CHAPTER - II

MATHEMATICAL MODELLING OF HIV/AIDS AND LITERATURE SURVEY
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2.0 INTRODUCTION

Mathematical models are an important tool in the study of the transmission of HIV and for short and long term prediction of HIV and AIDS incidence. Models are useful in furthering our knowledge and understanding of many aspects of HIV dynamics including the effects of behavioral changes and preventive measures on its transmission dynamics, its effects on demographic parameters and the results of its direct interaction with the immune system.

For accurate prediction, various epidemiological parameters that determine the spread and distribution of the infection and the disease have to be studied. We need to have accurate information on many processes including the duration and intensity of infectiveness of HIV infecteds, the probability of transmitting the infection to a susceptible sexual partner as a function of the type and duration of sexual activity, the proportion of infecteds who will develop AIDS and prevailing level of heterogeneity in sexual activity with defined communities. Any model used to predict the number of infected people and AIDS cases must take into account the variability in duration of infections proceeding AIDS which is necessary to
predict accurately the correct distribution of people developing AIDS. Models are also helpful in determining the demographic and economic impact of the epidemic which in turn help us to develop reasonable, scientifically and socially sound intervention plans in order to reduce the spread of the infection. For modelling purpose, it is generally assumed that once symptoms of AIDS are diagnosed, such individuals are effectively isolated and removed from circulation and cease to contribute to viral transmission within the community. This means that the infectious period is contained within the incubation period. It is noted that the latent period is a matter of days or a few weeks, Anderson et al. (1986), which may be taken as negligible when compared with the incubation period but it is almost uncertain how long the infectious period lasts and whether or not infectivity remains constant throughout. In case of seropositivity but apparently 'healthy' patients the situation is more uncertain. Here seropositivity implies persistence viral infection, probably lifelong and hence individuals may constitute a pool of potentially infectious people, however, it may be that their infectiousness is some what less than individuals who go on to develop 'full blown' AIDS, Anderson et al. (1986), Blythe and Anderson (1988).

2.1 OUT LINE OF RELEVANT LITERATURE: MODELLING THE TRANSMISSION OF HIV/AIDS

As pointed out earlier, the transmission of HIV/AIDS depends upon many epidemiological factors such as latent period, the infections period, the proportion of infected people in the populations having AIDS, type of sexual
activity, heterogeneity in sexual activity etc. Various investigations have been conducted with some of the above mentioned factors but none of them accounts for all.

2.1.1 Simple Models

A simple deterministic model describing the incubation of AIDS is as follows. Let $Y(t)$ denote the proportion of infectives (all of whom infected with HIV at time $t=0$) who have AIDS at time $t$. If we assume that the rate of conversion from seropositivity to 'full blown' AIDS is $\delta(t)$ at time $t$ from the point of infection, then the rates of change of $Y(t)$ and $X(t)$ (the proportion who do not have AIDS; $X+Y=1$) are given by Anderson et al. (1986).

$$\frac{dX}{dt} = -\delta(t)X(t) \quad (2.1)$$

$$\frac{dY}{dt} = \delta(t)X(t) \quad (2.2)$$

The initial condition is $X(0) = 1$ and $Y(0) = 0$. We assume for simplicity that all infecteds develop AIDS. A simple assumption concerning the form of the function $\delta(t)$ is that it is linear with an intercept at zero ($\delta(t) = \alpha t$). A rationale to support this assumption would be that the progressive impairment of the patient's immune system through time from the point of infection with HIV results in a linear rise with time in the probability that an opportunistic infection or cancer develops in that patient. With these assumptions the solution of equations (2.1-2.2) is
\[ X(t) = \exp\left(-\frac{1}{2}at^2\right) \quad Y(t) = 1 - X(t) \] (2.3)

The simple model defined by (2.1-2.2) provides a more biologically orientated description of the observed pattern and may thus be more general application in the formulation of models of the transmission dynamics of HIV.

Now we consider a closed population of fixed size \( N \) of homosexuals with no recruitment of susceptibles and no mortality other than that induced by disease. Let this population be subdivided into two classes of \( X(t) \) susceptibles and \( Y(t) \) infectives at time \( t \). The susceptibles becomes infected with a transmission efficiency \( \beta \). In this case model can be written as follows, Anderson et al. (1986),

\[
\frac{dX}{dt} = \frac{\beta cXY}{N} \quad X(0) = X_0 \quad (2.4)
\]

\[
\frac{dY}{dt} = \frac{\beta cXY}{N} - \delta Y \quad Y(0) = Y_0 \quad (2.5)
\]

where \( \frac{\beta cXY}{N} \) denotes the incidence term, \( Y/N \) the probability that a randomly chosen partner will be infected and \( c \) is the average number of sexual partners in a unit time. \( \delta \) is the rate of movement out of infectious class so that \( 1/\delta \) denotes the average incubation period.

In early stages of epidemic, i.e. \( X \equiv N \), equation (2.5) gives
\[ \frac{dY}{dt} = (\beta c - \delta)Y \quad (2.6) \]

Hence

\[ Y(t) = Y(0) \exp[(\beta c - \delta)t] \quad (2.7) \]

Time \( t_d \) of doubling the infection in early stages is found from equation (2.7) as

\[ t_d = \frac{\ln 2}{(\beta c - \delta)} \quad (2.8) \]

The basic reproduction rate \( R_0 \) of HIV infection, defined as the average number of secondary infections generated by one primary infection in a totally susceptible population, is given by

\[ R_0 = \beta c D \quad (2.9) \]

where \( D \) is the average incubation period. The doubling time is, therefore, obtained as

\[ t_d = \frac{\ln 2}{R_0 - 1} \quad (2.10) \]

clearly if \( R_0 > 1 \), the infection triggers an epidemic, otherwise epidemic prevalence is zero if \( R_0 < 1 \). The change in sexual habits among homosexuals, needed to reduce transmission of HIV infection below this threshold, can be obtained from equation (2.9).
From this simpler model the magnitude of $R_0$ can be estimated if doubling time $t_d$ of the epidemic during its initial phase of growth is given in a closed homosexual community.

2.1.2 Models for Homosexual Population


Anderson et al. (1986) described some preliminary attempts to use mathematical models for HIV transmission in a homosexual community. The epidemic data available on HIV infection and the incidence of AIDS was surveyed. After the risk groups and transmission mechanisms were described, doubling times for AIDS incidence were given for risk groups in various geographic locations. Some data were also given for the HIV infectious period, the proportion who develop AIDS, and measures of sexual activity. Models of the early stages of the AIDS epidemic in homosexual men were used to find the reproductive number from the distribution of the AIDS
incubation period and the initial doubling time. The purpose of their modelling was to investigate the effects of various parameters and to help improve our general understanding of the transmission dynamics of HIV infection. Pickering et al. (1986) formulated a model for the spread of HIV and AIDS incidence in the homosexual male population in three large cities. They used a discrete time nonlinear model for the sexual transmission of HIV with several possible courses of progression after infection. The models used trends in anal-rectal gonorrhea incidence to determine the changes in homosexual behaviour. Bailey (1989) presented a model for HIV infection and AIDS in which infected people proceed through a sequence of stages to AIDS and then to death. Mode et al. (1989) considered a stochastic population model of an AIDS epidemic in a population of male homosexuals. Tan (1989) used a stochastic model for the spread of the AIDS virus in a homosexual population. In his model, susceptible persons become HIV latent, infective and then develop AIDS. These equations were solved numerically to assess the effects of various factors on AIDS spread. Kaplan (1989) developed dynamic models that apply to needle sharing population and assumed that a susceptible individual using an infected needle removes the virus from the needle. He illustrated the sensitivity of the model to various parameters and computed basic reproduction.

Blythe and Anderson (1988) also considered on HIV transmission model that encapsulates temporal variation in the infectiousness of HIV-infected persons and variability in the incubation period for AIDS. Variable infectivity was modeled in two ways for a homogeneously mixing homosexual
population. They found their first approach, based on a multi-stage classification, more useful at present. Using two infectivity peaks (one after a short latent period and the other before the onset of 'full blown' AIDS). They observed that the initial phase of the infectiousness will tend to drive the early doubling time of the epidemic, while both peaks will determine the overall magnitude of the epidemic and the magnitude of the unique endemic state. Castillo-Chavez et al. (1989) have analyzed a model where the mean rate of acquisition of new partners depends on the size of the sexually active population. Thieme and Castillo-Chavez (1989) have carried out the theoretical analysis of a more general model and have shown that the exclusive existence of a single initial peak could potentially force the incidence to oscillate.

Lin et al. (1993) developed a HIV-transmission model for a homosexual population of varying size with recruitment into the susceptible class proportional to the active population size and with stages of progression to AIDS and established criteria that determine whether the population size decays asymptotically exponentially to zero or grows asymptotically exponentially to infinity.

2.1.3 Models with Heterogeneity in Various Ways

Most of the above mentioned models consider only one population but HIV transmission takes place in populations that are heterogeneous in a variety of ways and this aspect should be taken in modelling HIV, Knox (1986), Hethcote (1987), Colgate et al. (1989), Jacquez et al. (1989),

A general model for HIV transmission and AIDS has been formulated by Hethcote (1987, 1989). The comprehensive model proposed contains all known transmission routes including homosexual and heterosexual intercourse, needle sharing among intravenous drug users, and blood transfusions. The risk groups in the model were sexually active homosexual and bisexual men, prostitutes, sexually active heterosexual women and men, and intravenous drug using women and men. Koopman et al. (1989) considered selective mixing which specifies the selection of contacts within a mixing group. The contact matrix involves conversation contact activity levels, the mutual acceptability of conversation contacts for sex, and the proportion of mutually acceptable encounters, which result in new sexual partnerships. An example for a homosexual male population shows the difficulty of estimating the relative risk of HIV infection during anal and oral sex.

Some of the important factors in the dynamics of HIV relate to the
heterogeneity of the host population. These considerations include sexual performance (homosexual, bisexual and heterosexual), degree and type of sexual activity (number of partners, length of partnerships, anal sex), age structure, intravenous drug use, socio-economic factors (which affect the level of education and hence the degree of response to education programs) and cultural factors (different degrees of sexual activity for males and females, acceptability and frequency of use of prostitutes etc.). Hyman and Stanley (1988) have developed some risk-based models based on the assumption that individuals with multiple sexual partners are usually infected first and tend to become the major source of spread into those groups with fewer sexual partners. In addition, they have also explored the role of variable infectivity in the context of their model. Dietz (1988) presented a model which takes into account the duration of a partnership and the number of contacts with the same partner and gave an explicit formula for the number of partners during a lifetime which is necessary to maintain the infection at an endemic level. Brauer (1990) described models for the spread of universally fatal diseases like AIDS by incorporating nonlinear contact rates and population dynamics as well as differences in the distribution of infective periods. He has shown that the stability of endemic equilibrium for some kinds of population dynamics may depend on the distribution of infective periods. Hethcote et al. (1991) presented a simulation model for the spread of HIV and subsequent development of AIDS in the population of homosexual men in San Francisco. The dynamic simulation model includes sexually very active subpopulations, migration and a staged progression of HIV infected
persons to AIDS and death. Lin (1991) discussed the HIV/AIDS transmission model with proportionate mixing and found that when the no-disease equilibrium is unstable, the model can have multiple positive endemic equilibria. Dickman et al. (1991) provide a framework for calculating basic reproduction rate for AIDS taking into account simultaneously variable infectivity and pair formation. Gao and Hethcote (1992) considered a number of models for the spread of an infectious disease with density dependent restricted growth of population and disease-related deaths. He concluded that persistence of the infectious disease and disease-related deaths can lead to a new equilibrium population size below the carrying capacity can even cause the population to become extinct. Jong et al. (1993) studied the dependence of transmission on the total population size assuming that the relevant contacts between individuals occur by random encounters. Tan and Byers (1993) developed a stochastic model for the HIV epidemic in a homosexual population and used the model to characterize the HIV infection distribution and seroconversion distribution involving different sexual activity levels and different mixing patterns. Dietz et al. (1993) investigated the effect of variable infectivity on the calculation of basic reproduction rate for AIDS models with partnerships. Williams and Anderson (1994) studied a model of the transmission dynamics of HIV-1 in England and Wales by taking transmission within and between different sexual activity classes and within and between different risk groups such as male homosexuals, intravenous drug users and heterosexuals and described patterns of mixing and sexual contacts. Busenberg et al. (1995) proposed a model for HIV/AIDS epidemic
growth in Asia by assuming that the spread of disease in the community is mainly caused by the sexual interaction between a core group of female prostitutes and young unmarried males. They obtained several threshold parameters to determine persistence of endemic proportions, persistence of total population, and the persistence of infective population. West and Thompson (1996) developed models which reflect the transmission dynamics of both T.B. and HIV and discussed the magnitude and duration of the effect that the HIV epidemic may have on T.B. They found the effect that HIV will have on the general population to be dependent on the contact structure between the general population and the HIV risk groups as well as a possible shift in the dynamics associated with T.B. transmission. Garnett and Anderson (1996) described in detail the role of sexual behavior regarding sexually transmitted diseases and discussed on levels of behavior required for the spread of STDs, how heterogeneity in behaviour and partner choice influences the spread and how the immunity acquired by some individuals acts within a population to alter the effectiveness of control strategies. Velasco-Hernandez et al. (1996) studied models for sexual transmission of HIV/AIDS that incorporate changes in behaviour and the effects associated with HIV treatment. The recruitment rate into the core is assumed to be a function of the prevalence of the disease within the core, and it may trigger the existence of periodic solutions provided that there is at least a weak demographic interaction with the noncore. Gani et al. (1997) considered models for the spread of HIV in prisons in both deterministic and stochastic cases. The possibilities for intervention in a prison are outlined and a simple cost-
effectiveness analysis in the context of screening and quarantine in undertaken. Chen (1997) presented a dynamic model for HIV transmission for a homogeneously mixing population of varying size with constant recruitment rate and with stages of progression to AIDS. Hyman et al. (1999) studied the impact of variations in infectiousness by taking into account different levels of virus between individuals during the chronic phase of infection and the increase in the average time from infection to AIDS that goes along with a decreased viral load.

Since the work of McKendrick (1926), it has been recognized that the age-structure of a population is an important factor which affects the dynamics of disease transmission. Several epidemic models incorporating age-structure have been studied, Hoppensteadt (1974, 1975), Dietz (1975), Gripenberg (1983), Schenzle (1984), Anderson and May (1985), Dietz and Schenzle (1985), Tudor (1985), Busenberg et al. (1988). Inaba (1990) studied a mathematical model for an epidemic spreading in an age-structured population with age-dependent transmission coefficient and established some local and global stability results. Greenhalgh (1988) investigated the age-structured epidemic model in case that the transmission coefficient depends on the age of both susceptibles and infectious people.

Gupta and Anderson (1990) described the development of an age-structured model of the transmission dynamics of HIV in a male homosexual population with age-dependent rates of sexual partner acquisition and explored the properties of the model by means of numerical methods. Age-
dependency in rates of sexual partner change acts to increase the initial
growth rate of the epidemic and raises the equilibrium level of endemic
infection in the population when compared with the prediction of a model
without age-structure but with identical initial overall population mean rate of
partner acquisition. In addition, age-dependency in sexual activity acts to
induce demographic changes in the population where the younger more
sexually active males represent an increasing proportion of the population as
the epidemic develops over time. One consequence of this is an increase in
the overall population mean rate of sexual partner change as a direct result of
the mortality induced by AIDS in the older less sexually active classes who
acquired infection at a younger age. Garnett and Anderson (1994) described a
mathematical model of the transmission dynamics of HIV in a heterosexual
population stratified by age, sex and sexual activity. The model represents an
extension of previous studies with a special focus on patterns of mixing or
contact between sexual activity and different age classes of the two sexes.
The relative importance of variation in transmission probabilities and means
rates of partner change on the course of HIV epidemic is also illustrated.

2.1.4 Models with Demography

One of the most important issues before the developing nations is to
determine the demographic consequences of the AIDS epidemic. The impact
of demographic changes is most strongly felt by the young adults which is
also the most economically productive category of the population. Since HIV
infection and subsequent development of AIDS has led to increased death

Many epidemiological models are formulated so that the infectious disease spreads in a population which either is a fixed closed population or has a fixed size with balancing inflows and outflows due to births and deaths or migration. Results for the simplest epidemiological models of these types are given in Hethcote (1976, 1989). Surveys of results for models with constant size populations are given in Hethcote et al. (1981) and Hethcote and Levin (1989). These models have been developed more extensively partly because they are easier to analyze than variable population size models and partly because they are often realistic for human diseases.

For varying population size $N$, one of the simplest models with constant immigration at the rate $Q_0$ and death rate proportional to the population size with constant coefficient $d$ is given by,

$$\frac{dN}{dt} = Q_0 - dN,$$

$$N(0) = N_0$$

(2.11)

where the population approaches an equilibrium size $Q_0/d$. 
Another way is to assume birth and death rates proportional to the population size i.e.

\[ \frac{dN}{dt} = bN - dN, \quad N(0) = N_0 \quad (2.12) \]

where \( b \) and \( d \) are birth and death rate coefficients respectively. The population grows exponentially if net growth rate \( r(=b-d) > 0 \), is constant if \( r = 0 \) and decays exponentially if \( r < 0 \). The population extinction due to exponential decay is demographically unlikely and also exponential growth to infinity is unrealistic due to limited finite resources. Therefore, a demographic structure with density dependent restricted growth is often given by the logistic equation,

\[ \frac{dN}{dt} = rN \left(1 - \frac{N}{K}\right), \quad (2.13) \]

where \( K \) is the carrying capacity of the environment. It may be noted that for \( r > 0 \), \( N \to K \) as \( t \to \infty \).

Most of the demographic models of HIV transmission were developed and analyzed by May, Anderson, and their collaborators. May et al. (1988, 1989) and Anderson et al. (1988) introduced some of the first age-structured models for the sexual transmission of HIV. Conventional demographic models (see Castillo-Chavez, 1989) were combined by May, Anderson and McLean with simple epidemiological models in order to explore the effects of horizontally and vertically-transmitted AIDS upon total population growth.
rates as well as upon age-profile growth rates. Busenberg et al. (1991) analyzed a model of the transmission of the HIV virus that takes demographic change into account and derived thresholds for the persistence of the disease in increasing or decreasing populations. Several HIV models which try to assess demographic impacts are based on the numerical evaluation of very complicated equations incorporating demographic and epidemiological aspects and are aimed at the question whether a population growth can turn into a population decline, UN/WHO (1991). Naresh and Omar (2001) presented a simple deterministic mathematical model to study the transmission of HIV/AIDS in a population with variable size structure. The model is applicable to a population of homosexual males with constant immigration rate and natural mortality rate. Aggarwala (2002) analyzed an HIV/AIDS model with a high risk and low risk population and concluded that in Canada, people at high risk are more likely to contact the disease than those who are at low risk.

The classical models for sexually transmitted infectious diseases assume homogeneous mixing either between all males and females or between certain subgroups of males and females with heterogeneous contact rates. This implies that everybody is all the time at risk of acquiring an infection. These models ignore the fact that the formation of a pair of two susceptibles renders them in a sense temporarily immune to infection as long as the partners do not separate and have no contacts with other partners. Many pair formation models for sexually transmitted diseases and HIV have been studied, Dietz and Hadeler (1988), Dietz (1988), Waldstatter (1989), Dietz (1989),
Kretzchamar et al. (1994), Inaba (1997), Kretzchmar and Dietz (1998). In particular Dietz and Hadeler (1988) takes into account the phenomenon of pair formation by introducing explicit a pairing rate and a separation time. The infection transmission dynamics depends on the contact rate within a pair and the duration of a partnership. They shown that endemic equilibria can only exist if the separation rate is sufficiently large in order to ensure the necessary number of sexual partners. Dietz (1989) described and analyzed pairing models without infection and with constant and variable infection probability per contact. Castillo-Chavez (1989) formulated a pair formation model structured by disease-age. Dieckman et al. (1991) provide a framework for calculating basic reproduction rate for AIDS taking into account simultaneously variable infectivity and pair formation. Diekmann et al. (1990, 1991), Heesterbeek (1992) and Dietz et al. (1993) described the transmission dynamics for sexually transmitted diseases as a discrete process on generations of infected individuals and established the algorithm for calculating basic reproduction rate which can take into account an arbitrary but finite number of disease-states and partnership-states. Knolle (1990) considered the transmission process of HIV as a Markov process to calculate its basic reproduction ratio. Mode and Dietz (1994) pointed out that many results derived from deterministic pair formation models for STD could be induced by some stochastic model for individual process. Inaba (1997) developed a structured population model for the HIV infection spread by pair formation in bisexual populations structured by disease-age and pair duration. By linearizing the basis system he derived a linear system describing HIV
invasion process in a demographically steady population and calculated the basic reproduction ratio in order to examine possible effects of parameter changes on $R_0$. Under the assumptions that infected individuals do not develop AIDS he proved that the basic reproduction ratio depends on the pair formation rate and transmission probability in a monotone way. Kretzschmar and Dietz (1998) studied the transmission of an infection without recovery with and without partnership formation in a non-closed population under the assumption that an infected individual's infectivity is constant during the infectious life time. The demographic process is assumed to be simple with a constant recruitment into the population and the time spent in the population is exponentially distributed with a constant mean. The models were also extended to include variable infectivity.

2.1.5 Models for IDUs

Intravenous drug users (IDUs) are particularly vulnerable to infection from HIV/AIDS of all the different ways that the HIV can be passed on, directly injecting a substance contaminated with HIV into the blood stream is one of the most efficient way.

drug injection equipment in shooting galleries. Greenhalgh (1996, 1997) illustrated the importance of heterogeneity in the needle sharing rate and efficiency of needle cleansing. Seitz and Muller (1994) have also argued that variable infectivity can have a substantial effect on the spread of HIV among both IDUs and heterosexual populations. Greenhalgh and Lewis (2001) examined the spread of HIV when this disease is transmitted through the random sharing of contaminated drug injection equipment and explored the extent to which control strategies such as needle exchange and improved needle cleaning can reduce the risk of a HIV epidemic. Capasso et al. (1995) discussed a deterministic model, which assumes that addicts share needles in friendship groups. They showed that for the prevalence of disease to reach an endemic equilibrium among the population, the basic reproduction number must exceed unity. If the basic reproduction number is less than or equal to unity then the disease will die out in all addicts and all needles.