INTRODUCTION

1.1 Background

Eventhough enormous progress in prolonging and improving the quality of life of those infected with Human Immuno deficiency Virus (HIV) have been made, the world still has neither a cure for, nor a vaccine to prevent this disease. Human Immuno deficiency Virus (HIV) is the causative agent responsible for AIDS which was recognized for the first time in the United States in 1981 (CDC, 1982) and later in India in 1986 (NACO, 1994). The sharp increase in the rate of infection and spread of HIV is a matter of concern to the medical persons, researchers and for those in governance of the different countries in the world.

Human Immuno deficiency Virus (HIV) belongs to the family of retroviruses, whose genetic material is RNA. In 1984, researchers discovered the primary causative viral agent, the Human Immuno deficiency Virus (HIV-1). In 1986, a second type of HIV, called HIV-2
was discovered in West Africa, where it might have been present decades earlier. AIDS is first and foremost a consequence of behavior: it is not who one is, but what one does, that determines whether he or she will be exposed to HIV (Fishbein, 2000).

AIDS is preventable disease; and new medicines can help people with AIDS live for longer periods. AIDS is the most advanced stage of HIV infection. The definition of AIDS includes all HIV-infected people who have fewer than 200 CD4 cells per microliter of blood. The CD4 cell count is a key measure to a healthy immune system. The lower the count, the greater the damage HIV has done. Anyone who has less than 200 CD4 cells is considered to have AIDS. CD4 counts are used together with viral load (the amount of viral particles that prevails in the blood) to estimate how long someone will stay healthy.

The United Nations Aids Department / World Health Organization has reported that the HIV prevalence is leveling off and there is a fall in the number of new infections globally. Although HIV/AIDS is showing a decline, it remains one of the leading obstacles to health and development for poor countries. There are still a huge number of people infected and affected by HIV. In 2007, around 33.4 million people were estimated to be living with HIV globally, of which about 2.7 million people were newly infected and around 2.0 million lost their lives due to AIDS in the same year. In fact, Sub-Saharan Africa accounts for 22.4 million infections, which is about 67% of the total HIV burden. The number of people estimated to acquire new infections is around 1.9 million accounting for 68% of the total number of new infections.
1.1. Background

The transmission of HIV through different modes is the factor for the spread of this epidemic. The prevalence of this infection has assumed alarming proportions in the past two decades all over the world. The increase in the number of HIV infected is a matter of concern not only for the government but also for the social organizations. The rehabilitation of the infected by providing an Anti Retroviral Therapy (ART) is very expensive and considerable amount has to be set apart for this purpose. The psychological problems and social apathy are all adding to the magnitude of the problem. Hence serious efforts have been put up by researchers to contain this problem. Since no cure is still available, the medical researchers are devoting a considerable time for finding medicines to arrest the spread of the infection as well as to reduce the suffering of the infected.

Globally, 32.2 million-38.8 million people were living with HIV at the end of 2012. There is a decrease from previous years, as more people are receiving the life-saving antiretroviral therapy. There were 1.9 million-2.7 million new HIV infections worldwide, showing a 33% decline in the number of new infections from 3.1 million-3.7 million in 2001. At the same time, the number of AIDS deaths is also declining with 1.4 million-1.9 million AIDS deaths in 2012, down from 2.1 million-2.6 million in 2005.

The annual number of new HIV infections among adults and adolescents decreased by 50% or more in 26 countries between 2001 and 2012. Antiretroviral coverage among pregnant women living with HIV reached 62% in 2012, and the number of children newly infected with HIV in 2012 was 35% lower than in 2009. HIV prevalence among the people
who inject drugs remains high-up to 28% in Asia. India has 2.4 million HIV positive people. It is estimated that out of the total positive cases, 61% are male, 39% are female, and from among them 3.5% are children.

It is observed that there is no drugs are available for the cure of HIV infection and AIDS. The only possible method of avoiding the transmission as well as the outcome of the infection is to use preventive strategies against infection of HIV. The suffering from HIV can be mitigated as well as the life span of infected can be increased by adopting the so called Anti Retroviral Therapy (ART). Such drugs have fairly toxic side effects and they are exorbitantly expensive also. Hence, the strategies towards the propagation of information and education is much sought for. Many measures have been taken by the governments in different countries in various directions to counter the aftermath of the spread of HIV in a large scale. A meticulous health care can greatly improve the quality and length of life of people infected by HIV. Care includes practical, emotional and spiritual support for HIV positive people. The greatest difficulty is that this kind of care is not available to the people in the communities of poor resources, rehabilitation of the infected and keeping the isolated people in good spirit is really a challenge for the government and also for the social organizations.

The first National AIDS Control Programme (NACP) was launched in 1992 for prevention and control of HIV/AIDS in India. This was followed by NACP II in 1999 and NACP III in 2007. During the different phases of the programme, the focus shifted
from raising HIV/AIDS awareness to behavior change, from a national response to a more
decentralized response and to increasing involvement of Non Governmental Organizations
(NGOs) and networks of People Living with HIV/AIDS (PLHIV). NACP Phase-III has
the overall goal of halting and reversing the epidemic in India. This phase has, therefore,
placed the highest priority on preventive efforts by integrating prevention with care, support
and treatment through a four-pronged strategy:

(i) Preventing new infections in high risk groups and general population through
saturation of coverage of high risk groups with targeted interventions and scaled up
interventions in the general population.

(ii) Providing greater care, support and treatment to larger number of PLHIV.

(iii) Strengthening the infrastructure, systems and human resources in prevention, care,
support and treatment programmes at the district, state and national levels, and

(iv) Strengthening the nationwide Strategic Information Management System.

The U.S. Public Health Service (PHS) has made a series of recommendations
regarding HIV infection in the workplace. These recommendations explicitly say that the
transmission of HIV is unlikely even in work settings in which close non-sexual person-to-
person contact occurs.
These occupations include:

(i) Food Service workers, including cooks, waiters, bar tenders and airline attendants,

(ii) Personal-service workers, including hair-dressers, barbers, cosmetologists and manicurists and

(iii) Health care workers, including nurses, doctors, dentists, optometrists, lab technicians and emergency medical technicians.

Women in India are more vulnerable to HIV infection because of their limited role in decision making and limited opportunity to discuss issues related to sex and sexuality. According to UNAIDS estimates 50% of new infections occur among women. In this context, informing the women about sexual health and empowering them to make decisions and negotiation with their partners on condom use, becomes essential. The first phase of a project on sexual health and AIDS awareness has been implemented in seven districts of Tamil Nadu.

Intensive research is in progress throughout the world in an effort to understand the AIDS epidemic and develop therapies and vaccines for eradicating the horrible disease. To analyze AIDS data, statisticians usually assume some parametric distributions for the HIV infection with due regard for the dynamics of the HIV epidemic and biology of HIV. It is important to note that the assumption on HIV infection and seroconversion distribution plays a vital role in the estimation and projection.
1.2 Some Important Concepts and Models of Stochastic Process

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

1.2.1 Stochastic process

Since the last century there have been marked changes in the approach to scientific enquiry. There has been greater realization that probability models are more realistic than deterministic models in many real life situations. Observations taken at a fixed period of time began to engage the attention of researchers in probability. This has led to the new concept of indeterminism.

Many a phenomenon occurring in physical and life sciences occur now not only as random phenomena but also as the ones changing with time or space. The scope of applications of random variables which are function of time or space or both has been on the increase. Families of random variables which are functions of time are known as stochastic processes. Stochastic process is concerned with sequences of events governed by probabilistic laws.
1.2. Some Important Concepts and Models of Stochastic Process

A stochastic process is defined to be simply an indexed collection of random variables \( \{x_t\} \) where the index \( t \) runs through a given set \( T \). The relationships are specified by considering the joint distribution function of every finite family of variables of the process. Many applications of stochastic process occur in physics, biology, medicine, psychology and other disciplines. For more details one may refer the book, A first course of stochastic process, by [66] Karlin and Taylor (1975).

1.2.2 Survival analysis

In survival analysis, a group or groups of subjects are followed for certain time period and for each subject there is a defined outcome. For a subject, the time period between the beginning of the follow-up and the occurrence of an event is defined as survival time. Often the event is called as failure. Usually the survival time can be thought of as years, months, weeks or days depending upon the nature of the problem and represented by the letter ‘ \( T \)’, a non-negative random variable.

The survival function estimates the probability that a subject survives longer than some specific time \( t \) (i.e.)

\[
\text{Survival function} = S(t) = P(\text{a subject survives longer than } t) = P(T \geq t), 0 \leq t < \infty
\]

Let \( F(t) \) be the cumulative distribution function of \( t \). Then,
1.2. Some Important Concepts and Models of Stochastic Process

The survival function has the following theoretical properties:

(i) Survival function is monotonically non-increasing,

(ii) As no event can occur before the start of the study, at time \( t \to 0 \), survival function takes the values 1, i.e., \( S(0) = 1 \) and

(iii) Theoretically, if any study period is increased to infinity, eventually no one will survive and at \( t = \infty \), i.e., \( S(\infty) = 0 \).

1.2.3 Shock Model and Cumulative Damage Process

The concept of shock model and cumulative damage process helps in the interpretation of the behavior of complex mechanisms. Any component or device is exposed to shocks which cause damage to the device or system which is likely to fail when the total accumulated damage exceeds a level called threshold. We assume 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 \( F(.) \), is independent of the threshold whose distribution function is \( G(.) \). Then the probability that the device survives ‘\( k \)’ damages is denoted as,

\[
\overline{P}_k = \int_0^\infty F_k(x) \, dG(x), \quad k = 1, 2, \ldots
\]
where \( F_k(x) \) is the \( k \) fold convolution of \( F(x) \) with itself and \( F_0(x) = 1 \) for \( x \geq 0 \) and \( F_0(x) = 0 \) for other values of \( x \). The reliability \( R(t) \) of the device is

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

where \( V_k(t) \) is the probability that \( k \) damages are caused during \((0, t]\). The above model has been considered by [43] Esary et al. (1973), with the underlying process generating the shocks as Poisson process, non homogeneous Poisson process and birth process. [92] Ramanarayanan (1976) has considered a cumulative damage process introducing the concept of alertness of the worker.

1.2.4 Order statistics

In shock model approach the time interval between successive contacts is a random variable. It is of interest to investigate the consequences by taking into consideration the influence of inter-arrival times between contacts. In doing so, the concept of order statistics can be incorporated to define the distribution of the random variable, which indicates the inter-arrival times.

Let \( X_1, X_2, \ldots, X_n \) denote a random sample from a population with continuous cumulative distribution function \( F_x \). Suppose \( X_{(1)} \) denotes the smallest order of the set \( X_1, X_2, \ldots, X_n \); \( X_{(2)} \) denotes the second smallest, and \( X_{(n)} \) denotes the largest order of the set. Then \( X_{(1)} < X_{(2)} < \cdots < X_{(n)} \) denote the random sample after arrangement in
increasing order of magnitude, and these are collectively termed as the order statistics of the random sample \( X_1, X_2, \ldots, X_n \). \( X_{(r)} \), for \( 1 \leq r \leq n \), is called the \( r \)th order statistics.

The subject of order statistics generally deals with the properties of \( X_{(r)} \) itself or functions of some subset of the \( n \) order statistics.

\[
f_{X_{(n)}}(y_n) = n! \int_{-\infty}^{y_n} \int_{-\infty}^{y_{n-1}} \cdots \int_{-\infty}^{y_2} f_X(y) \, dy_i
given \quad f_X(y) = n! \int_{-\infty}^{y} \int_{-\infty}^{y_2} \cdots \int_{-\infty}^{y_2} f_X(y) \, dy_i
dy_{i=1,2,\ldots,n}
\]

Similarly, for the smallest order element \( X_{(1)} \),

\[
f_{X_{(1)}}(y_1) = n! \int_{y_1}^{\infty} \int_{y_2}^{\infty} \cdots \int_{y_{n-1}}^{\infty} \int_{-\infty}^{y_1} f_X(y) \, dy_i \, dy_{i=1,2,\ldots,n-1}
\]

Contribution to the Study of Stochastic Models in AIDS Epidemiology

Ph.D. Thesis
1.2.5 Organization of the thesis

The following is the organization of various chapters of this thesis.

Chapter 1 contains a brief introduction to the various aspects of HIV infection in general and its implications. Some preliminary mathematical results used in the thesis are briefly explained in this chapter.

Chapter 2 gives a brief account of the biological aspects of HIV infection.

Chapter 3 gives a brief summary of research work carried out by various authors in this area of study is given as the Review of Literature.

In Chapter 4 a stochastic model for estimation of expected time to seroconversion of HIV infected and its variance are derived.

In Chapter 5 a stochastic approach to determine seroconversion time of HIV infected under alertness is presented.

In Chapter 6 a stochastic model to estimate the expected time to two sources of HIV transmission due to the sharing of unsterilized needle is presented.

In Chapter 7 a stochastic model for the estimation of time to seroconversion of HIV transmission using order statistics has been dealt with.

Chapter 8 gives the conclusion part of the thesis.