CHAPTER 1

MODELING OF HIV/AIDS AND RELATED CONCEPTS

1.0 INTRODUCTION

The Acquired Immune Deficiency Syndrome (AIDS) is a devastating disease caused by Human Immunodeficiency Virus (HIV) that is transmitted by either sexual or other contacts in which body fluids are exchanged. Following a few recognized cases among homosexual men in the United States in the year 1981, new cases of AIDS were subsequently reported in a majority of the countries throughout the world. It has now reached a pandemic proportion, as no country in the world is free from it. This epidemic ranks as one of the most destructive microbial scourges in human history and has posed a formidable challenge to the biomedical research and public health communities of the world.

AIDS and its related syndromes have also changed virtually every aspect of medicine and society at large. AIDS has affected basic science, clinical practice and social perspective. First and foremost, we were required to accept the reality that even at the beginning of 21st century, it is still possible for a previously unknown pathogen to initiate a pandemic that spared no country. Secondly we were made to realize that the distinction between those who perform basic research and engage in applied research on AIDS,
AIDS challenges the usual compartmentalization of medical disciplines. To specialize in AIDS one requires a depth of knowledge in almost every field of social and medical science. For those who view AIDS from a public health policy perspective, there must be a growing recognition that AIDS and poverty are strongly related. For those with a medical orientation or clinical agenda in AIDS, they will have multifaceted civil implications as to the rights and expectation of individuals who may already be facing oppression from society at large.

The global pandemic of HIV infection comprises many different epidemics, each with its own dynamics and influence because of many factors, e.g., time of introduction, population density, and cultural and social issues. Spread of the epidemic has varied considerably between developed and developing countries, depending on the culture as well as other social and behavioral patterns. Incidence rates have been the highest in developing countries where heterosexual transmission is most common.

The first case of AIDS was reported in India in the year 1986. Now India’s entry into the third phase of the HIV epidemic, as envisaged from the increasing number of HIV infections detected even among housewives and children, signals major AIDS crisis in the offing (Nagaraja Rao Chillale, 2002). The first phase of HIV was recognized when rising trend of HIV prevalence was established between the Commercial Sex Workers (CSW) in 1988 and the professional blood donors in 1989. The second phase
started after 1989 when several of the clients of CSW and blood recipients were found to be infected.

1.1 BIOLOGICAL ASPECTS OF HIV/AIDS AND ITS TRANSMISSION

AIDS is a condition in which the inbuilt immune mechanism of the human body would breakdown completely. The process is gradual but ultimately suppresses the immunity of the individuals. It is a medically accepted fact that the HIV is one among the causal agent of AIDS. Those who are affected by AIDS are susceptible to opportunistic infections like Candida, Mucormycosis and Aspergillus's etc.

1.1.1 The Pathogenic Process of HIV Infection

Within a few weeks of its entry into the blood stream of an individual, the HIV sets an insidious and progressive attack on the immune system of the individual by bonding itself to one of the T4 helper cells. The viral attachment to the cell is initiated by means of antibodies to the virus. On infecting the T4 cell, the viral ribonucleic acid (RNA) is injected into the target cell along with viral transcriptase and viral integrase. The viral reverse transcriptase transcribes the viral RNA into viral deoxyribonucleic acid (DNA) and the viral integrase bind the viral DNA with that of the host. The integrated viral DNA may remain latent or in an activated form. In the activated form, genomic RNA and messenger RNA are transcribed from the integrated viral DNA. The regulatory proteins such as tat and rev are translated from
messenger RNA. These proteins together with the genomic RNA cause the production of new HIV viruses, which bud on the cell wall. These buds accumulate on the cell wall and after a random length of time from the time of infection the infected cell disintegrates (i.e. the cell undergoes a lyses) releasing a random number of HIV viruses and this process continues indefinitely. This mechanism of killing the T4 cells takes place continuously. The HIV virus in the blood progressively destroys the immune-competence of the host. The viral load (the amount of free HIV in the blood) increases following infection and peaks at the time of sero-conversion (i.e. the time at which detectable levels of antibodies develop in the blood) and falls to a level (called set-point) by about 2 years thereafter and then remains at that level throughout the asymptomatic period. A low level of set point corresponds to a low risk of AIDS and a high level of set point corresponds to a high risk of AIDS. The viral load measured at arbitrary base line is a good prognostic marker at all stages of the development of AIDS. On the other hand, the T4 cell count in the blood decrease rapidly in the initial months following infection and thereafter at a slower rate. After a period of several years, when the level of T4 cells depletes to roughly 400 cells/mm³, the person exhibits symptoms and signs associated with HIV disease. These symptoms and signs do not meet the surveillance definition of AIDS and we say that the person is suffering from AIDS related complex (ARC). The level of T4 cells further continues to decrease to roughly below 200 cells/mm³ and AIDS defining diseases (ADD's) such as Kaposi's sarcoma and Pneumocystis carinii
pneumonia occur. At this stage, the patient is said to have developed AIDS (Moss and Bacchetti, 1989).

1.1.2 Modes of Transmission

HIV epidemic is a delicate and sensitive issue with social stigma. It is to be noted that HIV is not transmitted through air, water, food, insect bites, sharing toilet, coughing and sneezing, kissing, shaking hands or hugging. The four known transmission modes of AIDS virus are

i. Homo or heterosexual contacts

ii. Transfusion of infected blood products

iii. Sharing of unsterile needles

iv. From the mother to the child, either during pregnancy or during childbirth or during breast-feeding.

The most common mode of transmission is through sexual contacts. Another potential mode of transmission, which comes next, is through the transfusion of contaminated blood. Even though virus particles, very few in number, have been detected in saliva, tears and breast milk of individuals, the chances of infection through these modes are very remote (Pavri, 1992).

Poor awareness and knowledge about AIDS, increase in Sexually Transmitted Diseases (STD), long incubation period, low social status of women, poor medical services, associated social stigma and non-availability
of effective vaccine are the main reasons for the fast spread of HIV to all sections of population and across the country.

1.1.3 Test for HIV infection

For the diagnosis of HIV infection some indirect or antibody detection tests are available. The most commonly used test is called Enzyme Linked Immune Sorbant Assay (ELISA). However, it is not a confirmatory test although it is easier to carry out the same as it is less costly. Another test is the so-called Western Blot test, which is a confirmatory test. But it is very costly and requires the use of radioisotopes.

1.1.4 High Risk Groups

The following groups of persons are considered to be at high risk of HIV infection.

i. People who have sex with multiple partners who include CSWs, truck drivers, homosexuals, STDs clinic attenders, migrant workers, slum dwellers, traveling salesmen and street youth.

ii. Professional blood donors and recipients

iii. Intravenous drug abusers (IVDUs)

Though heterosexuals form the predominant risk group, it is noted that there is a rising trend of HIV infection in blood transfusion (Basu et al, 1998).
1.2 CURRENT GLOBAL SITUATION

According to the latest report by the Joint United Nations Programme on HIV/AIDS (UNAIDS) and the World Health Organisation (WHO), 2002, the AIDS epidemic claimed more than 3 million lives in 2002 and an estimated 5 million people acquired the HIV in 2002. The estimated total number of people living with HIV/AIDS is about 42 million, out of which 22 million are women and children. The following table gives the regional HIV/AIDS statistics at the end of 2002.

Table 1.2.1
Regional HIV/AIDS Statistics and features at the end of 2002

<table>
<thead>
<tr>
<th>Region</th>
<th>Adults and Children Living with HIV/AIDS</th>
<th>Adults and Children newly Infected with HIV</th>
<th>Adults Prevalence Rate (%)</th>
<th>% of HIV positive adults who are women (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sub-Saharan Africa</td>
<td>29.4 million</td>
<td>3.5 million</td>
<td>8.8</td>
<td>58</td>
</tr>
<tr>
<td>North Africa &amp; Middle East</td>
<td>550,000</td>
<td>83,000</td>
<td>0.3</td>
<td>55</td>
</tr>
<tr>
<td>South &amp; South East Asia</td>
<td>6.0 million</td>
<td>700,000</td>
<td>0.6</td>
<td>36</td>
</tr>
<tr>
<td>East Asia &amp; Pacific</td>
<td>1.2 million</td>
<td>270,000</td>
<td>0.1</td>
<td>24</td>
</tr>
<tr>
<td>Latin America</td>
<td>1.5 million</td>
<td>150,000</td>
<td>0.6</td>
<td>30</td>
</tr>
<tr>
<td>Caribbean</td>
<td>440,000</td>
<td>60,000</td>
<td>2.4</td>
<td>50</td>
</tr>
<tr>
<td>Eastern Europe &amp; Central Asia</td>
<td>1.2 million</td>
<td>250,000</td>
<td>0.6</td>
<td>27</td>
</tr>
<tr>
<td>Western Europe</td>
<td>570,000</td>
<td>30,000</td>
<td>0.3</td>
<td>25</td>
</tr>
<tr>
<td>North America</td>
<td>980,000</td>
<td>45,000</td>
<td>0.6</td>
<td>20</td>
</tr>
<tr>
<td>Australia &amp; New Zealand</td>
<td>15,000</td>
<td>500</td>
<td>0.1</td>
<td>7</td>
</tr>
<tr>
<td>Total</td>
<td>42 million</td>
<td>5 million</td>
<td>1.2</td>
<td>50</td>
</tr>
</tbody>
</table>

The HIV/AIDS pandemic has evolved in different ways in different parts of the world at varying speeds. In many regions it is still in its early stages. Sub-Saharan Africa is worst affected region in the world. This region has the highest prevalence with an average of 8.8% of the population infected with HIV/AIDS. At 29.4 million, this region has more people living with HIV/AIDS than all other regions of the world, out of which about 58% are women. The Caribbean is the region with second highest infection rates. Adult HIV prevalence is 2% and 50% of infections are women. Almost 1 million people in Asia and the Pacific acquired HIV in 2002, bringing to an estimated 7.2 million people living with the virus. About 490 000 people are estimated to have died of AIDS in the past years. Eastern Europe and Central Asia region is experiencing the fastest rate of new infection, especially in Russia and Ukraine. About 20 % of those living with HIV/AIDS are women. North Africa and the Middle East are slow but with a marked spread of HIV/AIDS.

In India, about 4 million people were living with HIV at the end of 2002. The AIDS prevalence rate is estimated to be less than 1 %. Although constituting only 1 % of the population, 4 million infected in India make it the second largest HIV infected population in the world. During recent years, the epidemic in several Indian states moved out from high-risk groups like injecting drug users, commercial sex workers and truck drivers into the
general population. Some states in India, like Maharashtra and Tamil Nadu have very high rates of HIV infection.

The epidemic in India is still growing at a very fast rate and there is a need to check the growth of the epidemic. Keeping this alarming problem in view, we have made attempts to project the HIV/AIDS epidemic in India and Tamil Nadu by developing various parametric models on the surveillance data in this thesis. This is the major thrust of the present research work.

1.3 APPROACHES FOR HIV/AIDS MODELING

In general, HIV/AIDS epidemic modeling is categorized based on the following four broad approaches but not mutually exclusive ones (Tan, 2000).

1.3.1 Deterministic Models

In this type of modeling the parameters such as number of susceptible individuals, infected individuals and number of AIDS cases are assumed to be deterministic. These models are described by a system with differential or integral equations. The progression of the epidemic is studied using these equations. Some of the deterministic models for AIDS epidemic were developed by Anderson (1988), Hyman and Stanley (1988), Jager and Ruittenberg (1988), Wilkie (1988), Anderson et al (1989), Hethcote et al (1991) and Anderson and May (1992).
1.3.2 Stochastic Models

Stochastic models assume that some of the key parameters are random variables. It is assumed that the HIV epidemic is a continuous time stochastic process. Stochastic models are considered to be more realistic than deterministic models and with some special assumptions, the results of deterministic models can be approximated through stochastic models. But there are studies, which show that stochastic models give a better interpretation of the epidemic than the deterministic models. Some of the literature on stochastic modeling of HIV/AIDS epidemic includes Mode et al (1988), Isham (1991), Tan and Wu (1998) and Tan and Xiang (1999).

1.3.3 Statistical models

The statistical models are developed based on AIDS epidemiological and survey data. These models make full use of the available data compared to deterministic and stochastic models. But in this type of modeling the mechanism and prior information system are usually not taken into consideration. The backcalculation approach for HIV/AIDS projection can be categorized into this type of modeling. Some of the literatures for statistical modeling of the epidemic are Jewell et al (1992), Bachetti et al (1993) and Brookmeyer and Gail (1994). Backcalculation approach is studied in detail in this thesis.
1.3.4 State Space Models

Wu and Tan (1995) have introduced the state space models for AIDS epidemic, which takes the advantage of stochastic and statistical models. The state space models were originally proposed by Kalman (1960) for engineering control and communication. This model was also used by Cazelles and Chau (1997) and Tan and Xiang (1998, 1999). A detailed description of the state space models is given in Tan (2000).

1.4 PROJECTION OF HIV/AIDS

Projections of HIV/AIDS using the statistical modeling approach are done based on the following three methods.

(i) Fitting a model to the incidence of HIV/AIDS and extrapolating the curves into the future (Healy and Tillet, 1988). The estimates obtained using this method depends on the mathematical function used and hence some function can produce anomalous results. Also this method is less efficient as this does not include important information on the epidemic like incubation period, infection density and nature of the spread of the epidemic.

(ii) The next approach is based on modeling the dynamics of the epidemic (Anderson et al, 1986 and Isham, 1988). This approach requires certain knowledge about mixing pattern of HIV individual with probabilities
of infection per contact, size of high risk behavior group, probabilities of infection through blood product, needle sharing etc. In developing countries like India, knowledge about these key parameters, in general, is incomplete. Also stochastic modeling of the epidemic demands many parameters, which are generally difficult to estimate due to limitation of appropriate data especially in the Indian context. There is a lot of literature on deterministic and stochastic models for the spread of HIV epidemic. Tan (2000) gives a good review of the stochastic models for the HIV epidemic.

(iii) One of the most popular methods used for projection of HIV/AIDS is the backcalculation method (Brookmeyer and Gail, 1986,1988). This method is used to reconstruct the past pattern of HIV infection and to predict the future number of AIDS cases, apart from knowing the present infection status. This method depends on three important factors namely, the incubation period distribution, incidence curve and the observed number of AIDS cases over a time period. There are also uncertainties associated with this approach because of lack of certain information about incubation period distribution, the effect of intervention therapy on incubation period and errors in reported AIDS incidence. However backcalculation method is very popular, as it requires few information and assumptions.
1.5 **BASIC CONCEPTS USED IN BACKCALCULATION**

Brookmeyer and Gail (1994) have presented the basic concepts in respect of the backcalculation method. The terminologies used are explained below:

(i) **Infection Rate**: This quantity represents the number of new HIV infections per unit time at calendar time. Infection rate is also called infection curve.

(ii) **AIDS Incidence**: AIDS incidence is the number of new cases that develop in a population per unit time (usually per year).

(iii) **HIV Incidence Rate**: The HIV infection and incidence are two related concepts. The incidence rate is the ratio of the infection at calendar time ‘t’ to the number of infected individuals in the population at that time period ‘t’.

(iv) **Prevalence Rate**: The prevalence is the number of people alive and infected with HIV at a calendar time ‘t’. The prevalence rate is the ratio of prevalence to the total number of population at the calendar time ‘t’.

(v) **Susceptible**: Susceptible individuals are referred as the non-infected individuals still at risk.
(vi) **Seroconversion**: Infected individuals remain seronegative until they develop detectable HIV antibodies. The event of development of HIV antibodies after infection is known as seroconversion. The seroconversion period is usually short and it has a median of 2 to 3 months.

(vii) **Incubation Period**: The time duration between seroconversion to AIDS is called incubation period. Some authors also define incubation period as the time between infections to development of AIDS. But these two definitions can be considered as equivalent since seroconversion period is usually short and infection is known only after HIV positivity. Moreover, the incubation periods are very long and highly variable across groups. Several models for incubation period distribution are described further in the thesis.

### 1.6 BACKCALCULATION METHODOLOGY

Brookmeyer and Gail (1986,1988) introduced backcalculation method for short-term projection of AIDS epidemic. This method uses a form of infection curve, either parametric or non-parametric, for the number of past HIV infections or equivalently a density function for HIV infections as noted by Ding (1995,1996). The time between HIV infection and the diagnosis of AIDS is known as incubation time and it is modeled by a known distribution.
Future AIDS incidence can be projected by the estimated infection curve and the known incubation distribution.

Most of the research on the projection of AIDS epidemic is based on the backcalculation method. A survey of research in this area is given by many authors like Bachetti et al (1993), Brookmeyer and Gail (1994) and Brookmeyer (1996). There are various sources of uncertainties associated with the backcalculation estimates of AIDS. A detailed study of uncertainties of backcalculation can be found in Brookmeyer and Gail (1994) and Mariotti and Cascioli (1996). Major sources of uncertainties may be due to the inaccuracies of reported AIDS cases, the assumptions about the incidence curve and the incubation period distribution. The inaccuracies in the reported AIDS cases may be due to the reporting delays, under diagnosis and under-reporting. Reporting delays of AIDS incidence has also been modeled by many authors including Brookmeyer and Damiano (1989), Harries (1990) and Bachetti et al (1993). Evans and McCormick (1994) observed that only very few studies address the problem of under-reporting. Various forms of incidence curves and several parametric incubation distributions have been used in the literature. Uncertainties of AIDS incubation time and its effect on backcalculation estimates are discussed by Dueffic and Castagliola (1999) and Gigli and Verdecchia (2000).
Bellico and Marschner (2000) have given methodology to include information from the results of surveillance to improve the accuracy of projection of AIDS cases. Bayesian approaches for AIDS projection have also received a lot of attention (Liao and Brookmeyer, 1995; De Angelis et al 1998). Swaminathan et al (2000) presented the survival experience of a group of HIV patients. Rao and Srivenkataramana (2001) discussed the problem of applying backcalculation to Indian data and proposed an alternative methodology to project HIV infections based on the information about seropositivity rate. In this thesis we have shown that the infection curve obtained using the seropositivity rate can be incorporated into the backcalculation method for projection of AIDS cases. Venkatesan (2002) discussed the various mathematical and statistical approaches for projection of HIV/AIDS epidemic. Projections using backcalculation method for Tamilnadu surveillance data is explored by Anbupalam, Ravanand Venkatesan (2002). It has been observed that the estimates obtained through backcalculation method are found to be close to the reported AIDS cases of Tamilnadu.

1.7 AIMS AND OBJECTIVES

In this thesis we have concentrated mainly on understanding the current state of epidemic and forecasting the future path via backcalculation method. The broad objectives of the present research study are:
i. To collect and unify the methods of construction of parametric models in the projection of HIV/AIDS epidemic.

ii. To propose and investigate new parametric models for the distribution of incubation period.

iii. To study the nature and extent of uncertainty in backcalculation due to incubation period distribution, incidence curve and likelihood construction.

iv. To provide HIV/AIDS estimates using surveillance data for India and Tamilnadu.

Chapter II deals with different incubation period distributions. Various approaches for the backcalculation method are discussed in Chapter III. Chapter IV contains a simulation study to quantify the uncertainties involved in backcalculation methodology. Chapter V analyses the results relating to the projection of HIV/AIDS in India and Tamilnadu.