.B. (1995) A Back-calculation method to estimate the age and period HIV infection intensity, considering the susceptible population. *Statistical Medicine*, Vol. 14(14), pp. 1513 – 1530.

Wei, X., Ghosh, S.K, Taylor, M.E., Johnson, V.A., Emini, E.A., Deutsch, P., Lifson, J.D., Bonhoeffer, S., Nowak, M.A., Hahn, B.H., Saag, M.S. and Shaw, G.M. (1995) Viral dynamics in human immunodeficiency virus type 1 infection. *Nature*, Vol. 373, pp. 117-122.

Wei, X., Ghosh, S.K., Taylor, M.E., Johnson, V.A., Emini, E.A., Deutsch, P., Lifson, J.D., Bonhoeffer, S., Nowak, M.A., Hahn, B.H., Saag, M.S. and Shaw, G.M. (1995) Viral dynamics in human immunodeficiency virus type 1 infection. *Nature*, Vol. 373, pp. 117 – 122.

Weiss, R. (1986) Co-factors and HIV: What determines the pathogenesis of AIDS. *Science*, Vol. 232, pp. 697 – 698.

Weiss, R.A. (1993) How does HIV cause AIDS? *Science*, Vol. 260, Issue 5112, pp. 1273 – 1279.

WHO HIV Statistics 2007

Wick, D. (1999) On T-cell dynamics and the hyperactivation theory of AIDS pathogenesis. *Mathematical Biosciences*, Vol. 158, pp. 127 - 144.

Wu, H. (2005) Statistical Methods for HIV dynamic studies in AIDS clinical trials. *Statistical Methods in Medical Research*, Vol. 14, pp. 171- 192.

Wu, H. and Ding, A.A. (1999) Population HIV-1 dynamics in vivo: Applicable models and inferential tools for virological data from AIDS clinical trials. *Biomerics*, Vol. 55, No. 2, pp. 410 – 418.

Wu, H., Ruan, P., Dind, A.A., Sullivan, J.L. and Luzuriaga, K. (1999) Inappropriate model-fitting Methods may lead to significant underestimates of viral decay rates in HIV dynamic studies. *Journal of Acquired Immunodeficiency Syndromes and Human Retrovirology*, Vol. 2, No. 5, pp. 426 – 427.