Chapter 3

REVIEW OF LITERATURE

3.1 Introduction

The statistical studies on HIV throughout the world have focused on modeling methods for CD4+ cell changes, survival probabilities, progression of the disease, HIV incidence from prevalence, incubation distribution, transmission probabilities, short term or long term projection, and evaluating, alternative surrogate markers for assessment of progression and monitoring. In the studies relating to infection and spread of AIDS at the global level, mathematicians and statisticians have carried out remarkable studies in various areas focusing on social, medical and biological aspects. Their work has led to the development of mathematical and statistical models in the study of HIV infection and AIDS based on the assumptions of different hypothetical situations. It is observed that the mathematical tools applied in the analysis are quite elegant, in spite of the fact that many such models lack practical applicability in real life situations. The literature is rather very enormous
and it would be a formidable task to review all such results contributed by various authors. Hence, it is proposed to give a brief outline of some chosen papers in this chapter.

The papers previewed here may be classified as those pertaining to the following areas in the study of HIV infection and AIDS.

1. Models relating to the transmission and dynamics of HIV spread,

2. Models relating to the distributions of random variables (Latency period, Incubation period and Seroconversion time) and

3. Models relating to infectivity, projection and other aspects.

3.2 Models Relating to the Transmission and Dynamics of HIV Spread

[6] Anderson (1988) has discussed on the epidemiology of HIV infection taking into consideration the variable incubation period, infectious period and the heterogeneity in sexual activity. The author considers that a homosexual community of size $N$ can be divided into $X =$ number of susceptible, $Y =$ number of infected and $A =$ AIDS patients ($N = X + Y + A$). The simplest set of equations that are used for the transmission of HIV in a closed community (i.e., no influx of susceptible from outside and no deaths other than
those who die due to AIDS) is given by

\[
\begin{align*}
\frac{dX}{dt} &= -\lambda X \\
\frac{dY}{dt} &= -\lambda X - vY \\
\frac{dA}{dt} &= -vY - \alpha A \\
\frac{dN}{dt} &= -\alpha X
\end{align*}
\]

where the parameter \( v = 1/D \) defines the rate of leaving the infected class \( Y \) to join the AIDS class \( A \), where \( D \) is the average duration of stay in \( Y \).

Here \( \lambda \) is the per capita force of infection defined as

\[
\lambda = \frac{\beta CN}{N}
\]

where \( C \) is the average number of sexual partners per unit of time and \( \beta \) is the probability of infecting a susceptible partner. The expression for \( R_0 \) which is the average number of secondary cases of infection is obtained as \( R_0 = \beta CD \) with the assumption that the infected individuals are infectious throughout the duration of their stay in class \( Y \). The expression for doubling time \( t_d \), is given by

\[
t_d = t[ln(2)/(R_0 - 1)]
\]

The author has also discussed various extensions of this model taking into consideration variable incubation, infection periods and also the variations in the rate of sexual partners.
The use of mathematical models to understand the AIDS epidemic has been presented by [57] Hymann and Stantley (1988). The authors have indicated how the various factors, qualitative and quantitative, should be incorporated into a mathematical model that is used for depicting the spread of AIDS epidemic. The concepts like population risk structure, the sexual activities and their impact on risk, the drug use etc., have been discussed in detail in this paper. In addition to this the authors have given some simplified mathematical models for spread of the epidemic.

[58] Isham (1988) has given a review of the mathematical modeling of the transmission dynamics of HIV infection and AIDS. The paper deals with a simple epidemic model of deterministic type is discussed initially. A fixed population of size n is separated into two groups namely a group of \( X(t) \) the susceptible and \( Y(t) \) the infectives, where \( X(t) + Y(t) = n \) and \( X(t), Y(t) \) are sufficiently large so that they can be regarded as continuous variables. Assuming the population mixes homogeneously so that in any small time interval \( (t, t + \delta) \) the number of contacts between susceptible and an infective is proportional to both \( X(t) \) and \( Y(t) \) (and \( \delta \) ) and that a fixed proportion of these contacts results in the susceptible becoming infected. It has been shown that the number of new cases of infection in the time intervals is \( \alpha X(t), Y(t), \delta \) for some \( \alpha \) which is a constant of proportionality, \( X(t) \) satisfies the differential equation

\[
\frac{dX(t)}{dt} = -\frac{\alpha X(t)}{Y(t)} = \alpha X(t)[n - X(t)]
\]
and the solution of this equation is given by

\[ X(t) = nX(0)[X(0) + [n - X(0)] \exp(nat)]^{-1} \]

\(dy(t)/dt\) is the rate at which the new infections occur and it can be obtained from the solution of the differential equations given above. Assuming \(X(0) \approx n\), for \(t\)

\[ Y(t) \approx Y(0)e^{nat} \]

The expression for doubling time is obtained as

\[ t_d \approx (n\alpha)^{-1}\ln2 \]

The author has also discussed a simple model for the spread of AIDS in terms of stochastic behavior and obtained a deterministic approximation to the stochastic process. In doing so, a number of assumptions are made. They are enumerated as follows:

(i) The spread of HIV infection is within a closed male homosexual community,

(ii) The population of a fixed size \(n\) at time \(t\) is divided into \(X(t)\) susceptible and \(Y(t)\) infectives,

(iii) The latent period of infection is considered to be negligible,

(iv) Each susceptible acquires new sexual partners at a rate \(k\),

(v) The population mixes homogeneously so that at time ‘\(t\)’ the probability that such a
partner is an infective is $Y(t)/n$ and

(vi) $\beta$ is the probability of getting infected from a particular infective partner.

A deterministic approximation of the stochastic process is given by the differential equation

$$\frac{dX(t)}{dt} = \left[-\beta KX(t)Y(t)\right]/[n]$$

satisfied by $X(t)$. Assuming that at time 0, the number of infectives is small, the expression for $Y(t)$ is

$$Y(t) \approx Y(0)e^{-\beta K t}$$

The expression for doubling time is

$$t_d \approx (\beta k)^{-1} \ln 2.$$
of persons, namely $S$ (Susceptible person), $L$ (Latent person), $I$ (Infective person), $A$ (AIDS case) $S(t)$, $L(t)$, $I(t)$ and $A(t)$ are taken to be the number of persons in the four categories at time $t$. A set of assumptions are also provided by the authors before developing the model. These assumptions include

(i) Homogeneous mixing of persons among the category $S$ and $I$,

(ii) $S(t)$ is assumed to be large for all $t \geq t_0$ so that $S(t)$ is assumed to be a deterministic function of $t$.

Under some assumptions regarding AIDS spread ($S \rightarrow L$), latency ($L \rightarrow I$) and incubation ($I \rightarrow A$), the probability generating function (pgf) of $L(t)$, $I(t)$ and $A(t)$ at time $t_0$ is given by

$$ q(t_0, t) = Q(x, y, z, t_0, t) $$

Using the p.g.f, the first order differential equation called Kolomogorov’s forward equation for the p.g.f has been obtained. The expected value of $L(t)$, $I(t)$ and $A(t)$ are also obtained. The effects of changing the contact rate between the susceptible person and the infective person is also investigated in this paper.

[22] Billard and Zhao (1991) have discussed a three stage stochastic epidemic model with applications to AIDS. In the three stage model discussed, the assumption is that at time $t$ the population size is $N$, of which $X(t)$ are infected individuals, and $Y(t)$ the total
number of AIDS cases so that $S(t)$, the number susceptible individuals in the population,

$$S(t) = N - X(t) - Y(t)$$

It is also assumed that AIDS epidemic is a time continuous Markov process. The infinitesimal transition probabilities in the time interval $(t, t + h)$ are

$$Pr\{X(t + h) = x + 1, Y(t + h) = y|[X(t) = x, Y(t) = y]\} = \lambda(x, y, t)h + o(h)$$

$$Pr\{X(t + h) = x - 1, Y(t + h) = (y + 1)|[X(t) = x, Y(t) = y]\} = \mu(x, y, t)h + o(h)$$

$Pr\{\text{two or more changes in } (t, t + h)\} = o(h)$

where $o(h)$ is defined by $\lim_{h \to 0} \frac{o(h)}{h} = 0$.

Let us denote

$$P_{x,y}(t) = Pr\{[X(t) = x, Y(t) = y]|X(0) = x_0, Y(0) = y_0]\}.$$ 

Then the forward differential difference equations can be written as

$$\frac{d}{dt} P_{x,y}(t) = -[\lambda(x, y, t) + \mu(x, y, t)]P_{x,y}(t) + \{\lambda(x - 1, y, t)P_{x-1,y}(t)\}$$

$$+ \{\mu(x + 1, y - 1, t)P_{x+1,y-1}(t)\} \text{ for } (x, y) \in B,$$

where $B$ is the state space of the Markov process. The solution of the set of a differential difference equations has been obtained in this paper. The expression for the mean and variance of AIDS cases in a closed population and also in an open population have been
[76] Mode (1991) has discussed a stochastic model for the development of AIDS epidemic in a heterosexual population. The author has listed out a number of classical models which have not taken into account the concept of bisexual population. The author has introduced a two sex model for the spread of HIV in a heterosexual population. The progression of HIV disease in any individual is described using six states $e_0, e_1, e_2, e_3, e_4$ and $e_5$ where $e_0$ is the susceptible state, $e_1$ is the infected but not seropositive state, $e_2$ is the seropositive but asymptomatic state, $e_3$ is the AIDS related complex state, $e_4$ state of full blown AIDS and $e_5$ is the death due to AIDS. The conditional probabilities governing the transitions among the states are assumed to be constant over time. Couples in partnership are taken into account in a heterosexual population; and the state of the couples is denoted $j, k$ which means that the female in state $e_{jk}; j,k = 0, 1, 2, 3, 4$ which indicates that both the partners are alive. Based on these assumptions and also taking into account the risk of infection due to the use of drug intravenously, a matrix of probabilities $B$ is defined. In this paper using random functions, the course of the epidemic has been obtained. The results have been obtained by using computer simulation.

[10] Arca et al. (1992) have authored a paper on the interaction between intravenous drug users and heterosexual population. A general mathematical model related to the transition dynamics of HIV infected is given in this paper. A compartmental structure with three compartments namely Susceptible ($X$), Infected ($Y$) and Removed ($Z$) and
with two possible transitions from \( X \) to \( Y \) and \( Y \) to \( Z \), is considered. The change per unit in the number \( X \) of susceptible is given by

\[
\frac{dX}{dt} = -\lambda(X, Y, t)X(t)
\]

Here, \( \lambda(X, Y, t) \) is the force of infection at ‘\( t \)’ given by

\[
\lambda(X, Y, t) = c \frac{Y(t)}{X(t) + Y(t)} + \beta(t)
\]

where, \( c \) is the rate at which people establish contacts, \( \beta \) is the probability of getting infected in a single contact. Similarly the equations for the infected and removed are

\[
\frac{dY}{dt} = \lambda(X, Y, t)X(t) - \nu Y(t)
\]

\[
\frac{dY}{dt} = \nu Y(t)
\]

where, \( \nu = [E(D)]^{-1} \) which gives the constant rate at which the infected developed AIDS, and \( D \) is the length of the incubation period.

[85] Perelson et al. (1993) have discussed the dynamics of HIV infection of \( CD4 + T \) cells. A model for the interaction of HIV with \( CD4 + T \) cells is considered taking four different populations namely uninfected \( T \) cells, latently infected \( T \) cells, actively infected \( T \) cells and free of virus. Two steady states such as uninfected state with no virus present and an epidemically infected state in which virus infected \( T \) cells present are considered in this model. The model mainly of HIV uses the fact that the depletion of \( CD4 + T \) cells
as a consequence of HIV infected. A model for $T$ cells growth in an uninfected is first considered. The $T$ cell dynamics is described by the equation

$$\frac{dT}{dt} = S + rT \left(1 - \frac{T}{T_{\text{max}}}\right) - \mu_T T$$

where $T$ is the number of $CD4+T$ cells as measured in the blood. $S$ is the rate of supply of immune complement $T$ cells from precursors in the thymus. $\mu_T$ represents the average per capita death rate of $T$ cells, $r$ is the average specific $T$ cell growth rate. A model for the influence of HIV on $T$ cell growth is also considered. The model is given by means of a set of differential equations.

$$\frac{dT}{dt} = S - \mu_T T + rT \left(1 - \frac{T + T^* + T^{**}}{T_{\text{max}}}\right) - k_1 VT$$

$$\frac{dT^*}{dt} = k_1 VT - \mu_T T^* - k_2 T^*$$

$$\frac{dT^{**}}{dt} = k_2 T^* - \mu_b T^{**}$$

$$\frac{dT^*}{dt} = N\mu_b T^{**} - k_1 VT - \mu_v$$

where $T^*$, $T^{**}$ denote the concentration of latently infected and actively infected $CD4+$ cells. The concentration of free infectious virus particles is denoted by $V$. The values of $T^*$ and $T^{**}$ are obtained. In addition to this the stability of the infected state and the dynamics of $T$ cells depletion is also discussed.

[23] Billard and Zhao (1994) have introduced a multistage non homogeneous Markov model for AIDS epidemic. To start with, the authors take a five stage stochastic
3.2. Models Relating to the Transmission and Dynamics of HIV Spread

The population at risk is of size $N$ and divided into five categories susceptible, infected, seronegative, seropositive asymptomatic, pre AIDS and AIDS. The number of persons in these categories are denoted as $X_4(t), X_3(t), X_2(t), X_1(t)$ and $X_0(t)$ with $\sum_{i=0}^{4} X_i(t) = N$. $P_{X_0}(x(t_0, t))$ denotes the conditional probabilities of finding the system at state $X = (X_4, X_3, X_2, X_1, X_0)$ given that it was at the instant $t_0$ in the state $X_0$.

$$P(X, t) = P_{X_0, x}(t_0, t) \text{ for } X \in S \text{ and } P(X, t) = 0 \text{ for } X \in S.$$  

The differential difference equations for this model are

$$\frac{d}{dt}P(X, t) = -\left(\sum_{j=1}^{4} \lambda_j(X, t)\right) + \lambda_1(X + e_4 - e_3, t)P(X + e_4 - e_3, t)$$

$$+ (\lambda_2(X + e_3 - e_2, t)P(X + e_3 - e_2, t))$$

$$+ (\lambda_3(X + e_2 - e_1, t)P(X + e_2 - e_1, t))$$

$$- (\lambda_4(X + e_1 - e_0, t)P(X + e_1 - e_0, t)) \text{ for } X \in S$$

where $e_i$ is the five component vector with elements

$$e_\nu = \delta_{\nu i}, \ i, \gamma = 4, 3, 2, 1, 0.$$

The above equations have been solved by using a technique developed by [109] Severo (1969) and [21] Billard (1973). The results of this model are extended to the case of a general $m + 1$ multiple stage models.

Modeling the effects of treatment and behavioural change in HIV transmission
dynamics has been discussed by [54] Hernandez and Hsich (1994). In this model the authors considered two types of infected individuals which are infected but do not know their serological status and therapeutical treatment. The two groups of infectives differ in their incubation time and the probability of disease transmission. There are several studies related to transmission dynamics of serological status on the sexual activity, behavioural changes and prevalence of the infection.

([55] Hethcote et al. (1991), [49] Gail et al. (1990), [7] Anderson et al. (1991) and [24] Brauer et al. (1992)). In this paper the authors considered only a male homosexual population whose infected individuals belong to either of the two compartments. The first is composed of those recently infected individuals that have not changed risky sexual behavior and the second one is treated individuals. Infected individuals enter this compartment after spending some time in the previous one. The speed at which they are recruited depends on the rate at which newly infected individuals are detected and on the effectiveness of the treatment program. The authors also developed the qualitative analysis of the model at the disease-free equilibrium to determine the relative importance of changes in incubation time, probability transmission and sexual behavior for an HIV infectious person. The relationship between the extensiveness of the treatment program and prevention of epidemic are discussed.

One of the models of transmission of HIV is from the mother to the fetus which is called the prenatal transmission. [13] Balasubramanian and Lagakos (2001) have discussed
the estimation of the timing of prenatal transmission of HIV. Knowledge of the timing of prenatal transmission of HIV would be valuable for the determination and evaluation of preventive treatments. The authors have pointed out the difficulty in the estimation of the distribution of the time of prenatal transmission. The timing of transmission should be estimated using diagnostic test. Non-parametric and semi-parametric inferences about the distribution of the time of prenatal HIV transmission as well as the cumulative probability of prenatal transmission have been developed. The authors give a systematic derivation of the incomplete density of $\tau_1$ denoted as $g(\tau)$ where $\tau_1$ is a random variable denoting the time of transmission of HIV which can range from conception to birth. The random variable $I$ denotes the infant’s true infection status. That is, $I = 1$ if $\tau_1 \leq 0$ and $I = 0$ if $\tau_1 = \infty$. The authors use the concept of likelihood contribution and derive the conditional probability mass function of $(r, I)$ where $r = (r_1, \ldots, r_n), r_j$ taking the value zero or one depending upon whether the test result at time $r_j$ is negative or positive. The authors have discussed the asymptomatic properties of the ML estimators of the parameters of the cumulative distribution function for the timing of prenatal transmission.

[78] Naresh et al. (2006) have considered a non-linear mathematical model for HIV epidemic that spreads in a variable size population through both horizontal and vertical transmission. Vertical transmission can be accomplished through transplacental transfer of disease agent. In recent years, a few studies of vertical transmission have been carried out to describe the effects of various epidemiological and demographical factors. ([2] Agarwala (2002), [25] Brauer (1995), [30, 31] Busenberg and Cooke (1993, 1998) and
In this paper the authors devoted a model for transmission of HIV into a population of varying size with vertical transmission and other demographic and epidemiological factors. This is a model for AIDS epidemic that may be transmitted either directly or vertically in populations, and to study its behavior qualitatively and numerically.

In the model, the authors assumed that the susceptible become HIV infected via sexual contacts with infectives which may also lead to the birth of infected children. It is assumed that a fraction of new born children are infected at birth; and hence are directly recruited into the infective class with a rate \((1 - \psi)\theta\), and others die effectively at birth \((0 \leq \psi \leq 1)\). They considered only the vertical transmission. The interaction between susceptible and infectives is assumed to be standard mass action type. It is also assumed that some of the infectives move to join pre-AIDS class, depending on the viral counts, with rate \(\sigma\delta\) and then proceed with a rate \(\mu\) to develop full blown AIDS while others with series infection directly the AIDS class with a rate \((1 - \sigma)\delta\) where \(0 \leq \sigma \leq 1\).

In view of the above assumptions, the spread of the disease is determined by the system of equations:
\[
\frac{ds}{dt} = Q_0 - \frac{B_1cSI}{N} - \frac{B_2cSP}{N} - \frac{B_3cSA}{N} - dS,
\]

\[
\frac{dI}{dt} = \frac{B_1cSI}{N} + \frac{B_2cSP}{N} - \frac{B_3cSA}{N} - (\delta + d)I + (1 - \epsilon)\theta(I + P + A),
\]

\[
\frac{dP}{dt} = \sigma\delta I - (\mu + d)P,
\]

\[
\frac{dA}{dt} = (1 - \sigma)\delta I + \mu P - (\alpha + d)A,
\]

\[
S(0) = S_0, I(0) = I_0, P(0) = P_0 \text{ and } A(0) = A_0,
\]

where \(N(t)\) - population size at time \(t\) with constant inflow of susceptible with rate \(Q_0\).

\(S(t)\) - susceptible, \(I(t)\) - infectivity, \(P(t)\) - pre-AIDS patients and \(A(t)\) - AIDS patients with natural mortality rate, \(c\) - average number of sexual partners per unit time, \(\delta\) - rate of movement from infectious class so that \(1/\delta\) denotes the average incubation period, \(\beta_i\) \((i = 1, 2, 3)\) are the constant rates of susceptible with infectives, pre-AIDS patients and \(\alpha\) is the disease induced death rate due to AIDS.

[79] Nirav Dalal (2006) observes in his study that many mathematical models have been developed to describe a viral dynamics of HIV-1, mostly using a system of ordinary differential equations. [122] Verotta and Schaedeli (2002) used non-linear models to present the virus dynamics of HIV-1 which can incorporate different factors associated with resurgence. They have discussed a non-linear model of HIV-1 dynamics, that included exposure, compliance to treatment and insurgence of resistance HIV-1 strains. They have also illustrated the application of the model using real AIDS clinical data involving patients.
treated with combination of antiretroviral drugs. [32] Ciupe et al. (2006) have discussed the dynamics of HIV-1 infection consisting of three distinct phases starting with primary infection, then latency and finally AIDS or drug therapy. In this paper, the dynamics of primary infection and the beginning of latency have been modeled. They have shown that with the data available, the results are highly sensitive to the chosen model.

[103] Sani et al. (2007) have discussed the stochastic model to study the spread of HIV in a mobile heterosexual population. A new mathematical model has been developed by them for the spread of HIV that includes the factors such as mobility, heterosexual transmission and varying population size, which have impact over for countries such as Indonesia, with its different regions. The model will be stochastic in nature since it is opposed to the more common deterministic models. However, the authors showed natural stochastic approach, which can be analyzed in more detail, with respect to equilibrium behavior. They have derived stochastic diffusion approximations, which show that the original process around the equilibrium can be approximated well by Ornstein- Hollenbeck process. [69] Kurtz (1970) and [90] Pollett (1990) have discussed the deterministic and diffusion approximations by using the theory of development process.

[80] Nirav Dalal et al. (2008) have analysed the stochastic model representing HIV interval virus dynamics. They have shown that their model possesses non-negative solutions since it is essential in any population dynamics model. They have explained the stability aspect of the model and proved that the number of infected cells and virus
particles tended asymptotically to zero exponentially almost surely. Their work showed that stochastic differential equations provide another option to model viral dynamics.

[102] Samira Khalili et al. (2008), in their study, have discussed the simulation results and investigated the effect of treatment initiation latency on infection dynamics. They have observed that immediate initiation of treatment leads to a significant decrease of Infection Probability Percentage (IPP). They have concluded that with the stochastic model IPP can be determined; and in order to minimize the IPP with minimum amount of (efficacy) drugs, an optimization problem was formulated. The results show that scheduling optimal medication is successful in decreasing the IPP with respect to constant medication strategy. The results also show that sooner the optimal medication strategy starts, more successful it is to decrease IPP.

[126] Yong Sheng Ding et al. (2008) conclude in their paper that the disease transmission rate should be down under its critical value as to decrease the proportion of population infected with HIV against total population. They have observed that the AIDS epidemic can die out at last, in this way. The theoretical results for the stochastic model describing AIDS transmission are improved as far as mathematical biology is concerned. By computer simulation, the authors demonstrate the stability condition for AIDS to die out. Then, the authors conclude that AIDS will perish when they make measures to make the corresponding parameters changing according to their results. In this way, the authors offer a feasible way for AIDS prevention and control.
3.3 Models Relating to Random Variables Associated with the Concepts of three periods of HIV and their Corresponding Probability Distributions

The statistical studies on HIV throughout the world have focused on modeling methods for $CD4+$ cell changes, survival probabilities, progression of the disease, HIV incidence from prevalence, incubation distribution, transmission probabilities, short term and long term projections and evaluating alternative surrogate markers for staging and monitoring.

There are many external factors that interact with HIV to influence disease progression and are called risk factors. Some may be potentially modifiable and the knowledge that they affect disease progression may be useful. Others may not be modifiable but the knowledge of their effect on disease progression may provide information about HIV pathogenesis and prognosis. Thus, the identification of risk factors may suggest possible new therapeutic strategies, either to prevent initial infection or to slow down disease progression. The importance of age at seroconversion of HIV progression has been widely documented ([38] Darby et al. 1996; [44] Eyster et al 1987). However, other possible cofactors include racial or social background ([108] Schechter et al. 1994; [41] Easterbrook et al. 1996), certain behavioural characteristics such as sexual activity, illegal drug use or smoking status ([29] Burns et al. 1991, [87] Phair et al, 1994) and co-infection with other virus ([99, 100] Sabin et al. 1995, 1997).
3.3. Models Relating to Random Variables Associated with the Concepts of Three Periods of HIV and Their Corresponding Probability Distributions

In contrast, a marker of the disease progression may not necessarily influence the disease progression but indicates the rate of disease advancement in an individual. The marker is useful in disease staging and in assessing future prognosis. Until recently, the most frequently quoted marker of progression is the $CD4^+$ lymphocyte counts ([113] Stein et al. 1992 and [88] Philips et al. 1992). However, other markers, including immune activation markers such as beta-2 micro globulin ([98] Sabin et al. 1994) and immunoglobulin ‘A’ ([33] Coater et al. 1992) and [89] Philips Sabin et al. 1993) have also been considered. Currently, more interest is focused on the viral load ([73] Mellors et al. 1996), which has been shown to be a good marker of progression.

The $CD4^+$ cells play a critical role in the life history of HIV and the progressions of AIDS. According to the Centres for Disease Control and Prevention (CDC), a diagnosis of AIDS is made when HIV infection has been confirmed by repeated screening and the $CD4^+$ count is below 200 or an HIV+ related syndrome. Therefore, [42] Easterbrook et al. (1999), [56] Hogg et al. (2001) and [15] Bennett et al. (2002) have attempted to model the $CD4^+$ cell.

Regarding the projection of the AIDS epidemic figures, many papers have come up. One such paper is by [52] Healy et al. (1988) in which log linear model with exponential weighting are used to forecast the AIDS epidemic. The authors state that in the study of AIDS epidemic there are six key dates namely (i) date of infection, (ii) date of seroconversion, (iii) date of onset of AIDS symptoms, (iv) date of diagnosis, (v) date of
3.3. Models Relating to Random Variables Associated with the Concepts of Three Periods of HIV and Their Corresponding Probability Distributions

report and (vi) date of death. It is also observed that the date of infection and date of seroconversion are very rarely known. The date of onset is a vague indication and the date of diagnosis is not always recorded. However the authors have used curve fitting of two types, namely (a) unweighted fit and (b) a log linear fit. Using the curves the doubling time has been found out.

An annotated bibliography of over 100 articles containing quantitative methodology relating to AIDS epidemic is by [48] Fusaro et al (1989). It gives a lot of information on the various types of models used in the study of AIDS epidemic.

[39] Decruttola et al. (1991) have analysed the role of the CD4+ cell count and the viral load as prognostic markers of the disease progression. [27] Brookmeyer and Gail (1994) have found that the onset of aids can be delayed in an HIV infected individual.

[17] Berman (1992) has discussed the concept of the tail of the convolution of densities and its application to the model of HIV latency time which was previously discussed by [16] Bermann (1990). In this model, if \( p(x) \) and \( q(x) \) are the density functions, and if \( (p \ast q)(x) \) is their convolution, defining \( w(x) = (-d/dx)\log q(x) \) and \( v(x) = (-d/dx)\log p(x) \), the asymptotic form of \( (p \ast q)(x) \) for \( x = \infty \) is obtained under the hypothesis of regular oscillation of the functions \( w \) and \( v \). The results of this paper are used to obtain the posterior density of the latency period.

[116] Tan (1993) has discussed the incubation distribution of the HIV epidemic. The characterization of the incubation distribution has been presented in this paper. The
3.3. Models Relating to Random Variables Associated with the Concepts of Three Periods of HIV and their Corresponding Probability Distributions

The author considers a continuous time Markov chain \( X(t), \ t \geq 0 \) with state space \( S = (e_1, e_2, \ldots, e_k, e_{k+1}) \) where \( e_{k+1} \) is the absorbing state and other states are transient states \( e_i \) (\( 1 \leq i \leq k \)) with probability one, \( e_i \) will eventually be absorbed into \( e_{k+1} \), as time increases. Starting at time \( t = 0 \) the random time \( T_i \) denotes the time for \( e_i \) to get absorbed into \( e_{k+1} \). The author has given the probability density function of \( T_i \). The author has also shown that

\[
    f(t) = \exp(-At)A_{1_k}
\]

where \( 1_k \) is the unit vector and \( A \) is positive semi definite. The author has discussed a modified model also together with some special cases.

[46] Finkelstein et al. (1993) have discussed a proportional hazards model for truncated AIDS data. They have pointed out the distribution of the latency period for AIDS has to be estimated and the estimate is obtained directly from prospective studies of individuals who are at risk. An alternative method to obtain an estimate of latency distribution from retrospective studies of individuals has been suggested. The authors have also taken up the case of HIV infected due to contaminated blood transfusions.

The pair of random variables \( (X, T) \) where \( X \) is the time of infection and \( T \) the time from infection until the disease onset are taken. Assuming the random variables to be independent, they consider the cumulative distribution function \( W \) and \( F \) for the above two random variables with the p.d.f.‘s \( w \) and \( f \) respectively. The joint density of \( (X, T) \) has also been derived. Estimation of the distribution of incubation period has been carried
out using the proportional hazards model. The authors have also indicated the use of score test. The score test is used for testing the hypothesis $\beta = 0$ and $\beta \neq 0$, where $\beta$ is the parameter of the proportional hazards model describing the survival distribution and this model contain covariates, $\beta = (\beta_1, \beta_2, \ldots, \beta_m)$ are the coefficients of the covariates. Simulation studies are also indicated for the verification of the results obtained.

[114] Stilianakis et al (1994) have discussed the antigenic diversity threshold model for AIDS. The model suggests an antigenic diversity threshold above which the immune system is unable to suppress the virus population. It is observed at this juncture that this paper has served as basis for using the threshold models discussed in this thesis. The authors have used a model under the assumption that HIV induces two kinds of responses (i) responses against the specific viral strains and (ii) non-specific responses against all viral strains. A system of countably many differential equations is used to describe the model.

For $i + 1, \ldots, N(t)$, the equations

\[
\begin{align*}
\frac{dv_i}{dt} &= v_i(\alpha - \beta z - \gamma x_i) \\
\frac{dx_i}{dt} &= \lambda v_i - \xi v x_i \\
\frac{dz}{dt} &= v(\epsilon - \xi z) \\
v &= \sum_{i=1}^{N(t)} v_i
\end{align*}
\]

are considered where

\[
v_i = \begin{cases} 
0 & \text{for } \{t; N(t) < i\} \\
v & \text{for } \inf\{t; N(t) = i\}
\end{cases}
\]
3.3. Models Relating to Random Variables Associated with the Concepts of three periods of HIV and their Corresponding Probability Distributions

The model parameters are

\[ \alpha \] replication rate of HIV of strain \( i \),

\[ \beta \] HIV elimination rate per nonspecific immune cell,

\[ \gamma \] HIV elimination rate per specific immune cell,

\[ \lambda \] number of new specific immune cells per unit of time per virus,

\[ \epsilon \] number of new non-specific immune cells per unit of time per virus and

\[ \xi \] elimination rate per HIV organism of specific and nonspecific immune cells.

The variations of mutation rate, the effect of the variation in the size of the initial virus population, the effect of the initial viral diversity are all discussed in this paper. In addition to this the authors have discussed the variation of the antigenic diversity threshold also.

[74] Minggao Shi et al. (1996) have studied incubation and residual time to AIDS distribution based on stochastic models for the marker process \( X(t) \) and a marker dependent hazards \( h(.) \). Here the marker is the \( CD4 \) cells count. A problem with the estimation of AIDS incubation period distribution is that HIV infection dates for seropositives in most studies are not accurately known. Multiple imputation of the unknown dates of HIV infections is a method of approach to this problem. The authors have shown that the residual time to AIDS onset depends solely on the current marker value for some plausible marker process \( X(t) \) such as \( X(t) = [a + bt + BM(t)]^4 \) where \( a \) is
3.3. Models Relating to Random Variables Associated with the Concepts of Three Periods of HIV and their Corresponding Probability Distributions

A normal random variable, $b$ is a parameter and $BM(t)$ is Brownian motion. Furthermore the authors have shown that a simple parametric regression model for the residual time to AIDS provides a good approximation. The authors have developed a marker dependent hazard and survival function. The marker dependent hazard of failure at time $t$ is given by the equation

$$H[t/X(s) : 0 < s < t] \equiv \lim_{\delta t \to 0} P\{T[t, t + \delta t]/T > t, X(s) : 0 \leq s \leq t]/\delta t$$

The marginal distribution of the time from infection to AIDS onset is given by

$$S(t) = P[T > t]\{exp[- \int_0^t h[X(u)du]]\}$$

The above expression involves expectation over all possible paths of marker process which is theoretically impossible to compute. Therefore they have used numerical approximation for solving the above expectation based on the hazard function given by $h[X(t)]$.

They have also derived the survival functions assuming several forms for the marker process $X(t)$ such as

1) Random intercept marker process $X(t) = a + bt$, $a \sim N(\mu, \sigma^2 a)$ $b < 0$, a constant,

2) Random effects marker process $X(t) = a + bt$, $(a, b)^T \sim N[(\mu, \nu)^T, \theta]$ and

3) Integrated Orustein - Uhlenbeck marker process $X(t) = [a + bt + IOU(t)]^4$ where $IOU(t)$ denotes Orustein - Uhlenbeck stochastic process.
The authors have presented numerical illustrations also.

[117] Tan et al. (1996) have given characterization of HIV incubation distributions and some comparative studies. Some Monte-Carlo data have been generated under different conditions and the fitting of HIV incubation distributions by some well known parametric and non-parametric methods have been discussed. In finding the distribution of incubation period, it is necessary to consider the factors like age, race and treatment by anti-viral drugs etc., because these factors affect the transition of infective stages.

It is assumed that there are \( k \) infective stages namely \( I_1, I_2, \ldots I_k \). The absorbing state is the AIDS state. The transition rate from state \( I_i \) to \( I_{i+k} \) is denoted by \( \gamma_i(s, t) \) and the reversal transition from state \( I \) to \( I - 1 \) is denoted as \( \beta_s(s, t) \). From any state \( I_i \) transition to AIDS state is possible and this rate is given by \( \mu_i(s, t) \). The authors have taken into account the treatment effects obtained by the use of anti-retroviral drugs such as AZT. So, they redefined the transition rates as

\[
\gamma_i(s, t) = \theta_i(t)\gamma_i(i; s, t) \\
\beta_s(s, t) = \theta_i(t)\beta_i(i; s, t) \\
\mu_i(s, t) = \theta_i(t)\mu_i(i; s, t)
\]

where, \( \theta_i(t) \) is a monotonic decreasing function of \( t \) defined over \( (t_i, t_{i+1}) \) to account for the decreasing effects of treatment over time. Under the above assumptions, the HIV incubation distribution in the absence of drug treatment has been obtained using Markov
models and also non-Markovian models. The distribution of incubation period has also been obtained when the transitions are influenced by using the anti-viral drugs. Here also, the Markovian models have been obtained and the authors have suggested non-Markovian models.

[112] Srinivasa Rao and Kakehashi (2005) have discussed the incubation-time distribution of back-calculation applied to HIV/AIDS data in India. Information on accurate population sizes of HIV infected persons and AIDS cases and the trend of these figures are requisite to the planning of preventive policies and public-health management. Sophisticated statistical models have been developed to facilitate the provision of information. Among the models, a simple extrapolation method is easy to apply and useful for summarizing the trend of the spread of infection, but it is difficult to clarify how long the obtained trend stays unchanged. By comparison, mathematical models of the spread of sexually transmitted diseases use information on sexual behavior in the population to investigate the effect of behavioral change caused by a preventive program. But mathematical models usually require detailed information on sexual behavior in the population, which is not always available. In contrast, the back-calculation method connects infection with HIV and the development of AIDS to incubation time. Because of the long incubation period, this method can provide a very reliable prediction of future AIDS development from prevalent HIV data.

Traditionally, back-calculation method is applied to estimate past HIV trends and to
predict future AIDS cases by using reported AIDS cases and the assumed incubation time distribution. Information on HIV incidence is not directly used in the attempt. This is to be expected where detailed information on AIDS cases and incubation time may be more easily obtained about than figures about HIV incidence. But there is another situation in which information on HIV incidence is more available than information about incubation time. This is likely when HIV surveillance is started but medical treatment is not generally available or is inadequate. In any case it is helpful to use all these data to obtain more reliable outcomes especially when the quality of each kind of data is insufficient. A recent attempt to take advantage of the information on HIV in back-calculation has been made ([36] Cui and Becker (2000)), but it requires more detailed information on reported HIV.

[20] Berxuini and Allemani (2004) have analyzed data from a seroincident cohort of 457 homosexual men who were infected with the human immunodeficiency virus, followed within the multicentre Italian seroconversion study. These data include onset times to Acquired Immunodeficiency Syndrome (AIDS), longitudinal measurements of CD4+ T - Cell count taken on each subject during the AIDS - free period of observation and the period of administration of a Highly Active Antiretroviral Therapy (HAART), for the subset of individuals who received it. The aim of the study is to assess the effect of HAART on the course of the disease. They analyze the data by a Bayesian model in which the sequence of longitudinal CD4+ cell count observations and the associated time to AIDS are jointly modeled at an individual subject’s level as depending on the treatment. They discuss the inferences obtained about the efficiency of HAART, as well as modeling and computation
difficulties that were encountered in the analysis. These later motivate a model criticism stage of the analysis, in which the model specifications of CD4+ cell count progression and of the effect of treatment are checked. The approach to model criticism is based on the notion of a counterfactual replicate data set $Z^c$. This is a data set with the same shape and size as the observed data which they might have observed by rerunning the study in exactly the same conditions as the actual study if the treated patients had not been treated at all. They draw samples of $Z^c$ from a null model $M_0$, which assumes absence of treatment effect, conditioning on data collected in each subject before initiation of treatment. The model checking has been performed by comparing the observed data with a set of samples of $Z^c$ drawn from $M_0$. Also a model has been proposed to analyze longitudinal data from 457 HIV-positive homosexual men followed within the multicentre Italian seroconversion study ([94] Rezza et al. (1989), Italian seroconversion study team (1992), [40] Dorrucci et al. (1999) and [86] Pezzotti et al. (2001)). The seroconversion data of each of the subjects in the study was taken to be the middle point between the subject’s last negative HIV test result and his first positive result. The earliest seroconversion in sample is estimated to have been in 1984. The proposed model reflects ideas from previous work on the joint modeling of longitudinal measurements and event time data ([62] Jewell and Nielsen (1993), [110] Singpurwalla (1995), [19] Berzuini and Larizza (1996), [35] Cox (1999), [53] Henderson et al. (2000), [45] Faucett and Thomas (1996) and [118] Taylor et al. (2000)). An additional source of complexity in this model is the representation of the effect of treatment. It would be simple and computationally straightforward to concentrate exclusively on the treatment
included changes in \( CD4+ \) T - cell counts, ignoring the effect of treatment on the hazard of AIDS and the dependence of this on the \( CD4+ \) cell level.

### 3.4 Models Concerning Infectivity, Projection and other Aspects

Many papers on the projection of AIDS epidemic figures have come up and one such paper is by [52] Healy and Tillett (1988). This paper uses log linear model and exponential Weighting to arrive at forecast for regarding the AIDS epidemic. The authors have stated that in the study of AIDS epidemic there are six key dates namely (i) date of infection, (ii) date of seroconversion, (iii) date of onset of AIDS symptoms, (iv) date of diagnosis, (v) date of report and (vi) date of death. It has also been observed that the date of infection and date of seroconversion are very rarely known. The date of onset of vague indication and the date of diagnosis are not always recorded. However, the authors have used curve fitting with two types of curves. (a) unweighted fit and (b) logarithm of linear fit. Using the curves the doubling time has been found out.

The statistical analysis of HIV infectivity is based on partner studies and the per-contact transmission probability of virus is called infectivity. The statistical study of HIV infectivity has been discussed by [61] Jewell and Shiboski (1990). In the application of the epidemic model to project the spread of the virus, the level of infectivity plays a major role. In the analysis the concept of hazard function of reliability theory is used to define the
prevalence function as \( 1 - S_k \), where \( S_k \) is defined as the probability that infection has not occurred during first \((k - 1)\) contacts. The hazard function \( \lambda(k) \) is defined as conditioned probability

\[
\lambda(k) = P \left\{ \text{infection occurs after } k \text{ contacts} \left| \text{infection has not occurred during earlier } k - 1 \text{ contacts} \right. \right\}
\]

The authors have discussed the non-parametric estimation of hazard function \( \lambda(\cdot) \). The conditional likelihood of \( n \) observations is defined as

\[
L = \prod_{i=1}^{n} \left\{ \left( \prod_{j=1}^{k_i} \left[ 1 - \lambda(j) \right] \right) \left( \prod_{j=1}^{Y_i} \left[ 1 - \lambda(j) \right] \right) \right\} = \prod_{i=1}^{n} \left[ 1 - p(k_i) (1 - Y_i) \right]^{Y_i}
\]

where \( Y_i = \begin{cases} 1 & \text{if parameter is infected by time } T_i \\ 0 & \text{if partner remains seronegative at time } T_i \end{cases} \),

\( k_i = \text{Number of contacts with the index case during period } [0, T_i] \) and \( p(k) = 1 - S_k \).

[81] Nowak and May (1991) have discussed a mathematical model that explores the quantitative consequences of the antigenic drift of HIV. The consequence of HIV transmission is the antigenic diversity and this kind of antigenic diversity is observed in the productive process of the HIV which infects the \( CD4 \) cells. A major property of many parasitic infections is the antigenic variation. The parasites evolve the capacity to escape the immunological surveillance by mutating their immune dominant epitaphs continuously during the time of infection. When the immune system generated cellular or humeral attack
against these targets, the parasite has escaped with mutated antigens which are called the antigens. HIV disrupts and confuses the immune regulatory network.

Aiming at the exploration model the quantitative consequence of the antigenic drift of HIV the authors [81] Nowak and May (1991) have developed a basic mathematical model. The basic set of equations consists of the following

\[ v_i = v_i (r - sz - px_i), \quad i = 1, 2, 3, \ldots n \]
\[ x_i = k v_i - u v x_i, \quad i = 1, 2, 3, \ldots n \]
\[ z = k' v - u v z, \]

where,
\[ v_i = \text{population size of virus strain } i \]
\[ r = \text{replication rate} \]
\[ r = bQ - d \]
\[ bQ = \text{birth rate} \]
\[ Q = \text{probability that the replication is done without error} \]
\[ d = \text{natural death rate of the virus} \]
\[ v = \sum v_i = \text{total virus population density} \]

The potential existence of a viral diversity threshold has been established. The immune system can control strain \( i \), if \( v_i < 0 \), which can be written as

\[ r - sz - px_i < 0 \]
The immune system can control each individual strain only if this condition holds for each \( i = 1, 2, \ldots n \), which implies the restriction that

\[
    n < n_c(x, z) = px/(r - sz)
\]

Hence there exists an upper limit \( n_c \) of different strains that can be suppressed simultaneously by the immune system given by

\[
    n_c = pk/(ru - sk')
\]

It is observed that the antigenic diversity is responsible for the depletion of the immune level or immune capacity of an individual progressively. So, mathematical models have been developed under the assumption that the magnitudes of damage to the immune system is directly proportional to the antigenic diversity and using this as the basis, the shock models have been introduced in this thesis.

[114] Stilianakis et al. (1994) have discussed on the antigenic diversity threshold model for AIDS. The model suggests an antigenic diversity threshold above which the immune system is unable to suppress the virus population. The author of this paper has used a model under the assumption that HIV induces two kinds of responses, namely

(i) Responses against the specific viral strains and

(ii) Non-responses against all viral strains.
A system of countably many differential equations is used to describe the model for 
\( i = 1 \ldots, N(t) \)

\[
\begin{align*}
\frac{dv_i}{dt} &= v_i(\alpha - \beta z - \gamma x_i) \\
\frac{dv_j}{dt} &= \lambda v_i \xi v x_i \\
\frac{dv_j}{dt} &= v(\epsilon - \xi z) \\
v &= \sum_{i=1}^{N(t)} v_i
\end{align*}
\]

where

\[
v_i(t) = \begin{cases} 
0 & \text{for } \{t; N(t) < i\} \\
v^* & \text{for } \inf \{t; N(t) = i\}
\end{cases}
\]

The model parameters are

- \( \alpha \) replication rate of HIV of strain \( i \)
- \( \beta \) HIV elimination rate per nonspecific immune cell
- \( \gamma \) HIV elimination rate per specific immune cell
- \( \lambda \) number of new specific immune cells per unit of time per virus
- \( \epsilon \) number of new nonspecific immune cells per unit of time per virus
- \( \xi \) elimination rate per HIV organism of specific and nonspecific immune cells.

[114] Stilianakis et al. (1994) have discussed the variations of mutation rate, the effect of the variation in the size of the initial virus population and the effects of the initial viral diversity. Furthermore the authors have discussed the variations of the antigenic diversity threshold also.
[124] Werawat Manosuthi et al. (2007) have discussed the impact of Antiretroviral Therapy (ART) for HIV and the side effects suffered by the HIV infected. The ART drugs like stavudine, lamivudine and nevirapine are used for patients over HIV infected. The Antiretroviral Therapy has its own side effects apart from the cost involved. In this paper the authors have collected the data regarding the ill effects of these drugs in addition to the efficacy of ART drugs. Cox regression model has been used for the data analysis and the impact of ART drugs between those patients with $CD4 < 50$ and $CD4 \geq 50$ cells per $mm^3$ has been compared.

[1] Adriana Weinberg et al. (2009) have discussed and concluded that resistance to antiretroviral in HIV infected pregnant women. The 14% prevalence of resistance to zidovudine and lamivudine in antiretroviral experienced women suggests that alternative Nucleoside analogue Reverse Transcriptase Inhibitors (NRTI) are desirable for this group of patients.

[111] Shan mei et al. (2010) in their paper introduced the concept of a complex agent network to model the HIV epidemic by combining multi-agent systems, in which the agents represent individuals who could have sexual interactions. They have reported that the model can be adopted to predict the future trend of HIV prevalence and incidence among (Men who have Sex with Men) MSM in Amsterdam (Netherland).

A study on Mortality and Progression to AIDS after starting higher active antiretroviral therapy was conducted by [120] Van Sighem, et al. (2003) of HIV Monitoring Foundation,
Academic Medical Centre, University of Amsterdam (Netherlands). The main objective of the study was to examine the survival and progression to AIDS among HIV-infected patients after starting Highly Active Antiretroviral Therapy (HAART). The data relating to 3724 patients available at the ATHENA observational cohort was taken up for analysis. A time-dependent multivariate hazard model was fitted to the patient data and 5 year survival probability under various therapy scenarios was estimated. For each patient the hazard for death or AIDS \( I(t) \), after \( t \) years of follow-up, is modeled as the product of an underlying hazard - \( h(t) \) common to all patients and a function containing patient-specific covariates. In order to estimate the underlying hazards in models with time-dependent covariates, a discrete-time generalized linear model was used for each patient follow-up time which split into 3 week intervals, such that the Poisson probability of having two or more events per patient in the same time interval could be neglected. The hazard \( h(t) \) of dying in time interval ‘I’ is then given by the expression

\[
h(t) = h_0(t) \exp\left[ \sum \beta_j(t) \right] \text{Covariate } j(t)\]

where the sum runs over all covariates \( j \) with corresponding hazard ratios \( \exp[\beta_j(t)] \). The survival probability \( S(t) \) up to time interval \( i \) is given by \( S(t) = \exp[-H(t) \] with \( H(t) \) the cumulative hazard at \( t \) is defined as \( H(t) = \sum_{t \leq j} h(t) \). [18] Bennet et al. (2005) in their study have examined the factors associated with clinical progression (AIDS events and death) in antiretroviral-naive patients who have started Highly Active Antiretroviral Therapy (HAART). 709 HIV-infected patients naive
3.4. Models Concerning Infectivity, Projection and other Aspects

...to antiretroviral therapy who were enrolled in a prospective hospital-based Cohort began HAART between June 1996 and December 2001. Progression was explained by baseline characteristics using Cox proportional hazards models.

The multivariate analysis undertaken by [18] Bennet et al. (2005) revealed the fact that the factors associated with an increased risk of progression were CD4 count < 50 199 cell/µl and between 50 and 199 cell/µl, when compared with patients with CD4 count > 350 cell/µl; AIDS events before HAART prescription; CD4 percentage, factors associated with progression were CD4 < 10 percent and 10 percent; < CD4 < 15 percent, when compared with patients with CD4 > 20 percent; CD8 count; AIDS event before HAART prescription and older age. In a third model including the CD4 : CD8 < 15 percent and 15 percent < CD4 : CD8 < 30 percent, when compared with patients with CD4 : CD8 > 45 percent; AIDS events before HAART prescription; and older age. To conclude, the study places its record of opinion that consideration of CD4 level in terms of CD4 : CD8 ratio or CD4 percentage can be a good alternative to absolute CD4 count. Other prognostic factors such as older age, CD8 count < 400 cell/µl and AIDS events also have to be considered in the decision to initiate HAART.

A study on risk factors for High Mortality in patients on Antiretro-viral treatment in a Rural District of Malaw was undertaken by [96] Rony Zachariah et al. (2006). The study showed that among individuals starting ART, the Body Mass Index and clinical staging could be important screening tools to identify and target individuals who, despite ART, are...
still at a high risk of early death.

This death occurred between April 2003 and June 2005 in Thyolo district of Malawi. All the adults who were ART naive and starting treatment in the main district hospital, HIV/AIDS clinic over 2 years period were included in the study. A structural record form and patient cards were used to gather information on basic demographic data WHO clinical stage, CD4+ cell counts and opportunistic infections including tuberculosis. CD4+ cell counts were systematically performed in all patients using strict quality control standards. Measures of risks were calculated by crude odds ratio (OR’s) which are further adjusted using multivariate logistic regression. Kaplan-Meier was used to estimate the survival between groups.

A study entitled correlation between Gag-specific CD8+ T-cell Responses, Viral load and CD4+ count in HIV-1 infection dependent on Disease status was undertaken by [125] Yang Jiao et al. (2006). The study was designed to investigate the role of HIV-specific CD8+ responses in patients with different disease status. The conclusion of the study suggests that the relationship between CD8+ response and viral load or CD4+ count is not universally consistent throughout the entire course of HIV-infection.

[68] Krishna Ray et al. (2006) in their study on CD4 / CD8 Lymphocyte Counts in Healthy, HIV-Positive Individuals and AIDS Patients, observed CD4 cell count as a useful predictor of AIDS in Indian conditions and confirmed that a significant percent of AIDS patients had CD4 count below 200/ml.
For the purpose of the study, blood samples collected from 125 HIV exonerative healthy volunteers comprising group I and 425 HIV positive patients divided into group II as asymptomatic and group III of AIDS patients in the age group of 17-60 years were analyzed for enumeration of $CD4^+$, $CD8^+$ cell/ml by flow cytometry. Differences between means of two groups were compared by student’s unpaired $t$-test. The percentages were compared by chi-square test. Data of the earlier studies with the availability of sample size, mean and standard deviation were used for comparison.

[95] Ron Brookmeyer (2010) has discussed the current approaches and methods for measuring the HIV/AIDS epidemic and their strength and weaknesses. The author summarises the main sources of errors and problems with these and other approaches and discusses opportunities for improving their reliability. Changing methods and data sources present new challenges, because incidence and prevalence estimates produced at different points in time are not directly comparable with each other, which complicates the assessment of time trends. The methodological changes help explain the changes in global statistics. As methods and data source continue to improve, the development of statistical tools for better assessing the extent to which changes in HIV/AIDS statistics can be attributed to changes in methodology versus real changes in the underlying epidemic is an important challenge.

[4] Akpa and Oyejola (2010) have discussed a review of modeling the transmission Dynamics of HIV/AIDS epidemics and this study reviews some of the model proposed by
various authors for describing the epidemiology as well the epidemiological consequences of the HIV/AIDS epidemic and how some of them could be modified to suit the situations in other countries. Four different types of basic modeling approaches can be used to develop mathematical models for HIV/AIDS and also for some other infection diseases. The four kinds are deterministic model, the stochastic model, the statistical model and Karman Filter model ([123] Wan Yuan (2000)).

[14] Beena Thomas et al. (2011) have discussed the unique socio-cultural issues of Men who have sex with men (MSM) in India and how they relate to HIV risk that could maximize the utility of future prevention effort. This article seeks to elucidate the specific challenges of providing effective HIV prevention program for this diverse and socially Marginalized risk group. It highlights the gaps in current HIV prevention efforts by providing insight into the patterns of Indian MSM behavior and sexual partnerships, and the specific cultural and psychological content in which HIV risk is occurring. Understanding the distinct social forces that shape the HIV risk environment could maximize the effectiveness of prevention interventions and heighten the acceptability of these programmers by MSM.

[63] Julia Braun et al. (2012) have discussed the predictive cross-validation for the choice of linear mixed-effects models with application to data from the swiss HIV cohort study. A predictive cross-validation approach has the advantage that the model has to be fitted just once and not in every cross-validation step. This saves a considerable amount of
time, especially in more complicated linear mixed-effects models with random effects and serial correlation. Empirical evidence suggests that this cross-validation approach is a good approximation of a true leave-one-out approach, but this of course depends on the nature of the concrete problem and data set. It is a well-known fact that predictions in the context of HIV are particularly challenging, because the viral load and its effect on the immune system can change so fast. Furthermore, one may wish to choose the best model, and for this task, the cross-validation procedure has shown to be effective.