CHAPTER I

INTRODUCTION

The Human Immunodeficiency Virus (HIV) and consequent Acquired Immune Deficiency Syndrome (AIDS) pandemic is one of the most serious socioeconomic and health problem prevailing all over the world especially in African countries. The first case of HIV infection was officially reported in 1986. Since then the pandemic continues to spread at an alarming rate. The adult HIV prevalence has increased from 1.8% in 1991 to 5% in 2013. The incidence of HIV infection and its spread involves a huge expenditure and a considerable part of the revenue of the government is spent to prevent the spread, of disease and also to give health care to the infected. The impact of HIV/AIDS in the workplace results in reduction of labour supply and increased medical expenditure. The increase in the orphans and disruption in economic performance are due to the spread of this infection. In many countries new programs are developed with a view to provide information regarding this infection and also the possible strategies to adopt to avoid the infection.

There are different modes of transmission of HIV and they are as follows

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 fetus or through injuries caused during child birth.
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 instilled optimism in the HIV/AIDS-affected community. Regretfully, it was later shown that treatment with AZT did not increase overall survival rate (Institute of Medicine 2005a) p43).
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 carry out 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 CD$_4$+ 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.

So the mathematicians and statisticians together with the research workers in biomedical areas try to develop suitable mathematical models which could be useful in the following aspects.

a. To develop mathematical models this could describe the rate the spread of the infection.

b. To identify the rate of antigenic diversity and virulence of the invading antigens.

c. To indentify antigenic diversity threshold and also the virulence threshold which are highly random in character and differ from one individual to another. If either antigenic diversity or the virulence crosses the threshold level of an individual then the seroconversion occurs. The expected time to seroconversion is derived as a mathematical formula which has practical field application.

These models are very much useful to determine the likely time at which an infected person becomes the seropositive provided the data regarding the intensity of exposure, the interarrival time between contacts are known.

The main objectives of this thesis is to derive some stochastic models to predict the likely time at which the seroconversion will occur, provided the data
regarding the necessary aspects are made available and the distribution of the random variable involved are found out fitting appropriate distribution for the data collected.

**HIV/AIDS in India**

Human Immunodeficiency Virus (HIV) is a lenti 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 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 epicenters 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 a 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 programs were implemented to target the increase in the 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 infection and its consequence and methods and strategies to avoid the infection.

**Background Information of HIV/AIDS**

Globally, HIV and AIDS has become a major public health issue and are posing a serious challenge to the developed as well as the developing world. It has become a leading cause of death in sub-Saharan Africa and in the worst hit countries, HIV and AIDS is reversing the gains of human development including life expectancy. In some of these countries, the epidemic is worsening the progress in human development by affecting the economic growth, human capital formation, health, education, and by increasing poverty and income inequalities (Mahbub-ul-Haq Human Development Centre, 2005).

As more and more women get infected and affected by HIV, the target of the Millennium Development Goals (MDG) of arresting and reversing the spread of HIV and AIDS by 2015 may not be met. The MDGs adopted by 189 countries,
including India, aim to promote gender equity and achieve universal primary education. It is feared that HIV and AIDS could be an impediment to achieving some of these goals as more and more women and girls get infected and affected by HIV and AIDS (UNDP, 2003). At the outset of the epidemic in the 1980s, women were considered marginally at risk from a virus that seemed to be mostly confined to the so-called high risk groups—intravenous drug users (IDUs), men who have sex with men (MSM) and sex workers. Now, HIV has infected tens of millions, many of them women, who are practicing monogamy within marriage or in a long-term relationship (Dixit, A.P. 2005). By the end of 2005, an estimated 40.3 million (36.7-45.3 million) people were living with HIV, worldwide. Close to 5 million people were newly infected with the virus in 2005 (UNAIDS/WHO 2005). Of these 40 million PLWHA, as many as 17.5 million i.e. More than 40 percent were women. As compared to 2003, one million more women were living with HIV in 2005. The “feminization” of the epidemic is most apparent in sub-Saharan Africa where an estimated thirteen and a half million (12.5 to 15.1 million) women live with HIV and women account for 57 percent of the infection among adults in this region. In the South and South–east Asia region, almost two million women now have HIV and women form more than one-fourth of the adults who are infected by the virus. Globally, there has been a dramatic increase in the number of young women being infected by HIV.

Young women account for over 60 percent of 15 to 24 year old PLWHA and they are 1.6 times more likely to be living with HIV and AIDS than young men (UNAIDS/ UNFPA/UNIFEM 2004).
According to NACO, in India, an estimated 5.21 million PLWHA in 2005, accounting for 13 percent of the PLWHA globally (NACO, 2005). Though the current prevalence rate is less than one percent of the country’s population, given the large population base, any rise in this ratio of the HIV-prevalence rates can push up the number of PLWHA to several millions. The rates of HIV infection amongst women in India are steadily rising. Women account for around 2 million of the approximately 5.2 million estimated cases of PLWHA, constituting 39 percent of all HIV infections. Of these, only 0.5 percent of the women are sex workers. Of the 1,11,608 cases of AIDS reported in the country till 31 July, 2005, females accounted for nearly 30 percent. The biggest HIV and AIDS risk for many women and girls is through heterosexual sex; almost 85 percent of infections in women result from sex with their husbands or primary partners.

In India, women are increasingly getting susceptible to HIV and a large proportion of new infections are occurring in women who are married and are infected by husbands who (either currently or in the past) frequent sex workers (See Barnett et.al. 2004, UNAIDS/WHO 2005). The surveillance data indicates that in high-prevalence states, the epidemic is spreading gradually from urban to rural areas and from high-risk groups to the general population. The epidemic continues to shift towards women and young people and is slowly moving beyond its initial focus among sex workers. HIV transmission through sex between men is also a major cause for concern in many areas of India as the research shows that many MSM also have sex with women. In 2002, behavioural surveillance in five cities among MSM found that 27 percent reported being married, or living with a female sexual partner.
Some Preliminary Concepts and Results Used

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. 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 damages 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 independent identically distributed random variables with distribution function $F(.)$, independent of the threshold whose distribution function is $G(.)$. Then the probability that device survives ‘k’ damages is denoted as,
\[ \bar{p}_k = \int_0^\infty F_k(x) dG(x), \quad k = 1, 2, \ldots \]

Where \( F_k(x) \) is the k-fold convolution of \( F(x) \) with itself and \( F_0(x) = 1 \) for \( x \geq 0 \) and otherwise. The reliability \( R(t) \) of the device is,

\[ R(t) = \sum_{k=0}^{\infty} \bar{p}_k V_k(t) \]

Where \( V_k(t) \) is the probability that \( k \) damages are caused during \((0, t]\). The above model has been considered by Essary 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 density 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 \( X \sim f(X, \theta) = \theta e^{-\theta x} \). 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 $x_0$ and it is $f(x, \theta_2)$ whenever $X > x_0$. This property is indicated by a condition denoted as follows

$$\frac{S(X + x_0, \theta_1, \theta_2)}{S(x_0, \theta_1)} = S(x_0, \theta_2)$$

where $S(x, \theta)$ is the survivor function.

**Change of Distribution at a Change Point**

The concept of 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 $x_0$. 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 probability density function $f(x)$ and cumulative distribution function $F(x)$ whenever $X \leq x_0$ and it has the probability density function $h(x)$ with cumulative distribution function $H(x)$ whenever $X > x_0$. $x_0$ is called the change point. It can be noted that

$$\int_0^{x_0} f(x) \, dx + \int_{x_0}^x h(x) \, dx = 1$$
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).

**Organization of the Thesis**

In Chapter I, gives a brief introduction of HIV/AIDS, its infections, surveillance, basic epidemiology and natural history of HIV/AIDS, background information of HIV/AIDS, are discussed.

In Chapter II, a brief account of basic concepts and the biological aspects of HIV transmission from the technical point of view have been discussed.

In Chapter III, research articles have been reviewed relating to the current work in the recent past.

In Chapter IV, the expected time to cross the antigenic diversity threshold in HIV infection using Shock model approach has been obtained. The expected time to cross the antigenic diversity threshold of the human immune system has been estimated by using suitable Stochastic models. Several variations of these models have been discussed. Numerical illustration is also discussed.

In Chapter V briefly gives the method of estimating the expected time to seroconversion of HIV infected when both antigenic diversity threshold and virulence threshold satisfy SCBZ property. The likely time at which the seroconversion of HIV infected takes place is a vital event indicating the progression of the infection. The antigenic diversity of the invading antigens due to successive contacts increases and similarly the virulence also increases.
The seroconversion occurs if either the total antigenic diversity crosses the threshold level or the total virulence crosses the threshold level. Using the Shock model approach the expected time to seroconversion has been derived.

It is assumed that the antigenic diversity threshold is a random variable which has a distribution that has the change of parameter. Numerical illustrations are also provided.

In Chapter VI, 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 under goes a parametric change after a truncation point and satisfies the SCBZ property. Using this property the expected time to seroconversion and its variance are derived. Numerical illustration is also provided.

In Chapter VII, a Stochastic model in the study of HIV/AIDS epidemic and its progression is discussed. Numerical illustration is also provided.

In Chapter VIII, the estimation of time to seroconversion when the antigenic diversity threshold has Generalized Rayleigh Distribution is discussed. The expression for \( E(T) \), the expected time to seroconversion and variance of the seroconversion time \( V(T) \) have been obtained.

A detailed summary and conclusions based on Chapter III to Chapter VIII is presented in Chapter IX.