CHAPTER I

INTRODUCTION

The rapid increase in the spread of the Human Immunodeficiency Virus (HIV) and consequent Acquired Immunodeficiency Syndrome (AIDS) all over the world has created a pandemic situation all over the world. It has not only affected the physical conditions of the infected but also the people around them. This is due to the fact that the infected people suffer from many diseases due to the immunodeficiency and the people around them suffer social and economic impact. The rate of spread is also on the increase. The government also suffers due to social impact, economic set back. Much of financial support is needed to fight against the spread of the infection. Even though the medical expects spend much of efforts to find a cure against this infection the solution is not yet available. The social impact due to the spread of this infection is also very much worrying. There is a need for proper planning of strategies and the execution of the same. Hence much of attention is paid to the control the spread of this infection.

However, there are more symptoms to this disease than other sufferings and that is the reactions of the people around. From the time HIV/AIDS was identified, this epidemic dilemma is accompanied by social responses like stigma, denial, fear and discrimination. Unlike sexual diseases such as Gonorrhea, Syphilis, Herpes Zoster and so on, HIV/AIDS at the present time, does not have a remedy. So, it brings fear of death to the people. For others, HIV/AIDS brought compassion, solidarity and support bringing out the best in people, their families
and communities, but we cannot deny the fact that it also brings negative responses, that it also associates stigma, repression and discrimination to the persons infected.

All around the world, persons living with HIV/AIDS faces many problems in their society. This includes not only the risk of losing the people close to them but also losing their reputation as an individual. Being treated differently likens one to an unwanted animal. Discrimination is the unfair treatment to these persons for they still are human beings like us. This happens because people are not knowledgeable enough of the virus – HIV. We know that we can easily be infected by such disease but in certain ways. Others may have the wrong understanding on how to acquire the virus that results to other forms of discrimination like; avoiding shaking of hands, sharing the same glass or plate and kissing. These acts cannot infect others with the virus but because a lot of people are still ignorant about the disease, it then leads to discrimination.

Another problem the infected people encounter is the unfairness towards their work, housing and education. Regarding their work, if ever an employer finds out an employee is under medication for such disease; it will most likely result for the employee to be looking for another job. Although it deeply depends on what type of workplace where the infected person works, still it affects the working relationship with their workmates, which leads to harassment and results in discontinuation working there. Same to those landlords that forbid HIV positive persons to rent their place and infected students who get kicked out of school for this reason.
Background Information of HIV/AIDS

AIDS was first formally recognised as a new disease in 1981 in the United States of America (Barnett and Whiteside (2002), Merson (2006), Pratt (1995), Smith (1996), Stine (2003) and WHO (2003)), in young homosexual men who were suffering with kaposi’s sarcoma and serious infections, mainly pneumocystis carinii pneumonia, that were unusual in men of this age group with no underlying disease. AIDS is characterised as the breakdown of the body’s immune system, which then allows “opportunistic” infections to occur (Bartlett and Finkbeiner (1998), Jonson (1988) and McMillan (1992)).

The Main Transmission Routes of HIV

i. Sexual contacts (Homo or Hetero).
ii. Transfusion of blood infected with HIV.
iii. For drug abusers the use of sharing the infected unsterile needles.
iv. The transfusion of the virus to the child in the fetes or through injuries caused during child birth.

All other transmission routes, for the most part case reports, are notably rare. Among these are transmissions due to transfusion of blood or blood products in countries where blood donations are not routinely screened for HIV. Extremely rare are transmissions due to contact with HIV-positive blood through open wounds or mucosa, or transmission of HIV after a bite (Bartholomew et al. (2006)). Recently three cases were reported where mothers infected their newborns probably via pre- chewed food (Gaur et al. (2008)). These transmission routes however are of a casuistic nature. Large case registries, in particular from
the Centres for Disease control and prevention, which have investigated into other transmission routes of HIV, clearly show that daily contacts of everyday life, such as the shared use of toilets or drinking from the same glass, cannot transmit HIV. Case registries in the health care setting, which analyze contact via saliva, urine, or infectious blood with intact skin, did not find a single transmission of HIV (Henderson et al. (1990)).

Although progress has been made in the global fight against HIV/AIDS, the epidemic continues to devastate the United States and the international community with an average of 50,000 new HIV infections each year in the United States and an estimated 34 million people living with HIV worldwide. As the leading U.S. government institute for HIV/AIDS research, NIAID (National Association for Information Distruption) is committed to conducting the research necessary to successfully end the fight against HIV/AIDS.

The process of seroconversion occurs after 8 to 10 years from the time point of infection. The progression of the HIV infection to the seropositive status and then to AIDS can be arrested to some extent by resorting to the anti retroviral therapy (ART). But the suffering of the infected during the time of administration of the ART and very high expenditure involved is a major problem faced by the infected. The best possible method of arresting the spread of the infection is by giving more stress on information education and communication counselling. The following strategies are suggested under this program.
i. Necessary and sufficient information in a simple way regarding the sources of infection and the possible symptoms of infection must be given to public.

ii. The awareness regarding the adoption of preventive strategies from this infection should be well explained.

iii. To create the congenial social atmosphere so that the infected people will be given a better social treatment and help for their survival.

**Antiretroviral Treatments**

Despite the discouraging outlook of HIV/AIDS progression, hope lies in the fact that viable treatments have been developed over the last two decades to curb the lethal course of this illness. The first antiretroviral drug approved by the FDA in 1987 was AZT (zidovudine), originally designed to treat cancer. This drug was successful in that sense it slowed disease progression and in that sense it slowed disease progression and instilled optimism in the HIV/AIDS-affected community. Regrettably, it was later shown that treatment with AZT did not increase overall survival rate (Institute of Medicine 2005a).

This outcome, which will be explained below, spurred drug development in several different directions ultimately producing four distinct classes of drugs.

The first were nucleoside reverse transcriptase inhibitors (NRTI), AZT included, which stop the process of elongation performed by the viral enzyme RT. As mentioned earlier, without functional RT, viral RNA cannot be converted to DNA, stopping HIV in its tracks. To produce DNA, this enzyme strings
nucleosides, the building blocks of genetic material, together in a sequence that complements a template strand of RNA. NRTIs work by resembling a nucleoside in every aspect except the portion that couples with the next nucleoside in sequence. If RT incorporates a NRTI into its DNA copy the reaction cannot continue, which leaves the enzyme blocked and the DNA strand unfinished. If RT were a machine that manufactures a long metal chain by connecting the links one at a time, administering a NRTI is essentially throwing scrap metal on the conveyor belt until the machine clogs and breaks down. A second group of medication targets RT with a different approach. Non-nucleoside reverse transcriptase inhibitor (NNRTIs) directly reacts with the RT enzyme and inhibits its activity. In the same analogy, NNRTIs take a sledgehammer to the chain-making-machine-the overall outcome is the same.

It is a matter of great interest that the medical personnel carryout very many efforts with a view to achieve the following results.

i. To find out the effective medicine or cure to wipe out disease infection.

ii. To improve the effectiveness of drugs which are used for ART.

iii. To bring down the cost of the medicines which are used for ART.

In HIV infection the invading antigens attack the human immune system mainly by destroying the CD4+T cells and also the antibodies which are generated by the human immune system to fight against the infection. There are two vital factors associated with the invading antigens. There are
two vital factors associated with the invading antigens namely antigenic diversity and virulence.

**HIV/AIDS in India**

Human Immunodeficiency virus (HIV) is a lentil virus that belongs to the retroviruses group may cause HIV infection / Acquired Immunodeficiency syndrome (AIDS). Among the many health targets in the Millennium Development Goals (MDGs), MDG 6 calls for unprecedented action to halt and begin to reverse the AIDS epidemic. As the United Nations Member States implicitly recognized when they endorsed the Millennium Declaration, the persistent burden associated with communicable diseases undermines efforts to reduce poverty, prevent hunger and preserve human potential in the world’s most resource-limited settings. AIDS remains an unfinished MDG, underscoring the need for continued and strengthened international solidarity and determination to address this most serious of contemporary health challenges. The latest ‘Global Report’ highlights continued progress towards the Global vision of zero new HIV infections, zero discrimination and zero AIDS – related deaths. The annual number of new HIV infections continues to decline, with especially sharp reductions in the number of children newly infected with HIV. More people than ever are now receiving life-saving antiretroviral therapy, contributing to steady decline in the number of AIDS-related deaths and further and buttressing efforts to prevent new infections.

Acquired Immunodeficiency Syndrome (AIDS) has emerged as one of the most serious public health problem in the country after reporting of the first case
in 1986. The initial cases of HIV/AIDS were reported among commercial sex workers in Mumbai and Chennai and injecting drug users in the north-eastern State of Manipur. The disease spread rapidly in the areas adjoining these epicentres and by 1996 Maharashtra, Tamil Nadu and Manipur together accounted for 77 percent of the total AIDS cases. Out of these, Tamil Nadu reporting almost half the number of cases in the country. However, the overall prevalence in the country is very low, as compared to many other countries in the Asia-Pacific region.

There are a few countries in the world where the population is very high and India is also one among such countries. It is matter of concern that in India also the incidence of HIV is very high. Since the population is very high the prevalence of HIV and also its spread is also very high. In 2006 UNAIDS estimated that there were 2.4 million people living with HIV in India. In 2009 the figure has gone up to 3.1 million. At the beginning of the 1990 the government has set up an organization called NACO (National AIDS Control Organization) to formulate the policies for prevention and control programs. The national AIDS control programs (NACP) was also formulated for HIV prevention. In 1999 the second phase of national AIDS control program (NACP-II) was formulated with the main aim of prevention of HIV transmission.

Many programs which targeted the intervention programs were brought in to practice. At present many programs of practical use and effective in the control of HIV spread are being implemented so that the rate of spread is arrested to a considerable level. During 2013-2014 National AIDS control strategies especially with high risk groups, such as female sex workers (FSW), Transgender (TG),
injecting drug user (IDU). The Link Workers Scheme which is the community based program was implemented to being in effective in HIV prevention.

The department of AIDS control successfully implemented the condom promotion program so that the spread is arrested. Programs relating to blood transfusion are also efficiency implemented. One of the interesting achievements is that the test for the HIV infected was carried out at the same time the counselling for the HIV infected was implemented. The information education and communication programs were given greater importance and the people were exposed to the information relating to HIV and its consequence and methods and strategies to avoid the infection.

**Use of Mathematics and Statistics in Modelling HIV/AIDS Epidemic**

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

- 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 strategies of prevention and control; that can be applied according to the severity of the epidemic in the different areas (Tan (2000)).
• The mathematical and statistical models can provide qualitative insight even when data are lacking or not readily available and they can help prioritize data collection.

• 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 treatment and/or vaccine, and may be a cure in the near future.

• The models can help reveal important parameters.

• 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.

• The knowledge of parameters can help to develop both mathematical and statistical models which can give computer simulations to compare different treatment outcomes.

• Models can be used to estimate simulation data on the basis of the known facts.

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 analysis of the data, the Gamma, Gompertz, Lognormal, Normal and Weibull distributions were used to model the distribution function \( F(t) \) of the incubation period (Brookmeyer and Gail (1984), Anbupalam et al. (2002)). The advantages and disadvantages of using each of these models are outlier. In particular, the Weibull model is used in
situations where it hypothesized that the hazard function $\lambda(t)$ increases indefinitely and is proportional to a power of time from infection. The hazard function quantifies how the risk of AIDS evolves with time from infection and is given by

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

Where $f(t) = F'(t)$ and $S(t) = 1 - F(t)$ are the probability density function and the survival function of the incubation period respectively. However, as they have pointed out, the hazard function $\lambda(t)$ should be consistent with epidemiological data and with theoretical consideration of the pathogenesis of HIV infection. Not much attention has been paid to the formulation of the distribution function (hence the hazard functions) of the latent and the incubation periods by considering the stochastic behavioural aspects of the members of the population work study.

**Some Preliminary Concepts and Results**

The following are some of the basic, existing and also recently developed concepts in mathematical statistics and probability theory that are used to develop some stochastic models that are discussed in this thesis.

**Shock Model and Cumulative Damage Process**

The concept of life as an expendable or usable feature over time has recently become a new line of development which is attractive since it immediately includes the concept of dynamic change or fatigue failure and latent. Physical theories the terms of “cumulative damage” which is important for the
concept instantaneous damage which cumulates to a largely unknown threshold value beyond which the system fails, and also the rate at which this threshold is approached. The distribution of these threshold values in terms of time is the accumulation of damage, but they all appear to be resolvable in terms of stochastic process (Medhi (2015), Chin Long Chiang (1968) and Lawless (1981)). This is an attractive concept and one which lends itself to intuitive interpretations of value, including the behaviour of complex mechanisms.

We consider a device exposed to shocks. We suppose that shocks cause damage and that damage accumulates additively. Let the device fail when the total damage exceeds a threshold level. We shall assume that the damages \( X_1, X_2, \ldots, X_n \) caused by successive shocks are mutually independently identically distributed random variables with distribution function \( F(\cdot) \), independent of the threshold whose distribution function is \( G(\cdot) \). Then the probability that device survives ‘k’ damages is denoted as,

\[
\overline{F}_k = \int_c^{\infty} F_k(x) \, dx, \quad k = 1, 2, \ldots
\]

Where \( F_k(x) \) is the k fold convolution of \( F(x) \) with itself and \( F_c(x) = 1 \) for \( x \geq 0 \) and otherwise. The reliability \( R(t) \) of the device is,

\[
R(t) = \sum_{k=t}^{\infty} \overline{F}_k \, V_k(t)
\]

Where \( V_k(t) \) is the probability that k damages are caused during \((0, t]\). The above model has been considered by Esary et al. (1973), Hameed and Proschan (1973)
with the underlying process generating the shocks as Poisson process, non
homogeneous Poisson process and birth process respectively.

**Setting the Clock Back to Zero (SCBZ) Property**

In stochastic processes we can consider a sequence of random variables. Each random variable has an associated probability distribution. So, the probability distribution function of random variable $X$ is denoted as $f(x)$. The corresponding distribution function is denoted as $F(x)$ and $S(x) = 1 - F(x)$ is called the survivor function. For every probability distribution, there are correspondingly one or more parameters. For example, if a random variable $X$ is distributed as exponential with parameter $\theta$ then we write it as $X \sim f(X, \theta) = \theta e^{-\theta t}$. There is a property called the Lack of Memory Property (LMP), which says that the life time of a component like that of an electric bulb is such that the past length of life time completed by the component has no influence over its lifetime in the future. The exponential distribution satisfies this property. A slight modification of this property has been suggested by Raja Rao and Talwaker (1990).

This property is called the setting the Clock Back to Zero Property (SCBZ). According to this property, the probability distribution of the random variable $X$ which is $f(x, \theta_1)$ undergoes a change of parameter after a particular value of $X$ denoted as $x_C$ and it is $f(x, \theta_2)$ whenever $X > x_C$. This property is indicated by a condition denoted as follows $\frac{S(x + x_C, \theta_1, \theta_2)}{S(x_C, \theta_2)} = S(x_C, \theta_2)$ where $S(x_C, \theta)$ is the survivor function.
Three Parameter Weibull Distributions

The use of Weibull distribution to describe real phenomena has a long history. This distribution was originally proposed by the Swedish physicist Waloddi Weibull. He used it for modelling the distribution of breaking strength of materials. Since then it has received applications in many areas. For a comprehensive review of applications, we refer the readers to Johnson et al. (1994) and Murthy et al. (2004). The probability density functions (pdf) of a three-parameter Weibull distribution.

\[
f(x) = \frac{\alpha}{\beta} \left( \frac{x-\sigma}{\beta} \right)^{\alpha-1} e^{-\left( \frac{x-\sigma}{\beta} \right)^\alpha}; \quad x > \sigma, \quad \alpha > 0, \quad \beta > 0.
\]

and the cumulative distribution function is

\[
F(x) = 1 - e^{-\left( \frac{x-\sigma}{\beta} \right)^\alpha}
\]

The corresponding survival function is

\[
S(x) = 1 - e^{-\left( \frac{x-\sigma}{\beta} \right)^\alpha}
\]

and the hazard function

\[
h(x) = \frac{\alpha \left( \frac{x-\sigma}{\beta} \right)^{\alpha-1} e^{-\left( \frac{x-\sigma}{\beta} \right)^\alpha}}{1 - e^{-\left( \frac{x-\sigma}{\beta} \right)^\alpha}}
\]

Respectively, for \( x > \sigma, \ \alpha > 0, \ \beta > 0 \), the parameters, \( \alpha, \ \beta \) and \( \sigma \) are known as the shape, scale and location parameters, respectively.
Change of Distribution at a Change Point

The concept of Setting the Clock Back to Zero (SCBZ) property indicates that a random variable $X$ with density function $f(x)$ undergoes a parametric change after a particular value of $X$ denoted as $x_c$. This is a slight modification of a lack of memory property. An extension of this concept leads to the concept of change of distribution after a change point. For example, if $X$ is a random variable denoting the life time of the component and $f(x, \theta)$ is the probability density function, we say that a random variable undergoes a change of distribution after a change point when the following condition is satisfied:

The random variable $X$ has the p.d.f. $f(x)$ and c.d.f. $F(x)$ whenever $X \leq x_c$ and it has the failure rate p.d.f. $h(x)$ with c.d.f. $H(x)$ whenever $X > x_c$, $x_c$ is called the change point. It can be noted that

$$\int_0^{x_c} f(x)\,dx + \int_{x_c}^{\infty} h(x)\,dx = 1$$

This property was initially introduced by Stangl (1995). An application of this property in shock model and cumulative process has been discussed by Suresh Kumar (2006).

Three Parameter Generalized Exponential Distribution

Gupta and Kundu (1999) introduced a new distribution called Generalized Exponential Distribution (GED). This distribution is very important when a skewed distribution is needed. This new family of distribution functions is always positively skewed, and the skewness decreases as both the shape parameters
increase to infinity. Interestingly, the new three-parameter distribution has increasing, decreasing, Uni-model and bathtub shaped hazard functions.

Exponential distribution is the most exploited distribution for life data analysis, but its suitability is restricted to constant hazard rate. This distribution can be used quite effectively in situations where a skewed distribution is needed. The exponential distribution is one of the most versatile distributions. The fact that the generalized exponential distribution on (GED) can be an excellent approximation to either the Gamma distribution or the Weibull distribution is very important.

Gupta introduced the three parameter generalized exponential distribution. We say that the random variable $X$ has a generalized exponential distribution if $X$ has the probability density function (pdf).

$$h(y; \alpha, \lambda, \theta) = \alpha \lambda (1 - e^{-\lambda(x-\theta)})^{\alpha-1} e^{-\lambda(x-\theta)}; \quad x > \theta, \quad \alpha, \lambda > 0.$$ 

and the cumulative distribution function is

$$H(y; \alpha, \lambda, \theta) = (1 - e^{-\lambda(x-\theta)})^\alpha; \quad x > \theta, \quad \alpha, \lambda > 0.$$ 

The corresponding survival function is

$$S(y) = 1 - (1 - e^{-\lambda(x-\theta)})$$

and the hazard function

$$h(y) = \frac{\alpha \lambda (1 - e^{-\lambda(x-\theta)})^{\alpha-1} e^{-\lambda(x-\theta)}}{1 - (1 - e^{-\lambda(x-\theta)})}$$

Here $\alpha$ and $\theta$ are the shape and location parameters, respectively.
Two-Parameter Burr-Type X Distribution

Burr (1942) introduced twelve different forms of cumulative distribution functions for modelling data. Among those twelve distribution functions, Burr-Type X and Burr-Type XII received the maximum attention. There is a thorough analysis of Burr-Type XII distribution in Rodriguez (1977), see also Wingo (1993) for a nice account of it.

In this thesis, we consider the Two-parameter Burr-type X distribution has the following Probability density function (pdf) is

$$f(x; \alpha, \lambda) = 2 \alpha \lambda^2 x e^{-\alpha \lambda^2 x} (1 - e^{-\alpha \lambda^2 x})^{\alpha-1} ; \quad x > 0, \quad \alpha > 0, \quad \lambda > 0.$$  

And the cumulative distribution function

$$F(x; \alpha, \lambda) = (1 - e^{-\alpha \lambda^2 x})^\alpha ; \quad x > 0, \quad \alpha > 0, \quad \lambda > 0.$$  

The corresponding survival function is

$$S(x; \alpha, \lambda) = 1 - (1 - e^{-\alpha \lambda^2 x})^\alpha$$

And the hazard function

$$h(x; \alpha, \lambda) = \frac{2 \alpha \lambda^2 x e^{-\alpha \lambda^2 x} (1 - e^{-\alpha \lambda^2 x})^{\alpha-1}}{1 - (1 - e^{-\alpha \lambda^2 x})^\alpha}$$

Where $\alpha$ and $\lambda$ are shape and scale parameters respectively.
Organization of the Thesis

In this thesis, we have discussed some of the issues relating to namely human immunodeficiency virus (HIV) and acquired immunodeficiency syndrome (AIDS) that have invaded the human race in the last thirty years by constructing the stochastic modelling of the dynamics of the viruses. The collaboration of medical scientists with scientists and theorists has in recent times made a big positive influence in containing spread of the Virus.

The contents of the thesis as arranged in the various chapters are briefly indicated below:

Chapter – I is devoted to a introduction on the origin, causes and spread of HIV/AIDS.

In Chapter – II a brief account of the biological aspects of infection from the technical point of view has been discussed.

In Chapter – III a brief summary of the research work carried out by various authors in this area of study has been given as the review of literature.

In Chapter – IV the study of stochastic model to estimate the expected time to seroconversion has been discussed; assuming the threshold level as Three-Parameter Weibull distribution. Using this the Mean and Variance are derived. Numerical illustration is also given.

In Chapter – V the estimation of expected time to seroconversion due to either antigenic diversity or virulence when virulence distribution undergoes a change is discussed. In this chapter, it is assumed that the virulence threshold is a
random variable which undergoes a parametric change after a truncation point and satisfies the SCBZ property. Using this property the expected time to seroconversion and its Mean are derived. Numerical illustration also provided.

In Chapter – VI the threshold following Three-Parameter Generalized Exponential distribution has been studied. The expected time to cross the threshold and variance are obtained. Numerical illustration is given.

In Chapter – VII a stochastic model of the estimation of the expected time to seroconversion of HIV infected and variance of the time to seroconversion have been derived, under the assumption that the threshold is a random variable distributed as Two-parameter Burr-type X distribution. In arriving at the expression for E(T), the expected time to seroconversion and variance of the seroconversion time V(T) have been obtained. It is supported by numerical illustration.

In Chapter – VIII a brief summary of results and conclusions obtained have been given. The possible areas in which the research could be taken in future have also been indicated.