CHAPTER 2
A MODEL OF HIV POPULATION TO SEROPOSITIVITY

2.1 INTRODUCTION

Acquired Immunodeficiency Syndrome (AIDS) is the most severe form of infection caused by a virus called the Human Immunodeficiency Virus (HIV). Human immunodeficiency viruses belong to a group of virus known as retroviridae (retroviruses). HIV has a RNA genome and a lipid-containing membrane surrounding their capsid. They also have a special viral enzyme, known as reverse transcriptase, which allows the virus to make a DNA copy of its RNA genetic material, facilitating its integration into the genetic material of the host cell. Once inserted into the nucleus of the host cell, it directs this cell to produce more RNA retroviruses. HIV is normally 100-120 nm in diameter, icosahedral in shape and contains a helical nucleocapsid (Figure 2.1). HIV has a special affinity to CD4+ T lymphocytes (T-4 helper cells) and infect them. Those infected are converted into a virus producing cells and eventually destroyed. Newly produced virus are emigrated (liberated) by budding out from the host cell and infect more helper cells, eventually leading to their destruction.

An extensive literature on the mathematical modeling and computer simulation of the spread of virus is given in Anderson (1982), Bailey (1975, 1985, 1986) and Isham (1987). Once an HIV is inside the T-4 cell, the virus remains latent and then it replicates. During this stage, antibodies are produced and detected in the blood shortly (nearly three months) after infection, whereupon the individual has ‘seroconverted’ and is referred to as seropositive. So at this stage, the interest is concerned only
Figure 2.1 Structure of HIV

1. p24
2. RNA
3. Reverse transcriptase
4. p18
5. gp41
6. lipid envelope
7. gp120
in the viral population as well as emigration which contributes for the seropositivity.

The object of the present chapter, is to obtain the first and second order moments and analyse the emigration process. The problem is dealt with by using the product density approach of order one and two of the point processes and the partial differential equations satisfied by these densities are solved to obtain the results for $h_{st}(t)$ (the time-dependent stationarity distribution for the emigration process) which leads to the same result obtained by the first and second order moments.

The layout of this chapter is as follows. In section 2.2, we give the formulation of the model. Section 2.3 is further subdivided into section 2.3.1, 2.3.2, and 2.3.3 respectively. Section 2.3.1, 2.3.2 and 2.3.3 deal with governing equations, moments of the HIV population and the emigration process respectively (Method I), whereas in section 2.4, we deal with the product density approach (Method II). Finally in section 2.5, we give some applications and conclusion.

2.2 FORMULATION OF THE MODEL

In AIDS, the incubation period after infection with HIV is extremely long and is measured in terms of years. The HIV behaves differently depending upon the type of host cells and its level of activity. When an HIV enters the blood stream, it tries to bind itself to the receptors of the T-4 cell. Once it is inside the T-4 cell, the virus remains latent for a considerable period of time and then replicates till the depletion of the cell takes place. The replication may be so rapid, the host cell being unable to hold all, is ruptured and lysis takes place with a release of $10^5$ virions. The HIV released after lysis looks for a new host (Figure 2.2). Thus the HIV population is assumed to evolve according to Kendall’s (1949) process of birth, death, immigration and emigration. The re-entry of HIV in the T-4
Figure 2.2 HIV infection and replication

1. HIV RNA enters the T lymphocyte
2. Reverse transcriptase converts viral RNA into viral DNA in the presence of thymidine
3. Viral DNA becomes incorporated into the host cell DNA
4. HIV infected T lymphocyte becomes a viral factory
cell is known as immigration whereas emigration is through lysis of host cell. The birth-rate is assumed to be specified by the time-dependent function $\lambda(t)$ given by

$$
\lambda(t) = \frac{\beta e^{-\lambda t} (\lambda t)^n}{n!}
$$

where $\beta$ and $\lambda$ are constants and $n$ is a positive integer.

The analysis of age-dependent population growth is rather intractable in its most general form (Bartlett 1966 and Harris 1963) and the moments of the population size can be estimated for some specific age-dependent birth-rates. Each of the HIV, conditional upon its survival, is assumed to have a lifespan consisting of two phases. In the first phase, the HIV is in the blood stream only (no attachment) and it is incorporated into the T-4 cell. The second phase is characterised by the replication of HIV inside the T-4 cell. An HIV, at any time $t$, is in

(i) first phase with probability $e^{\beta t}$ where $\beta$ represents the probability of an HIV incorporated into a T-4 cell and 
(ii) it is in second phase with probability $\beta e^{-\lambda t}$ where $\lambda$ is the probability of replication.

The HIV population immigrate and emigrate at random at constant rates $\nu$ and $\eta$ respectively.

2.3 METHOD I
2.3.1 Governing Equations

Let $X_i(t), \ i=1,2 \ be \ the \ size \ of \ the \ HIV \ population \ at \ time \ t \ in \ phase \ i \ with \ the \ generating \ function \ characterising \ the \ HIV \ population \ given \ by$
\[ g_i(z_1, z_2; t) = \mathbb{E}(z_1^x(t) z_2^{x_2(t)} \mid X_1(0) = 2 - i, X_2(0) = i - 1, v = 0), \quad i = 1, 2 \]  
\hspace{1cm} (2.1)

\[ g(z_1, z_2; t) = \mathbb{E}(z_1^x(t) z_2^{x_2(t)} \mid X_1(0) = X_2(0) = 0, v \neq 0), \quad i = 1, 2 . \]  
\hspace{1cm} (2.2)

We next obtain a relation connecting \( g \) and \( g_1 \). We note that the conditioning on the right hand side of (2.2) implies that the population processes is generated by immigrants. The time to the arrival of first immigrant is exponentially distributed with parameter \( v > 0 \) and that the immigrant will generate a population independent of further immigrants. Hence we obtain the following equation as

\[ g(z_1, z_2; t) = \exp (-ut) + u \int_0^t \exp (-uv) g(z_1, z_2; t-u) g(z_1, z_2; t-u) du. \]  
\hspace{1cm} (2.3)

Solving the above integral equation we obtain

\[ g(z_1, z_2; t) = \exp \left\{ -ut \int_0^t \left[ 1 - g_1(z_1, z_2; u) \right] du \right\} . \]  
\hspace{1cm} (2.4)

The equilibrium distribution of the population is obtained by taking the limit as \( t \to \infty \). We next invoke the branching nature of the process to obtain an equation for \( g_1 \) and \( g_2 \). The constancy of the population rates imply Markov nature and hence by analysing the various possibilities in the infinitesimal interval \((0, \Delta)\) we obtain the following Chapman-Kolmogorov backward equation as

\[ g_1(z_1, z_2; t) = [1 - \beta \Delta] g_1(z_1, z_2; t-\Delta) + \beta \Delta g_2(z_1, z_2; t-\Delta) + o(\Delta) . \]

The above relation is obtained by arguing that the HIV population which is in phase 1, initially
(i) can move to phase 2 in the interval \((0,\Delta)\) with probability 
\(\beta\Delta + o(\Delta)\) and

(ii) can continue to be in phase 1 with the residual probability 
\(1 - \beta\Delta + o(\Delta)\).

Proceeding to the limit as \(\Delta \to 0\) we obtain

\[
\frac{\partial g_1(z_1,z_2;t)}{\partial t} = -\beta g_1(z_1,z_2;t) + \beta g_2(z_1,z_2;t). \tag{2.5}
\]

In a similar way, we get

\[
\frac{\partial g_2(z_1,z_2;t)}{\partial t} = -(\lambda + \eta) g_2(z_1,z_2;t) + \lambda g_2^2(z_1,z_2;t) + \eta \tag{2.6}
\]

with initial conditions given by 
\(g_i(z_1,z_2;0) = z_i, \quad i = 1,2\).

The product term \(g_2^2(z_1,z_2;t)\) arises because of the assumption that 
an HIV population in phase 2 can generate a HIV population (hence in 
phase 2) at a constant rate \(\lambda\). The branching nature of the process leads to 
\(g_2^2(z_1,z_2;t)\).

### 2.3.2 Moments of the HIV Population

Let us introduce the moments \(A^i_k(t), B^j_k(t), A^i(t), B^j(t), i = j = k = 1,2\) as

\[
A^i_k(t) = \frac{\partial^i g_k}{\partial z_i} \mid z_1 = z_2 = 1, \quad A^i(t) = \frac{\partial^i g}{\partial z_i} \mid z_1 = z_2 = 1,
\]

\[
B^j_k(t) = \frac{\partial^2 g_k}{\partial z_i \partial z_j} \mid z_1 = z_2 = 1 \quad \text{and} \quad B^j(t) = \frac{\partial^2 g}{\partial z_i \partial z_j} \mid z_1 = z_2 = 1.
\]
We connect the above moments of $X_t$, $i=1,2$ with the corresponding conditional moments. Now by differentiating both sides of equation (2.4) we obtain

$$A^1(t) = \int_0^t A^1_1(u) \, du$$

(2.7)

$$B^i(t) = \int_0^t B^i_1(u) \, du + A^i(t) A^j(t) , \quad i = j = 1,2 .$$

(2.8)

We next differentiate (2.5) and (2.6) to obtain

$$\frac{d}{dt} A^1_1(t) = -\beta A^1_1(t) + \beta A^2_2(t)$$

(2.9)

$$\frac{d}{dt} A^1_2(t) = -(\eta - \lambda) A^2_1(t) , \quad i = 1,2 .$$

(2.10)

with initial conditions given by

$$A^1_1(0) = A^2_2(0) = 1, \quad A^1_2(0) = A^2_2(0) = 0 .$$

Solving the system of differential equations (2.9) and (2.10) we obtain

$$A^1_1(t) = e^{-\beta t} \quad A^1_2(t) = 0 \quad A^2_2(t) = e^{-(\eta - \lambda)t}$$

and

$$A^2_1(t) = \frac{\beta}{\eta - \lambda - \beta} [e^{\beta t} - e^{-(\eta - \lambda)t}] .$$

(2.11)

Again differentiating (2.5) and (2.6) successively we have

$$\frac{d}{dt} B^i_1(t) = -\beta B^i_1(t) + \beta B^i_2(t)$$

(2.12)

$$\frac{d}{dt} B^i_2(t) = -(\eta - \lambda) B^i_1(t) + 2\lambda A^i_1(t) A^j_2(t) , \quad i = j = 1,2 .$$

(2.13)
The above system of equations can be solved and an explicit expression for $B_i^{ij}(t)$ are given by $(i=j=k=l,2)$:

$$B_2^{12}(t) = B_2^{11}(t) = B_1^{11}(t) = B_1^{12}(t) = 0,$$

$$B_2^{22}(t) = \frac{2\lambda}{(\eta - \lambda)} \left[ e^{-(\eta - \lambda)t} - e^{-2(\eta - \lambda)t} \right] \quad \text{and}$$

$$B_1^{22}(t) = \frac{2\lambda}{(\eta - \lambda)} \left[ \frac{e^{-2(\eta - \lambda)t}}{(2\eta - 2\lambda - \beta)} - \frac{e^{-(\eta - \lambda)t}}{(\eta - \lambda - \beta)} \right] + \frac{2\beta e^{\beta t}}{(\eta - \lambda - \beta)(2\eta - 2\lambda - \beta)}. \quad (2.14)$$

The moments and cross correlations of the equilibrium distribution can now be obtained from equations (2.7) and (2.8) by proceeding to the limit at $t \to \infty$. Hence we get:

$$A_1^{11}(\infty) = \frac{u}{\beta}, \quad A_2^{11}(\infty) = \frac{u}{(\eta - \lambda)}, \quad B_1^{11}(\infty) = \frac{u^2}{\beta^2},$$

$$B_2^{12}(\infty) = B_2^{21}(\infty) = \frac{u^2}{(\eta - \lambda)\beta}, \quad \text{and} \quad B_2^{22}(\infty) = \frac{\lambda u}{(\eta - \lambda)^2} + \frac{u^2}{(\eta - \lambda)^2}. \quad (2.15)$$

### 2.3.3 Emigration Process

Generally we are interested in $N(t_0, t)$ the number of HIV emigrated in a scheme of counting over the interval $(t_0, t_0 + t)$. Now there are two ways of dealing with the emigration process. The first is to deal directly with the probability distribution of the number of HIV emigrated over the interval $(t_0, t_0 + t)$. The second method consists in dealing with the point processes generated by the epoch of emigration (Srinivasan (1988)). The probability distribution of $N(t_0, t)$ or rather $N(t)$ is best studied by introducing a more comprehensive generating function $G_i(z_1, z_2, z; t)$ where
\[ G(z_1, z_2, z; t) = E(z_1^{x_1(t)} z_2^{x_2(t)} z^{N(t)} \mid X_1(0) = 2 - i, X_2(0) = i - 1, \nu = 0) \]  
(2.16)

\[ G(z_1, z_2, z; t) = E(z_1^{x_1(t)} z_2^{x_2(t)} z^{N(t)} \mid X_1(0) = X_2(0) = 0, \nu \neq 0). \]  
(2.17)

The second line of approach is fruitful particularly in view of the results that are already available in sections 2.3.1 and 2.3.2. Hence we proceed as in section 2.3 to obtain these functions by appropriate conditioning at the origin and revert back to the equilibrium condition. Accordingly we define

\[ h_j(t) = \lim_{\Delta \to 0} \frac{\Pr(N(t+\Delta) - N(t) = 1 \mid X_1(0) = 2 - i, X_2(0) = i - 1, \nu = 0)}{\Delta}, \quad j = 1, 2. \]  
(2.18)

\[ h_1(t) = \lim_{\Delta \to 0} \frac{\Pr(N(t+\Delta) - N(t) = 1 \mid X_1(0) = X_2(0) = 0, \nu \neq 0)}{\Delta}. \]  
(2.19)

Now the Poisson nature of the immigration process implies

\[ h_j(t) = u \int_0^t \exp(-ut) [h_j(t-\tau) + h_1(t-\tau)] \, d\tau. \]

Solving the above relation we obtain

\[ h_1(t) = u \int_0^t h_1(\tau) \, d\tau. \]  
(2.20)

Using the definition of \( h_1(\tau) \) we directly obtain

\[ h_1(t) = \eta [A_1(0) + A_2(0)] \]  
(2.21)

where \( A_1(\tau) \) (j=1,2) are the conditional first order moments introduced in section 2.3.2 and are explicitly given in equations (2.11).

Next we note that \( h_1(\tau) \) and \( f_1(\tau) \) are connected by the relation

\[ f_1(\tau) = \lim_{t \to \infty} h_1(t) \]
where

\[ f_1(t) = \lim_{\Delta \to 0} \frac{\Pr(N(t + \Delta) - N(t) = 1 \mid \text{HIV population is in equilibrium initially})}{\Delta}. \]

Hence we get

\[ f_1(\bullet) = \frac{\eta v (\eta - \lambda + \beta)}{\beta (\eta - \lambda)}. \] (2.22)

In order to obtain the expression for \( h_{stty}(t), t > 0 \), we note that for the two emigrations separated by \( t \), the contribution can arise from the same population tree or from different population trees. Using the combinatorial arguments (Srinivasan (1974)) we have

\[ h_{stty}(t) = f_1(\bullet) h_1(t) + \eta \sum_{i,j=1}^{2} B_{ij} h_{ij}(t) \]

where \( B_{ij} \)'s are the equilibrium second order moments of the HIV population. Similarly the function \( h_1^2(t) \) is given by

\[ h_1^2(t) = \eta \left[ A_1^1(t) + A_2^2(t) \right]. \] (2.24)

Further we set \( \lambda = \beta \) for which the expression for \( h_{stty}(t) \) becomes

\[ h_{stty}(t) = h_1(\infty) h_1(t) + \eta [B^{11} + B^{21}] h_1^1(t) + \eta [B^{22} + B^{12}] h_1^2(t) \] (2.25)

where

\[ h_1(\infty) = \frac{\eta^2 v}{\lambda (\eta - \lambda)} \]
\[ h_1(t) = \frac{\eta^2 v}{\lambda (\eta - \lambda)} - \frac{(\eta - \lambda) \eta v}{(\eta - 2\lambda) \lambda} e^{\lambda t} + \frac{\eta v \lambda}{(\eta - 2\lambda) (\eta - \lambda)} e^{(\eta - \lambda) t} \]
Substituting the values for $B^{ij}$ from (2.15) for $i,j=1,2$, we arrive at a simple formula given by

$$h_{st}(t) = \frac{\eta^4 u}{\lambda^2 (\eta - \lambda)^2} \left[ \frac{\lambda^3}{\eta^2} e^{(\eta - \lambda)t} \right].$$

(2.27)

Further if we make the choice $u = \lambda^3 / \eta^2$, we get

$$h_{st}(t) = \frac{\eta^4 u^2}{\lambda^2 (\eta - \lambda)^2} \left[ 1 + e^{(\eta - \lambda)t} \right].$$

(2.28)

### 2.4 METHOD II: PRODUCT DENSITY APPROACH

Let $h^1_i(t)$ ($i = 1, 2$) and $h_1(t)$ be the first order product density of the process $N(t)$ in the absence and presence of immigration (already defined in equations (2.18 - 2.20) of section 2.3.3). Now let

$$h^2_{i}(t_1, t_2)$$

the second order product density of the process $N(t)$ in the absence of immigration defined by

$$\lim_{\Delta_1, \Delta_2 \to 0} \Pr[N(t_1 + \Delta_1) - N(t_1) = 1, N(t_2 + \Delta_2) - N(t_2) = 1 | \Delta_1, \Delta_2]$$

$X_1(0) = 2 - i, X_2(0) = i - 1, u = 0 / \Delta_1 \Delta_2, \quad i = 1, 2$

$h^2(t_1, t_2)$

the second order product density of the process $N(t)$ in the presence of immigration defined by

$$\lim_{\Delta_1, \Delta_2 \to 0} \Pr[N(t_1 + \Delta_1) - N(t_1) = 1, N(t_2 + \Delta_2) - N(t_2) = 1 | \Delta_1, \Delta_2]$$

$X_1(0) = X_2(0) = 0, u \neq 0 / \Delta_1 \Delta_2$. 

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To obtain an equation for $h_1^1(t)$, one observes that in $(0, \Delta)$, the HIV population initially in phase 1

(i) can move to phase 2 with probability $\beta \Delta + o(\Delta)$ and
(ii) can continue to be in phase 1 with the residual probability $1 - \beta \Delta + o(\Delta)$.

Thus

$$h_1^1(t) = (1 - \beta \Delta) h_1^1(t - \Delta) + \beta \Delta h_1^2(t - \Delta) + o(\Delta)$$

which leads to

$$\frac{d}{dt} h_1^1(t) = -\beta h_1^1(t) + \beta h_1^2(t) .$$

Similarly we have

$$\frac{d}{dt} h_i^1(t) = -(\eta - \lambda) h_i^1(t)$$

with initial conditions given by $h_i^1(0) = \eta, i = 1,2$. Solving the above equations (2.30) and (2.31) we obtain

$$h_1^1(t) = \eta \frac{1}{(\eta - \lambda - \beta)} [(\eta - \lambda) e^{\beta t} - \beta e^{-(n-\lambda)t}]$$

$$h_1^2(t) = \eta e^{(\eta-\lambda)t} .$$

The ultimate aim of this section is to find $h_1(t)$, since the limit of $h_1(t)$ as $t \to \infty$ yields the stationary product density of degree one of the point processes of immigration. To obtain $h_1(t)$ one can note that in $(0, \Delta)$, the following mutually exclusive and exhaustive events are possible:

(i) an HIV enters the system by immigration with probability $\nu \Delta + o(\Delta)$ and
(ii) no HIV enters the system by immigration; this occur with the residual probability $1 - uA + o(A)$.

In case (i), the contribution to the first order product density arising from a single HIV population present at time $\Delta$ is $h_1^1(t - \Delta)$; in addition, there is a contribution due to immigration in the interval $(\Delta, t)$ and this is obviously $h_1(t - \Delta)$. Thus one has

$$h_1(t) = uA[h_1^1(t - \Delta) + h_1(t - \Delta)] + (1 - uA) h_1(t - \Delta) + o(\Delta). \quad (2.34)$$

Proceeding to the limit as $\Delta \to 0$, we have

$$\frac{d}{dt} h_1(t) = uh_1^1(t) \quad (2.35)$$

with $h_1(0) = 0$.

Solving (2.35) one obtains

$$h_1(t) = \frac{\nu(\eta - \lambda + \beta)}{\beta(\eta - \lambda)} - \frac{(\eta - \lambda)\nu}{(\eta - \lambda - \beta)\beta}e^{\beta t} + \frac{\eta\beta e^{-(\eta - \lambda)t}}{(\eta - \lambda - \beta)(\eta - \lambda)} \quad (2.36)$$

which leads to

$$h_1(\infty) = \frac{\nu(\eta - \lambda + \beta)}{\beta(\eta - \lambda)} \quad (2.37)$$

Similarly the equations satisfied by $h_2^i(t_1,t_2)$, $i = 1,2$ are given by

$$\left( \frac{\partial}{\partial t_1} + \frac{\partial}{\partial t_2} \right) h_2^1(t_1,t_2) = -\beta h_2^1(t_1,t_2) + \beta h_2^2(t_1,t_2) \quad (2.38)$$

$$\left( \frac{\partial}{\partial t_1} + \frac{\partial}{\partial t_2} \right) h_2^2(t_1,t_2) = -(\eta - \lambda)h_2^2(t_1,t_2) + 2\lambda h_1^2(t_1)h_1^2(t_2) \quad (2.39)$$

with initial conditions $h_2^i(0,t_2) = 0$, $i = 1,2$. 
Similarly we get

\[
\left( \frac{\partial}{\partial t_1} + \frac{\partial}{\partial t_2} \right) h_2(t_1, t_2) = \nu h_2^1(t_1, t_2) + \nu \left[ h_1(t_1)h_1^1(t_2) + h_1(t_2)h_1^1(t_1) \right]
\]

(2.40)

the initial condition being \( h_2(0, t_2) = 0 \).

To solve (2.38) and (2.39) the well-known method of characteristics is used. In this case, the characteristics are given by

\[
\frac{dt_1}{t_1} = \frac{dt_2}{t_2}
\]

which on integration yields \( t_2 - t_1 = \) a constant.

Now rewriting equations (2.38) and (2.39) using the transformations \( t_1 = t_1, t = t_2 - t_1 \) and indicating the transformed functions \( h_i^j(t_1, t+t_1) \) \((i=1,2)\) and using the notation \( h_i^j*(s,t) \) to denote the Laplace transforms of the function \( h^j_i(t_1, t_2) \) with reference to \( t_1 \), the solution leads to

\[
h_2^1*(s,t) = \frac{2\lambda\eta^2 e^{(\eta-\lambda)t}}{(s + \eta - \lambda)(s + \lambda)(s + 2\eta - 2\lambda)}
\]

(2.41)

whereas the Laplace transforms solution of equation (2.40) is given by

\[
sh_2^2*(s,t) = \frac{\nu^2\eta^4}{\lambda^2(\eta-\lambda)^2} + \frac{2\lambda\eta^2 e^{(\eta-\lambda)t}}{(s + \eta - \lambda)(s + \lambda)(s + 2\eta - 2\lambda)}
\]

Setting \( \lambda = \beta \) and using \( \lim_{s \to 0} sh_2^2(s,t) = h_{sty}(t) \) we have

\[
\lim_{t_1, t_2 \to \infty} h_2(t_1, t_2) = h_{sty}(t) = \frac{\eta^4\nu}{\lambda^2(\eta-\lambda)^2} \left[ \nu + \frac{\lambda^3}{\eta^2} e^{(\eta-\lambda)t} \right].
\]
Choosing \( \nu = \frac{\lambda^2}{\eta^2} \) we obtain

\[
h_{st}(t) = \frac{\eta^4 \nu^2}{\lambda^2 (\eta - \lambda)^2} \left[ 1 + e^{(\eta - \lambda)t} \right]
\] (2.42)

a result in agreement with the first and second order moments of section 2.3.3.

\[ \square \]

2.5 CONCLUSION AND APPLICATIONS

In this chapter, a direct and simple method of calculating the correlation function of the emigration process which are the product densities of order one and two of the point processes have been provided. The above model is also dealt with the first and second order moments and expression for \( h_{st}(t) \) are obtained. The partial differential equations satisfied by these densities are solved to get results for \( h_{st}(t) \) which tally with those obtained in section 2.3.3.

The method of product density has many applications in various fields and in particular cascade processes (Bharucha-Reid (1960)). In this, the fluctuation of the total number of particles in the entire energy range can be calculated through the determination of the density of particles in any particular energy interval and the correlation between particles in two different energy intervals. It is this feature which distinguishes the 'Bhabha-Ramakrishna' product density method from the earlier method. The same method is also applied in particle physics as well as in optics (Srinivasan (1988)).