CHAPTER III

REVIEW OF LITERATURE

In any area of research the extent of work carried out regarding the various aspects of study and about a particular concept or particular topic is important. It is so because the full knowledge about the work carried out in the past by different authors in a particular area of study or topic of specific interest will help very much the work to be carried out in the future. Hence a clear idea about the work carried out by different authors must be listed out which forms the review of literature. In this thesis also a brief account of the work done by different persons in the particular area of interest are discussed briefly and this forms the review of literature presented in this chapter.

The heterogeneity in the sexual activity has considerable influence in the spread of the infection. The study of the incubation period also plays a vital role in the spread of the infection. Anderson (1988) has considered a model to derive the rate of spread and transmission of HIV. The author considers that a homosexual community of total size ‘N’ can be divided into

\[ X = \text{number of susceptible, } Y = \text{number of infected and } A = AIDS \]

patients \( N = X + A + Y \). The simplest set of equations that are used for the transmission of HIV in a closed community (that is no influx of susceptible from outside and no deaths other than those who die due to AIDS) is given by

\[ \frac{dX}{dt} = -\lambda X \]
\[ \frac{dY}{dt} = -\lambda X - vY \]

\[ \frac{dA}{dt} = -vY - \alpha A \]

\[ \frac{dN}{dt} = -\alpha A \]

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 \( Y \). The rate \( \alpha \) defines mortality in the AIDS class. Here \( \lambda \) is the per capita force of infection and is defined as

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

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 duration of their stay in class. The expression for doubling time \( t_d \) is given by \( t_d = D[ln(2)/(R_0 - 1)] \). The authors have also discussed various extensions of this model taking into consideration variable incubation, infectious periods and also the variations in the rate of sexual partners change.

Longini et.al. (1989) have discussed a model using a Markov model which contains four progressive stages (i) infected but antibody negative (ii) antibody-positive but asymptomatic (iii) pre-AIDS symptoms and/or abnormal haematological
indicator and (iv) clinical AIDS. A multi staged stochastic model to a set of charts is fitting using the method of maximum likelihood and used to estimate the probability density function of AIDS incubation period.

Taylor et.al. (1990) have discussed the estimation of the distribution of time from HIV seroconversion to AIDS using multiple imputations. Multiple imputations are a model based technique for dealing with missing data problems. The data set used in the analysis is from the multicentre AIDS cohort studies (MACS) and the study consists of 4954 homosexual or bisexual men. The authors define \( F \left( \frac{v}{x}, \theta \right) \) as the distribution of time to AIDS measured from the enrolment time, for the seropositive groups given covariates \( X \) and the parameter \( \theta \). Here \( \hat{\theta} \) and \( \text{cov}(\hat{\theta}) \) denote the maximum likelihood estimates and covariance is obtained from the observed information matrix. Also they use the relation \( T + U + V \), where \( T \) denotes the time from HIV seroconversion to AIDS, \( U \) the follow up time, \( V \) the residual AIDS free time. The distribution of \( T \) is estimated using the standard survival techniques. The imputation algorithm is also provided. Using the data from several cities like Baltimore, Chicago etc., they give the distribution times as numerical illustrations.

Statistical analysis of HIV infectivity based on partner studies has been discussed by Jewell and Shiboski (1990). Partner studies produce data on the infection status of partners of individuals known or assumed to be infected with the Human Immunodeficiency Virus (HIV) after a known or estimated number of contacts. This paper develops parametric and nonparametric procedures based on partner data in order to examine the risk of infection after a given number of contacts.
Bacchetti (1990) has discussed about the incidence of AIDS virus infections over time among gay men in San Francisco. It is nonparametrically estimated from interval-censored data by using the EM algorithm to maximize a roughness-penalized likelihood.

Because the distribution of AIDS diagnoses is the convolution of the infection and incubation distributions, the incubation distribution can be estimated by comparing the estimated infection distribution and the observed pattern of diagnoses. This is again accomplished by non-parametrically maximizing a roughness-penalized likelihood using the EM algorithm. The penalized log-likelihood is given by

$$\log(L) - \left(\frac{1}{2}\right)\lambda J, \lambda \geq 0,$$

where $L$ is the likelihood, $J$ measures the roughness of the hazard function, and $\lambda$ is a tuning constant that determines the relative importance of $L$ and $J$. The optimal degree of smoothness for the estimates is chosen using external data and subjective assessments of plausibility.

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 AIDS related complex state, $E_4$ is the 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 \( e_{j,k} \); \( j,k = 0,1,2,3,4 \) which represents that both the partners are alive. Based on these assumptions and also taking into account the risk of infection due to use of drug intravenously, and a matrix of probabilities \( B \) are defined. In their paper using random functions, the course of the epidemic is obtained. The results are mostly by using computer simulation.

Tan et al. (1996) have given characterization of HIV incubation distributions and some comparative studies in their paper. Some Monte-Carlo data have been generated under different conditions and the fitting of HIV incubation time distribution by some well known parametric and non parametric models, have been discussed. In finding the distribution of incubation period, it is necessary to consider the factor 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 \( l_1, l_2, \ldots, l_k \). The absorbing state is the AIDS state. The transition rates from state \( l_i \) and \( l_{i+1} \) is denoted as \( \gamma_i(s,t) \) and the reversal transition from state \( i \) to \( i-1 \) is denoted as \( \beta_i(s,t) \). From any state \( l_i \) 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

\[
\gamma_r(s,t) = \theta_i(t) \gamma_r(i; s,t) \\
\beta_r(s,t) = \theta_i(t) \beta_r(i; s,t) \\
\mu_r(s,t) = \theta_i(t) \mu_r(i; s,t)
\]
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 Markoff 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 non-Markovian models are suggested.

Atkinson (1996) has discussed a simulation model of the dynamics of HIV transmission and subsequent progressions to AIDS make use of traditional mathematical modeling techniques which are problematic. The previous model of Leslie and Brunham (1990) established the unity of a nonmathematical simulation language in modeling HIV transfer under conditions similar to those found among homosexual men. Their study considers the application of such an approach in modeling HIV spread among IDUs. Modeling HIV transmission in this population involves not only consideration of heterogeneity in partnership selection, but also the fact that spread of the virus is not directly from person to person, but via injection equipment. The general simulation system was used to create a hypothetical cohort of IDUs, drawing from a common needle supply. The model was then used to consider the effects of systematic variation in the frequency of infection and needle cleaning behavior.

The concept of “homing process” and “apoptosis” is something new and very interesting. These concepts have been studied by Krischner et al. (2000). The cause for the elimination of CD$_4^+$ T-cells in HIV infected individuals is an important aspect
and also the rate of elimination plays a vital role in the breakdown of the human immune system. According to the authors, HIV induces the secretion of a biochemical substance induces signals to the CD4+ T-cells to move from the blood stream to the lymphatic system, where oxygen is not available. This change over of CD4+ T-cells from blood stream to the lymphatic system is called "homing process". Due to the change over, large number of CD4+ T-cells suffers suffocation due to the non availability of oxygen. This process of death of CD4+ T-cell due to suffocation is called "apoptosis".

The authors have developed a set of differential equations and they are

\[
\frac{dT_p}{dt} = C_i T_i(t) - C_p T_p(t)
\]

\[
\frac{dT_p'}{dt} = C_i T_i'(t) - C_p T_p'(t)
\]

\[
\frac{dT_i}{dt} = C_p T_p(t) - C_i T_i(t) - kT_i(t) + \mu_a T_L^a(t)
\]

\[
\frac{dT_p'}{dt} = pk T_L(t) - C_L T_L'(t) + C_p T_p'(t) - \mu_i T_L'(t) - s_i T_L'(t) - s_L T_L^i(t)
\]

\[
\frac{dT_i^a}{dt} = r k T_i(t) - \mu_a T_L^a(t)
\]

\[
\frac{dT_L'}{dt} = q k T_L(t) - \mu_i T_L^i(t) - s_i T_L^i(t)
\]

Where

\[T_p(t)\] the total number of uninfected CD4+ T cells in the blood.
\( T_p'(t) \) the total number of latency infected CD4+ T cells in the blood.

\( T_L^a(t) \) the total number of abortively infected CD4+ T cells.

\( T_L^l(t) \) the total number of latency infected T cells.

\( T_L^l'(t) \) the total number of activity infected T cells.

These equations describe the rate of depletion of CD4+ T cells. This results in the sudden collapse of the immune system.

Wu and Tan (2000) have discussed about a state-space approach to model the HIV epidemic. The authors also incorporate the dynamic models, the observed AIDS incidence data and other information to estimate the past states and to project the future states, which include the susceptible people, the HIV prevalence at different stages and the AIDS cumulative numbers. Some other relevant issues on the HIV epidemic and the state-space approach are also discussed.

Wodarz and Nowak (2002) have discussed the mathematical models of HIV pathogenesis and treatment. The dynamics between virus infections and the immune system involve many different components and are multi-factorial. In such a scenario, the principles governing the dynamics and the outcome of infection cannot be understood by verbal or graphical reasoning. Mathematical models provide an essential tool to capture a set of assumptions and to follow them to their precise logical conclusions. They allow us to generate new hypothesis, suggest experiments and measure crucial parameters. In this review model, they show how mathematical models can be used to understand the dynamics of HIV infection and therapy. They
give a basic model for virus infection and continue to show how it was used to get some crucial insights into the dynamics during the asymptomatic phase of the disease. Also explore how HIV evolution can drive disease progression and how mathematical models can be used to design specific treatment regimes that can boost anti-viral immunity and induce log-term virus control.

The basic model of virus dynamic has three variables: the population size of uninfected cells $X$, infected cells $Y$, and free virus particles $V$. These quantities can either denote the total abundance in a host, or the abundance in a given volume blood or tissue. Free virus particles infect uninfected cells at a rate proportional to the product of their abundances, $\beta_{XV}$. The rate constant $\beta$, describes the efficacy of this process, including the rate at which virus particles find uninfected cells, the rate of virus entry, and the rate and probability of successful infection. Infected cells produce free virus at a rate proportional to their abundance $KY$. Infected cells die at a rate $aY$, and free virus particles are removed from the system at rate $uv$. Therefore, the average life-time of an infected cell is $1/a$, whereas the average life-time of a free virus particle is $1/u$. The total amount of virus particles produced from one infected cell, the ‘burst size’, is $k/a$.

Uninfected cells are produced at a constant rate $\lambda$, and die at a rate $dx$. The average life-time of an uninfected cell is $1/d$. In the absence of infection, the population dynamics of host cells is given by $X = \lambda - dx$. This is a simple linear differential equation. Without virus, the abundance of uninfected cells converges to the equilibrium value $\lambda/d$. 
Combining the dynamics of virus infection and host cells, they obtain the basic model of virus dynamics:

\[ X = \lambda - dx - \beta_{XV} \]

\[ Y = \beta_{XV} - ay \]

\[ V = ky - uv \]

This is a system of nonlinear differential equations. An analytic solution of the time development of the variables is not possible, but they can derive various approximations and thereby obtain a complete understanding of the system.

Srinivasa Rao and Kakehashi (2005) have discussed the incubation-time distribution in 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 provision of the 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 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 present 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 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 useful and 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 and effort to take advantage of the information on HIV in back-calculation is made (Cui and Becker (2000)), but it required more detailed information on reported HIV.

An interesting paper is by Suresh Kumar (2006) and it deals with the concept of shock model and cumulative damage processes when the threshold random variable has a distribution, which changes in it’s from after a truncation point. In this paper, the author has taken up the case where the threshold random variable follows exponential distribution prior to the truncation point and it follows Erlang 2 after the truncation point. Assuming the truncation point itself is a random variable, which follows exponential distribution, the author has derived the density function of the threshold distribution. Using this result, the author has obtained the expected time to cross the threshold under the shock model cumulative damage process approach.
Numerical illustration is also provided. It may be noted that this paper is of prime interest and would be of use in further research in different areas where reliability theory is involved.

There is some associated illness in those persons who are HIV infected. The concept of common mental disorder (CMD) suffered by the HIV infected individual is discussed by Zewdu and Nurilign (2015). It is a known fact that the people who are HIV infected have many complicated illness which will very much disturb the normal functioning of the human body. Intestinal problems lung problems and functioning of the heart are all getting disturbed due to HIV infection and its progression to AIDS. A part from the physical illness the HIV infected has mental depression and mental disorder. So even in the person of ART the prevalence of CMD is a common feature. The people especially in Ethiopia undergo a lot of change in the life style due to CMD that prevails among the HIV infected. The data have been collected from the affected patients and the authors have used the bivariate analysis to determine these factors which have influence on the prevalence of CMD especially among the people in living in Ethiopia.

Another interesting article is by McIntosh (2015). The author has identified that the Doctor-Patients Relationship and Active-Patients Involvement (DPR: API) is very much related to the long survivor status of HIV infection also due to factors having influence over the impact of HIV. It was identified that Doctor-Patients Relationship is a vital factor that prolongs the life of HIV infected. The Active-Patients Involvement was measured using the score system for the evaluation of extent of relationship and the mental background of the patients. The authors
concluded that the assessment of the degree of relationship between the patient and the doctor and the level of active patients involvement both influence the outcomes namely the impact of ART as well as the life span of the HIV infected.

Another interesting article is by Vechi et.al. (2015) which deals with the liver disease severity for decreased Bone Mineral Density in HIV as well as HIV/HCV co-infected patients. Here HCV implies the hepatitis C virus patients. The impact of HIV infection is not only the deterioration of health and immunity power but also other diseases attack the human system. Liver disease and decreased bone mineral density are as a result of HIV infection. It may be observed that the occurrence of liver diseases severity will affect the digestive system and the intestinal disorder will crop up. The authors have collected data from the patients who are undergoing (ART). The information regarding CD$_4^+$ T-cell count HIV-RNA levels are all collected from the chosen patients. They used the statistical tests such as Student’s ‘t’-test, Mann Whitney ‘U’ test, Fisher’s exact test and Chi-square tests, Pearson’s correlation etc., to draw the conclusions. Also multiple linear regression analysis was performed to estimate the independence of some related factors. It is observed that the life style namely the smokers and non smokers are also compared.

Bestawros et.al. (2015) have discussed the impact of antiretroviral therapy in the functioning of the human organs. The information associated with the cardiac and vascular dysfunction due to antiretroviral therapy. The HIV infected adults who are in South Africa and who are under their list is taken as the sample for the study. The authors indicate that the HIV infected adults with normal Body Mass Index (BMI) suffer CD$_4^+$T-cell suppression is subjected to antiretroviral therapy. The individuals
with normal BMI and without HIV infection have reduced heart rate variation increased cardiovascular events rates. So the under nutrition people who are HIV infected especially in South Africa show very high rate of suffering due to cardiovascular dysfunction.

Nowak and May (1991) have discussed the effect of antigenic variation in the HIV infection and spread. The parasites (Virus) generate the capacity to escape the antibodies by the so-called process of mutation. Therefore the newly produced HIV possesses greater capacity to survive against the antibodies, which are generated by the immune system to fight against the virus.

The authors discussed the interaction between the HIV and the immune system. The CD4+ T-cells are the basic cells, which organize the immune responses. The HIV directly infects and kills the CD4 cells. In addition to the direct action the HIV also use same indirect mechanisms such as the killing of processor cells, anti gp 120 antibody attack etc.,

The mathematical model is developed under some basic biological assumptions. The basic mathematical model is to find out the quantitative consequences to the antigenic diversity of HIV.

The following sets of equations are formulated

\[ V_i = V_i(r - PX_i - SZ), \quad i = 1, \ldots, n, \]

\[ X_i = KV_i - UV_iX_i, \quad i = 1, \ldots, n, \]

\[ \dot{Z} = KV - UVZ \]
These three equations describe the population dynamics for $n$ different virus strains. The authors also established a viral diversity threshold.

Nowak *et al.* (1991) have discussed the antigenic diversity threshold and the development of AIDS. In this model, study of patients infected with HIV-1 reveal a long and variable incubation period between infection and the development of AIDS. Data from a small number of infected patients show temporal changes in the number of genetically distinct strains of the virus throughout the incubation period, with a slow but steady rise in diversity interaction between viral diversity and the human immune system. This suggests the existence of an antigen diversity threshold, below which the immune system is able to regulate viral population growth but above which the virus population induces the collapse of the CD$_4^+$ lymphocyte population. The model suggests that antigenic diversity is the cause, not a consequence, of immunodeficiency disease. The model is compared with available data, and is used to assess how the timing of the application of chemotherapy or immunotherapy influences the rate of progress to disease.

Also the mathematical model consists of a system of ordinary differential equations, and its structure reflects the hypothesized three key features distinctive to HIV infections (i) The continuing appearance of new antigenic variants, or ‘escape mutants’, of the virus enables the overall virus population to evade elimination by the immune system. (ii) Immunological responses directed against the virus involve a specific response to individual strains along with a cross-reactive response that acts against all strains. (iii) Each viral strain can infect and subsequently kill all CD$_4^+$ T-cells, regardless of their specificity to a particular mutant.
The model resulting from these assumptions has four kinds of variables; \(v_i, y, x_i\) and \(z\) which denote the densities of virus strain \(i\), total \(CD_4^+\) T-cells, \(CD_4^+\) T-cells specific to strain \(i\), and \(CD_4^+\) T-cells that mount cross-reactive responses to all strain, respectively. The total virus population is represented by \(v = \sum v_i\). The rates of change of each variable with respect to time (\(t = 0\) being the point when the host acquires infection) are then:

\[
\begin{align*}
\text{Virus population } \frac{dv_i}{dt} & = f_i(v_i, y) - v_i(s_i z + p_i x_i), i = 1, 2, \ldots, n \\
\text{Total } CD_4^+ \text{ T-cells } \frac{dy}{dt} & = k - dy - vvy \\
\text{Strain-specific } CD_4^+ \text{ T-cells } \frac{dx_i}{dt} & = k v y - uv x_i, i = 1, 2, \ldots, n \\
\text{Cross-reactive } CD_4^+ \text{ T-cells } \frac{dz}{dt} & = k' vy - uv z
\end{align*}
\]

The variables \(x_i\) and \(z\) are some fraction of the total \(CD_4^+\) T-cell population. The above equations on solving given the solution:

\[
n < n_c = \frac{px}{(r - sz)}
\]

the number of antigenically distinct strains present, less than a critical antigenic diversity threshold \(n_c\).

Boer and Boerlijst (1994) have discussed a model for the interaction between HIV and the immune system. The authors define a dimensionless virulence parameter which combines both infectivity and antigenicity of a viral strain. They have introduced a model which contains the two thresholds namely the antigenic diversity
threshold and virulence threshold. The virus quasispecies not only increase in diversity but also evolve physiologically different strains. The term diversity threshold is used for the critical variability beyond which the immune system is no longer capable of controlling the virus. But the virulence threshold refers to a diversity in the physiological character of the different strains that all reproduce. The authors have derived the expression for virulence diversity threshold.

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 to the above cited paper used a model under the assumption the HIV induces two kinds of responses.

1. Responses against the specific viral strains and
2. Non-specific responses against all viral strains.

A system of countable many differential equations is used to describe the model for

\[ i = 1, \ldots, N(t) \]

\[ \frac{dv_i}{dt} = v_i(\alpha - \beta z - \gamma x_i) \]

\[ \frac{dx_i}{dt} = \lambda v_i - \xi v x_i \]

\[ \frac{dz}{dt} = v(\xi - \xi z) \]

where, \( v = \sum_{i=1}^{N(t)} v_i \) and \( v_i(t) = \begin{cases} 0 & \text{if} \; \{t; N(t) < i\} \\ v_i & \text{if} \; \inf \{t; N(t) = i\} \end{cases} \)
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

- $\xi$: number of new nonspecific immune cells per unit of time per virus

- $\zeta$: 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 effects of the initial viral diversity are all discussed in this paper. In addition to this the authors have discussed the variations of the antigenic diversity threshold also.

May et al. (1997) answer some points made in a recent paper by Stilianakis and his coworkers on the antigenic diversity threshold model for acquired immune deficiency syndrome pathogenesis. An extended version of the model is then used to compute hazard functions for the human immunodeficiency virus incubation period that are in agreement with empirically observed hazard functions. The hazard function for the extended model is explained by the following set of equations:

\[
\frac{dv_i}{dt} = -v_i(r - px_i - sz), \quad i = 1, \ldots, n,
\]

\[
\frac{dx_i}{dt} = kv_i - bx_i - uv_i, \quad i = 1, \ldots, n,
\]
\[ \frac{dz}{dt} = k' \nu - bz - uvz. \]

The variables \( \nu_i \) denote the population sizes of the different strains of virus. Specific to each viral strain \( i \), there is an immune response denoted as \( x_i \), which includes both cell-mediated and humeral immune responses and which acts only against that viral strain. Variable \( z \) denotes the cross-reactive immune responses that act against all viral strains. It is seen that this model displays three distinct behaviors, corresponding to three different regions of parameter space:

1. There is no asymptomatic phase, and the virus population quickly reaches high levels.
2. The virus produces a persistent infection, but is successfully controlled by the immune system.
3. There is a long asymptotic phase in which the virus level is controlled by the immune system, followed by disease in which the virus reaches high levels.

Sathiyamoorthi and Kannan (2001) have discussed about a stochastic model for estimating the expected time to seroconversion. They have used the shock model and cumulative damage process as discussed by Essary et al. (1973). In developing such model they have taken the antigenic diversity threshold as a random variable following the exponential distribution which has the so-called Lack of Memory Property.

Alexander Langa and Ferguson (2009) have discussed the concept of antigenic diversity, transmission mechanism and pathogens. The authors have discussed the above concept in general and applicable to the HIV infection also. The author indicate
that the successive volume of the transmitted pathogens depend upon several factors such as the nature of pathogens the frequency the nature of contact between the infected and uninfected. The subsequent rate of RNA virus has also been investigated and it’s a very much constant with RNA. The author have indicated that the HIV-I transmission depend upon the Viral load and risk of transmission increase very shortly.

The authors have used the dynamic contact network to calculate the reproduction number of HIV-I pathogens. It has also been shown that the evaluation of the antigenic diversity is a function of the contact rate and infectiousness of the invading pathogens. The antigenic diversity plays vital role in the transmission per contact probability. The authors developed a simple multistrains model of the within-host dynamic of infection. In doing so they used the system of ordinary differential equations. The network model is also used to explain the intensity of transmission dynamic.

Niyamathulla *et.al.* (2012) have discussed the Stochastic Model which could be used to determine the expected time to seroconversion of HIV infected. The authors indicate that the seroconversion occurs when the Antigenic Diversity of the invading antigens or the virulence of the invading antigens increase and cross the individuals’ threshold levels. The seroconversion occurs if any one of the two exceeds threshold level. In doing so the authors have used the concept of shock models and cumulative damage process by Essary *et.al.* (1973). The expression for computing the expected time to seroconversion and its variance have been obtained. The authors have discussed about the variation in the expected time to seroconversion due to the
changes in the parameters of the distributions of random variables involved in the model.

Bill (1994) has discussed about the parasite perspective virulence. According to the author the parasites harm their hosts and what is the reason for the same. The parasites may be classified as virulence type and virulent types. The concept of virulence is a matter of interest for the medical personnel and researchers and also to biologists. The traditional interpretation of virulence is based on mortality of the host’s cells. If the virulence of the invading antigens is higher then the mortality of the hosts cells will be at a higher rate. The authors have indicated several models of virulence evaluation due to direct transmission of the parasite in to hosts species.

Boer et.al. (1994) propose a model for the interaction between human immunodeficiency virus and the immune system. Two differential equations describe the interactions between one strain of virus and one clone of T lymphocytes. The authors use the model to generalize earlier results pertaining to the AIDS diversity threshold.

Lipsitch et.al. (1995) observe that the study on the relation between the transmission of pathogens and the evolution of virulence is given more of importance in recent times. The conventional approach is that the parasites should the relatively benign to their hosts but in recent times it is assumed that they develop more of resistance to immune clearance. Virulence has a number of different meanings and increase in the transmission results in increase the virulence which implies that the host cells suffer grater loss. The authors have discussed a model in which the
virulence namely the disease which induces death rate of the cells and its influence over the infectivity is discussed.

The authors have used the concept of law of diminishing returns which is a basic concept of economics. It is also observed that the increase in the sexual contact diversity promotes the evaluation of more virulent sexually transmitted parasites.

Frank (1996) has discussed about the various models of parasite virulence. According to the authors the virulence may be defined as the severity of the disease due to the infection by the parasite. The rapidity of the exploitation of the resources held by the host cells will lead to higher reproductive rates of the antigens. But at the same time damage is high as the strength of the host which leads to the non availability of the needed support. Several theories and models have been formulated regarding the virulence gained by the invading antigens. The so called trade off theory says that the relative rates of horizontal and vertical transmission of the antigens determine the virulence. In horizontal transmission the parasite usually gains by exploiting the host to increase the rate of infectious transfer that leads to higher virulence. The rate at which the hosts clear an infection can influence the virulence. Similarly the rate at which the transmission of the parasite takes place influences the virulence. The authors have also given a very detailed account of the relationship between the different factors of the host cell and their influence over the virulence gained by the invading antigens.

Bittner et.al. (1997) have used mathematical models for the interaction between virus replication and immune responses. The authors also show that the immune system can provide selection pressure for or against viral diversity. This
paper provides new insights into the relationship between virus load and antigenic diversity. Antigenic variation can increase virus load during infections, but the correlation between load and diversity in comparisons among different infected individuals can be positive or negative, depending on whether individuals differ in their cross-reactive or strain–specific immune responses.

The authors derive two models, first model applies to any replicating parasite that can escape from immune responses; second model includes immune function impairment and specifically describes infections with the human immunodeficiency virus (HIV).

Deitsch et al. (1997) focus initially on biological forms of antigenic variation and virulence of different protozoal, bacterial and fungal infections in humans. The authors also review the molecular determinants of the corresponding host-parasite interactions and finally explore common characteristics of hyper mutable genetic loci that mediate the high rate of phenotypic variation that facilitate adaptation to host micro environments and evasion of host clearance mechanisms. They have discussed about biological forms of antigenic variation and virulence of different bacterial infection in humans. The authors observed that the immunological factors responsible for disease controlling immunity remain uncertain. No increase was observed in parasitemia levels malaria frequency or rates of cerebral malaria in HIV positive patients. The differentiation of T-cell activation and reduced gamma macrophages in individuals with AIDS may thus not dramatically affect immunity to malaria. It is also observed that the phenotypic diversity is characteristic of many bacterial pathogens.
Alizon and Baalen (2005) have discussed how a convex trade off between transmission and virulence arises when the parasites enter into a human body. In most of the models it is assumed that the virulence is due to fact that parasites can increase its transmission and it is only by causing more harm to its host. Virulence is also due to fact that a parasite can increase its transmission rate. In many cases the immune system is incapable of clearing the parasite which results in persisting infection. The authors have derived the differential equations to describe the dynamics of within hosts system which is associated with the virulence of the invading antigens.

The authors have also stated that a parasite maximizes its basic reproduction ratio by optimizing the combination of transmission and virulence. So the reproduction of parasites depend open the extent of virulence the parasite poses.

Chen et.al. (2005) have discussed in detail the concept of virulence and its impact on the incidence of disease and its progression. According to the authors the term virulence refers to a quantitative measure of the pathogenicity or the likelihood of a pathogen causing infection. In recent years rapid progress in bacterial genomic sequencing has led to the discovery and characterization of many new virulence factors. The authors have discussed in detail the reference data base for bacterial virulence factors. The approach is from a software viewpoint and using the same software programs Identification of virulence factors for different types of bacterial is made possible.

Graham et.al. (2005) have discussed the concept of immune pathology and the impact of the same in the development of parasite virulence. Virulence in evolutionary terms is defined as the negative impact of infection upon host fitness.
Two sources of virulence are damage due to direct effects of parasites as well as damage due to infection-induced immune pathology. It is very difficult to identify the two sources of virulence but they have many different evolutionary implications. They impact of increasing virulence without increasing transmission may have body effect on the immune system of the host organisms or individuals. So the control of virulence is possible by pathological immune responses. The authors suggest that a theoretical study to explore how immune pathology has impact of evaluation of virulence is very useful.

Herbeck et.al. (2008) have discussed about of lack of evidence for changing virulence of HIV-I patients with particular reference to North America. According authors to the virulence of the invading antigens is a major consideration in the progression of HIV-I to the AIDS pandemic. It is observed that the host –pathogen interactions suggest that the host and pathogens can co-adapt to each other with pathogens becoming less virulent over time. The pathogens virulence is very commonly measured in host mortality. In the case of HIV-I the direct measure of virulence is the time from initial infection to the development of clinical AIDS symptoms and death. The study reveals that the virulence has its roll and play in the posses of seroconversion. However, it is the not clear whether the antiretroviral therapy will have negative impact on the virulence of the human immunodeficiency virus.

Mantal (2012) has discussed the concept of virulence and convestigated whether the virulence of the parasite after benefits to the parasite. According to the authors the survival of the parasite depends upon the condition in which the parasites grow and multiple. The death of the hosts cell the limit the evaluating process of the
parasite. Virulence is defined as the reduction in the host fitness due to parasite infection. Virulence is indicated by the mortality of the infected hosts. Evaluation of the parasite virulence is based on a tradeoff between the advantage of within host replication and disadvantage of such replication on host survival. So, if the virulence of the invading antigens is higher than the death of the host cell will be at a shorter duration. Over time the virulence of the invading antigens is likely to decrease because the host cells are poor in number and in their capacity to fight against the antigens.