

Some new approaches for modeling the incubation period of HIV/AIDS epidemic

RAVANAN, R.

Reader in Statistics, Presidency College, Chennai 600 005, India

VENKATESAN, P.

Deputy Director, TRC, ICMR, Chennai-600 031, India

Abstract: The time duration between HIV seroconversion to AIDS known as Incubation period is very long and highly variable across groups. Several models for incubation period distribution were studied by many author. In this paper we propose new approaches to model the distribution of the incubation period of HIV/AIDS epidemic using the stages of the disease, the threshold level and cumulative invasion of the immune system. But each model has its own limitations.

1. INTRODUCTION

The HIV incubation period is the random time between the HIV infection and the on set of clinical AIDS symptoms. The probability distribution of this non-negative random variable is known as HIV incubation period distribution. Medley *et al.*, (1987) showed that the incubation period of HIV is known to be very long and it is likely variable within and between cohorts.

The analysis of incubation period is very important in AIDS epidemic studies. Incubation period distribution is assumed to be exactly known in backcalculation methodology. Several authors including Kalbfleisch and Lawless (1989), Jewell (1990), Rosenberg and Gail (1990), Hethcote *et al.*, (1991), Bachetti *et al.*, (1993), Brookmeyer and Gail (1986, 88, 94), Mariotti and Cascioli (1996) and Tan (2000) have observed that backcalculation estimates are very sensitive to the choice of incubation period distribution. Anbupalam *et al.*, (2002), Anderson *et al.*, (1989), Soloman and Wilson (1990), Brookmeyer 19991, 96), Longini *et al.*, (1999), Rosenberg and Gail (1990), Becker and Marschner (1993), Lawless and Sun (1992), Liao and Brookmeyer (1995) and Tan *et al.*, (1996) including several others have shown that the HIV incubation distribution is significantly affected by age, treatment by antiviral drugs and other opportunistic infections. Hence for estimation of the HIV infection and projection of future HIV prevalence and AIDS, it is very much important to study the HIV incubation distribution under different conditions.

In this paper some of the probability distributions that were used in the literature for modeling incubation period are presented. Some new models for incubation period are also proposed.

2. STATISTICAL MODELS FOR INCUBATION PERIOD

The incubation period models are similar to survival models based on non-negative random variables and can be fitted using either parametric or semi-parametric approach. Here we restrict our attention to only parametric models for incubation period.

Weibull and Gamma Models

Weibull and gamma models are the most commonly used models for many real data applications and in particular for backcalculation approach. Between the two, Weibull model is a popular candidate for HIV incubation period because of its nice properties viz., proportional hazard as well as accelerated failure time.

The Weibull distribution function is given by

$$F(t) = 1 - e^{-(\lambda t)^\alpha} \quad \lambda > 0, \alpha > 0, t > 0 \quad (1)$$

The density function is given by

$$f(t) = \begin{cases} \alpha \lambda (\lambda t)^{\alpha-1} e^{-(\lambda t)^\alpha} & \lambda > 0, \alpha > 0, t > 0 \\ 0 & \text{otherwise} \end{cases} \quad (2)$$

The hazard function is given by

$$h(t) = \lambda^\alpha \alpha t^{\alpha-1} \quad (3)$$

The hazard function is increasing with t if $\alpha > 1$ and decreasing if $\alpha < 1$. The Weibull model reduces to negative exponential model is $\alpha = 1$ and has the constant hazard rate for this choice. Naturally Weibull models with increasing hazard ($\alpha > 1$) have been in many studies for modeling incubation period.

The earliest studies of Weibull incubation period have been attempted by Lui *et al.*, (1986) and Medley *et al.*, (1987). The study of incubation period distribution for transfusion associated AIDS cases is developed by Lui *et al.*, (1986) and is given below:

$$F(t) = 1 - e^{-0.0243 \cdot t^{2.286}} \quad (4)$$

These parameter values correspond to a median incubation period of 4.3 years. Medley *et al.*, (1987) studied incubation period of patients infected by blood transfusion. The fitted parameter values for the Weibull distribution are given in Table 1.

Table 1
Parameter values of Weibull model for patients infected by blood transfusion

Patient group	α	λ
Children (0-4 years)	1.9390	0.3843
Adults (5-59 years)	2.3960	0.1077

Boldson *et al.*, (1988) used gamma, Weibull and log-normal models for incubation time of cohort study for San Francisco AIDS cases. The fitted Weibull model for their data is given by

$$F(t) = 1 - \exp(-0.001296 t^{2.5}) \quad (5)$$

The Weibull HIV incubation model used by Anderson *et al* (1986) is given by

$$F(t) = 1 - \exp(-0.1190 t^{1.9974}) \quad (6)$$

Brookmeyer and Goedert (1989) used the Weibull incubation period distributions based on the study of haemophiliacs over 20 years of age. The fitted Weibull model for their data is given by

$$F(t) = 1 - e^{-0.0021 t^{2.516}} \quad (7)$$

This estimate corresponds to a median incubation of 10 years.

Based on 732 HIV-positive haemophiliacs enrolled in Italian registry, Chiarotti *et al.*, (1994) estimated the incubation distributions assuming three different parametric models: uniform U_1 , uniform in three sub intervals U_3 and truncated Weibull W_1 under two approaches namely the median (M) and median of three random values (R). There are altogether six different approaches to estimate the incubation time of individuals. They found that the incubation time obtained using U_1 and U_3 is same. Therefore they reported only four estimates MU_1 , RU_1 , MW_1 , and RW_1 . The MU_1 represents the incubation time ascertained by taking median of the interval (L , R) and RU_1 refers to median of the 3 different estimates obtained on the interval (L , R). Similarly MW_1 , and RW_1 can be interpreted with reference to Weibull model. The estimates of the four models are given in Table 2.

Table 2
Parameter values of Weibull model for HIV-positive haemophiliacs

Model parameter	Method of estimates			
	MU_1	RU_1	MW_1	RW_1
α	2.9	2.4	2.9	2.6
λ	0.0654	0.0571	0.0699	0.0658
Median incubation time (years)	13.5	15.0	12.6	13.3

Munoz and Xu (1996), based on a Multicentre AIDS Cohort Study (MACS), obtain the following estimated Weibull model.

$$F(t) = 1 - e^{-0.052087 t^{1.285347}} \quad (8)$$

The median incubation period corresponding to the above model is 7.5 years. Other important studies which used the Weibull model for HIV incubation period include, Isham (1989), Kalbfleisch and Lawless (1989) and Rosenberg and Gail (1990).

The gamma distribution is another important parametric distribution used to model incubation period of HIV/AIDS.

The gamma density function is

$$f(t) = \frac{1}{\sigma \Gamma(k)} \left(\frac{t}{\sigma}\right)^{k-1} \exp\left(-\frac{t}{\sigma}\right) \quad t > 0, \sigma > 0, k > 0 \quad (9)$$

The hazard function is

$$h(t) = \frac{f(t)}{1 - F(t)} = \frac{\frac{1}{\sigma \Gamma(k)} \left(\frac{t}{\sigma}\right)^{k-1} \exp\left(-\frac{t}{\sigma}\right)}{1 - \int_0^t \frac{1}{\sigma \Gamma(k)} \left(\frac{x}{\sigma}\right)^{k-1} \exp\left(-\frac{x}{\sigma}\right) dx}; \quad t > 0, \sigma > 0, k > 0 \quad (10)$$

One of the earliest studies that used gamma model for incubation period of HIV is by Medley *et al.*, (1987). The parameters estimates for the gamma models for adults and children are given in Table 3.

Table 3
Parametric values for the gamma models for adults and children

Patient group	K	σ
Children (0-4 years)	2.669	0.911
Adults (5-59 years)	2.473	11.001

The parameter estimates of gamma model obtained by Boldsen *et al.*, (1988) based on the San Francisco AIDS data are $k = 3.130$ and $\sigma = 5.715$ years.

2.2 Log-logistic and Log-normal models

The log-logistic distribution function is

$$F(t) = 1 - [1 + (\lambda t)^\nu]^{-1} \quad \lambda > 0, \nu > 0, t > 0 \quad (11)$$

The density function of the distribution is

$$f(t) = \frac{\nu \lambda (\lambda t)^{\nu-1}}{[1 + (\lambda t)^\nu]^2} \quad \lambda > 0, \nu > 0, t > 0 \quad (12)$$

The hazard function of the distribution is

$$h(t) = \frac{\nu \lambda (\lambda t)^{\nu-1}}{[1 + (\lambda t)^\nu]} \quad (13)$$

The earliest application of log-logistic models for incubation period of HIV among homosexual men was adopted by Lui *et al.*, (1986). Lawless and Sun (1992) also used the log-logistic model for HIV incubation period. The estimates of the parameters obtained

by them are $\lambda = 0.10$ and $\nu = 3.08$. In addition to Weibull model, Chiarotti *et al.*, (1994) used log-logistic model and generalized exponential model for their data. The parameter estimates of the log-logistic model are given in Table 4.

Table 4
Parametric values of log-logistic model

Parameters	Methods of estimates			
	MU_1	RU_1	MW_1	RW_1
λ	0.0694	0.0621	0.0746	0.0704
ν	3.0	2.6	3.0	2.8
Median incubation period (years)	14.4	16.1	13.4	14.2

The log-normal distribution has been used by and Boldsen *et al.*, (1988) for HIV incubation period. Study by Munoz and Xu (1996) have shown that log-normal distribution fits better than Weibull model.

The density function of the log-normal distribution is

$$f(t, \mu, \sigma^2) = \frac{1}{t\sigma\sqrt{2\pi}} \exp\left\{-\frac{1}{2\sigma^2}(\log t - \mu)^2\right\} \quad t > 0, -\infty < \mu < \infty, \sigma > 0 \quad (14)$$

The distribution function is

$$F(t) = \Phi\left(\frac{\log t - \mu}{\sigma}\right) \quad (15)$$

where

$$\Phi(t) = \frac{1}{\sqrt{2\pi}} \int_{-\infty}^t e^{-x^2/2} dx \quad (16)$$

denotes the cumulative distribution function of standard normal variate.

The hazard function of the distribution is

$$h(t) = \frac{\frac{1}{t\sigma\sqrt{2\pi}} \exp\left\{-\frac{1}{2\sigma^2}(\log t - \mu)^2\right\}}{1 - \Phi\left(\frac{\log t - \mu}{\sigma}\right)} \quad (17)$$

The parameter estimates obtained by Boldsen *et al.*, (1988) are given by $\mu = 1.099$ and $\sigma = 0.322$. This estimate corresponds to a median incubation period of 3 years. The parameter estimates for log-normal model based on the study of Munoz and Xu (1996) is given by $\mu = 2.208$ and $\sigma = 0.683$. This estimate corresponds to a median incubation period of 9 years.

2.3 Generalized family

The probability density function of generalized exponential distribution is

$$f(t) = \upsilon \lambda \exp \{-t\lambda\} [1 - \exp \{-t\lambda\}]^{\upsilon-1} \quad t > 0, \lambda > 0, \upsilon > 0 \quad (18)$$

The distribution function is

$$F(t) = 1 - [1 - \exp \{-t\lambda\}]^{\upsilon} \quad (19)$$

The hazard function of the distribution is

$$h(t) = \frac{\upsilon \lambda \exp \{-t\lambda\}}{[1 - \exp \{-t\lambda\}]} \quad (20)$$

The parameter estimates for the above model by Chiarotti *et al.*, (1994) is given in the Table 5.

Table 5
Parametric values of generalized exponential model

Parameters	Methods of estimates			
	MU_1	RU_1	MW_1	RW_1
λ	0.1266	0.1000	0.1351	0.1220
υ	4.2	3.2	4.2	3.8
Median incubation time (years)	15.0	16.5	14.0	14.6

The probability density function of the generalized log-logistic distribution is

$$f(t) = \frac{1}{[\beta(m_1, m_2)t\tau]} [H(t)]^{m_1} [1 - H(t)]^{m_2} \quad t > 0, m_1 > 0, m_2 > 0, \tau > 0 \quad (21)$$

The distribution function is

$$G(t) = \frac{1}{\beta(m_1, m_2)} \int_0^{H(t)} x^{m_1-1} (1-x)^{m_2-1} dx \quad t > 0, m_1 > 0, m_2 > 0 \quad (22)$$

where

$$H(t) = \frac{1}{1 + \exp \{-[\log(t) - \mu]/\tau\}} \quad -\infty < \mu < \infty, \tau > 0$$

and $\beta(m_1, m_2)$ is beta integral. The generalized log-logistic distribution reduces to log-logistic distribution when $m_1 = m_2 = 1$. Singh and George (1987) and Singh *et al* (1988) have shown that the three parameters generalized log-logistic distribution with $m_2 = 1$ fits better than the log-logistic distribution for data on cancer survival analysis. Tan and Byers (1993) have also used the generalized log-logistic distribution as the incubation distribution in their simulation study on stochastic model for HIV epidemic in homosexual population.

Stacy (1962) introduced a generalization of gamma distribution with three parameters. The density function of the three parameter generalized gamma distribution is given by

$$f(t) = \frac{k}{\sigma^\alpha} \frac{t^{\alpha-1} e^{-(t/\sigma)^k}}{\Gamma(\alpha/k)} \quad t > 0, \quad \alpha > 0, \quad k > 0 \quad (23)$$

This model is a generalization of many survival distributions. For example, the standard gamma density is obtained when $k = 1$. The Weibull distribution arises as a particular case when $\alpha = k$ and also the density reduces to negative exponential when $\alpha = k = 1$. Lawless (1980) has shown that the log-normal distribution can be obtained as a limiting case of the generalized gamma distribution.

Stacy has also given the convolution of independent generalized gamma distribution. But the explicit form of the density function is very complicated and therefore some special cases of the convolution have been used in the literature as survival models. The convolution of exponential distribution has been used as incubation model for HIV.

Let X_1, X_2, \dots, X_k be the k independent exponential random variables with mean λ_1 . Then the distribution $T = \sum_{i=1}^k X_i$ is a special case of the convolution of generalized gamma distribution. The probability density function of T is given by

$$f(t) = \sum_{j=1}^k B_{1k}(j) \exp(-\lambda_j t) \quad (24)$$

where $\lambda_j = 1/\sigma_j$ and $B_{1k}(j) = \left(\prod_{i=1}^k \lambda_i \right) / \prod_{\substack{i=1 \\ i \neq j}}^k (\lambda_i - \lambda_j)$ (25)

Longini *et al* (1989) used a staged Markov model to estimate the distribution and mean length of the incubation period from a cohort study of 603 HIV infected individuals who have been followed through various stages of infection. They used the generalized gamma model to describe the transition probabilities of the Markov model. The probability of going from a transient state i to a transient state k at time t is given by

$$P_{ik}(t) = \frac{(-1)^{k-i} \lambda_i \dots \lambda_{k-1} \sum_{j=1}^k \exp(-\lambda_j t)}{\prod_{\substack{l=i \\ l \neq j}}^k (\lambda_j - \lambda_l)} \quad i = 1, 2, \dots, n ; \quad k \geq i \quad (26)$$

In this formulation of the model the incubation period covers three stages going from initial infection stage to the third stage of pre-AIDS symptoms. The estimated parameter values for the incubation period distribution are $k=3$, $\lambda_1 = 0.4571$, $\lambda_2 = 0.019$ and $\lambda_3 = 0.0159$. The mean and median of the incubation period are 9.81 and 8.25 years respectively.

In the same study Longini *et al.*, (1989) formulated a six stage Markov model to describe the progression of HIV infection to ultimate death of the individuals. The parameter estimates obtained in their study are $k=6$, $\lambda_1 = 0.0764$, $\lambda_2 = 0.0665$, $\lambda_3 = 0.0499$, $\lambda_4 = 0.4290$, $\lambda_5 = 0.0408$ and $\lambda_6 = 0.0529$.

3. MIXTURE MODEL

One way to accommodate the variation between-different groups of the population is by using mixture models. Suppose certain proportions of infected individuals p have an incubation period distribution $F_1(t)$ and the remaining proportions $(1 - p)$ have the incubation period distribution $F_2(t)$. Then the incubation period distribution for the entire population of infected individuals is a mixture of $F_1(t)$ and $F_2(t)$ is given by

$$F(t) = pF_1(t) + (1 - p) F_2(t) \quad 0 < p < 1 \quad (27)$$

The infection density function is given by

$$f(t) = pf_1(t) + (1 - p) f_2(t) \quad 0 < p < 1 \quad (28)$$

The above can be generalized to many groups of individuals with the mixture of incubation period density function is given by

$$f(t) = \sum_{i=1}^k p_i f_i(t); \quad 0 < p_i < 1 \quad \text{and} \quad \sum_{i=1}^k p_i = 1 \quad (29)$$

Auger *et al* (1988) considered a mixture of two Weibull densities for the incubation period of pediatric AIDS cases. The mixture of two Weibull densities is given by

$$f(t) = p\alpha_1\lambda_1(\lambda_1 t)^{\alpha_1-1} \exp[-(\lambda_1 t)^{\alpha_1}] + (1-p)\alpha_2\lambda_2(\lambda_2 t)^{\alpha_2-1} \exp[-(\lambda_2 t)^{\alpha_2}]; \quad (30)$$

$$0 < p < 1, \alpha_i > 0, \lambda_i > 0, i = 1, 2; t > 0$$

The parameter estimates obtained by Auger *et al* (1988) were $p = 0.120$, $\alpha_1 = 3.540$, $\lambda_1 = 0.201$, $\alpha_2 = 1.160$ and $\lambda_2 = 0.010$. The mixture of two Weibull distributions was also used by Lui *et al* (1986) in a study of incubation period distribution of sample individuals drawn from San Francisco AIDS data.

4. STAGING MODEL

Under staging models the incubation period is considered to be comprised of stages. The progression from time of infection to AIDS was assumed to occur in 3 stages of Brookmeyer and Liao (1990). The stage 1 refers to HIV infection without immunology abnormalities, stage 2 is the development of pre-AIDS disease and stage 3 is the development of clinical AIDS. The incubation time of an individual by definition is the total time spent on stage 1 and 2. Therefore different models for these two stages can be assumed. Let $h_1(t)$ and $h_2(t)$ denote the hazard functions of the two stages. The

convolution equation for the incubation period comprising of these two stages as given by Brookmeyer and Liao (1990) is

$$F(t) = \int_0^t f_1(u) F_2(t-u) du \quad (31)$$

where

$$f_1(u) = h_1(u) \exp\left\{-\int_0^u h_1(s) ds\right\} \quad (32)$$

and

$$F_2(u) = 1 - \exp\left\{-\int_0^u h_2(s) ds\right\} \quad (33)$$

Suitable changes has to be made in the above formulations to account for calendar time of infection.

Suppose the times spent on the two stages are not independent, then the time spent on the stage 2 can be conditioned on the time spent on stage 1. Under this case Mariotti and Cascioli (1996) have given the survival functions for the second stage as

$$S_2(v/u) = \exp\left\{-\int_u^{u+v} h_2(s) ds\right\} \quad (34)$$

where u is the time spent on the first stage. The distribution function $F_2(\cdot)$ in the convolution equation (33) should be suitably modified by using the survival function $S_2(\cdot)$ given in equation (34).

5. CHANGE POINT MODELS

In this section, the author proposes a change point model for incubation period of HIV. Suppose the incubation time for an individual is t , it is reasonable to assume that between 0 to t , there is a time point τ at which the hazard of incubation changes. The point τ may be the time after infection when the individual realizes the threat of AIDS and seeks some kind of medication. In the following sections some change point hazard models are proposed.

5.1 Change point model with constant hazard

Suppose the hazard before and after the change point is constant, then $h(t)$ is given by

$$h(t) = \begin{cases} \alpha & t \leq \tau \\ \beta & t > \tau \end{cases} \quad (35)$$

The survival function of the change point model is given by

$$\begin{aligned} S(t) &= \exp\left\{-\int_0^t h(x) dx\right\} \\ &= \begin{cases} e^{-\alpha t} & t \leq \tau \\ e^{-\alpha \tau} e^{-\beta(t-\tau)} & t > \tau \end{cases} \end{aligned} \quad (36)$$

The distribution function is given by

$$F(t) = \begin{cases} 1 - e^{-\alpha t} & t \leq \tau \\ 1 - e^{-\alpha \tau} e^{-\beta(t-\tau)} & t > \tau \end{cases} \quad (37)$$

The density function of the change point model is given by

$$f(t) = \begin{cases} \alpha e^{-\alpha t} & t \leq \tau \\ e^{-\alpha \tau} \beta e^{-\beta(t-\tau)} & t > \tau \end{cases} \quad (38)$$

5.2 Change point model with varying hazard

Let the hazard function before and after the change point be as given below.

$$h(t) = \begin{cases} \alpha & t \leq \tau \\ \alpha \nu t^{\nu-1} & t > \tau \end{cases} \quad (39)$$

The survival function is given by

$$S(t) = \begin{cases} e^{-\alpha t} & t \leq \tau \\ e^{-\alpha(\tau-\tau'')} e^{-\alpha t''} & t > \tau \end{cases} \quad (40)$$

The distribution function is given by

$$F(t) = \begin{cases} 1 - e^{-\alpha t} & t \leq \tau \\ 1 - e^{-\alpha(\tau-\tau'')} e^{-\alpha t''} & t > \tau \end{cases} \quad (41)$$

The density function is given by

$$f(t) = \begin{cases} \alpha e^{-\alpha t} & t \leq \tau \\ e^{-\alpha(\tau-\tau'')} e^{-\alpha t''} \alpha \nu t^{\nu-1} & t > \tau \end{cases} \quad (42)$$

5.3 Change point model with Weibull hazard

Suppose the hazards before and after the change point is that of Weibull distribution then the hazard function of the change point model is given by

$$h(t) = \begin{cases} \lambda_1 \nu_1 t^{\nu_1-1} & t \leq \tau \\ \lambda_2 \nu_2 t^{\nu_2-1} & t > \tau \end{cases} \quad (43)$$

The survival function is given by

$$S(t) = \begin{cases} e^{-\lambda_1 t^{\nu_1}} & t \leq \tau \\ e^{-\lambda_1 [\tau^{\nu_1}] e^{-\lambda_2 [t^{\nu_2} - \tau^{\nu_2}]} & t > \tau \end{cases} \quad (44)$$

The distribution function is given by

$$F(t) = \begin{cases} 1 - e^{-\lambda_1 t^{v_1}} & t \leq \tau \\ 1 - e^{-\lambda_1 |\tau^{v_1}|} e^{-\lambda_2 |t^{v_2} - \tau^{v_2}|} & t > \tau \end{cases} \quad (45)$$

The density function is given by

$$f(t) = \begin{cases} v_1 \lambda_1 t^{v_1-1} e^{-\lambda_1 t^{v_1}} & t \leq \tau \\ e^{-\lambda_1 |\tau^{v_1}|} e^{-\lambda_2 |t^{v_2} - \tau^{v_2}|} \lambda_2 v_2 t^{v_2-1} & t > \tau \end{cases} \quad (46)$$

6. IMMUNE INVASION LEVEL MODEL FOR INCUBATION PERIOD

In this section the author propose a model for incubation period using the concept of invasion to immune system. Suppose at time $t = 0$, a member tested for HIV positive for the first time, experiences a random N number of invasion before he shows clinical symptoms to AIDS. The number of immune invasions N experienced by the individual is assumed to follow a Poisson process with parameter $\lambda (> 0)$. Let the probability that the individual who has already experienced n contacts up to a time t , shows the clinical symptom for AIDS in the interval $(t, t + \Delta t)$ be given by

$$n\mu\Delta t = o(\Delta t), \quad \mu > 0 \quad (47)$$

Then the incubation period of the individual T can be obtained as follows:

$$\text{By definition} \quad f(t) = \lim_{\Delta t \rightarrow 0} \frac{P[t < T < t + \Delta t]}{\Delta t} \quad (48)$$

Therefore $f(t) \Delta t$ denotes the probability that the individual becomes an AIDS case in the interval $(t, t + \Delta t)$ after experiencing n invasions. We assume that the system undergoes at least one invasion before the individual become AIDS in $(t, t + \Delta t)$. Hence

$$f(t) = e^{-\lambda t} \lambda \otimes e^{-(\lambda+\mu)t} \mu + e^{-\lambda t} \lambda \otimes \sum_{n=2}^{\infty} e^{-(\lambda+\mu)t} \lambda \otimes \dots \otimes e^{-(\lambda+(n-1)\mu)t} \lambda \otimes e^{-(\lambda+n\mu)t} n\mu \quad (49)$$

Taking Laplace transform on both sides of (2.5.3), we get

$$f^*(s) = \frac{\lambda}{s + \lambda} \sum_{n=1}^{\infty} \frac{n\lambda^{n-1}\mu}{(s + \lambda + \mu) \dots (s + \lambda + n\mu)} \quad (50)$$

By using partial fraction method, the above equation can be written as

$$f^*(s) = \lambda \sum_{n=1}^{\infty} \frac{1}{(n-1)!} \left(\frac{\lambda}{\mu}\right)^{n-1} \left\{ \sum_{j=0}^n \binom{n}{j} (-1)^j \frac{1}{(s + \lambda + j\mu)} \right\} \quad (51)$$

Inverting the equation (51) we obtain the probability density function as

$$f(t) = \lambda e^{-\lambda t} (1 - e^{-\mu t}) e^{\lambda(1 - e^{-\mu t})/\mu} \quad (52)$$

The density function is unimodal and is given by

$$t_m = \frac{1}{\mu} \log \left(\frac{2\lambda}{2\lambda + \mu - \sqrt{\mu^2 + 4\lambda\mu}} \right) \quad (53)$$

The distribution function can be written as

$$F(t) = \frac{\lambda}{\mu} \int_0^{(1 - e^{-\mu t})} u(1 - u)^{(\lambda/\mu) - 1} e^{(\lambda/\mu)u} du \quad (54)$$

If $\lambda = \mu$, then

$$F(t) = 1 - e^{-\lambda t} e^{1 - e^{-\lambda t}} \quad (55)$$

The hazard function of equation (55) is given by

$$h(t) = \lambda(1 - e^{-\lambda t}) \quad (56)$$

It can be noted that the hazard rate is increasing function of t .

Discussion: Back calculation is ividely held as the most statistically reasonable approach to predict the future AIDS epidemic. Several alternative approaches for both modeling incubation distributions and estimating past HIV infection curves of HIV/AIDS epidemic have been presented. Three new approaches will be broadly effective in providing quantitative estimates of HIV prevalence and AIDS incidence projections. It is not possible to remove all uncertainty surrounding the epidemic but the new model can provide consensus decisions for future planning.

REFERENCES

- [1] Anbupalam, T., Ramanan, R. and Venkatesan P. Backcalculation of HIV/AIDS in Tamilnadu; In Bio Statistical Aspects of Health and Rpidemiology (Eds; Pandey, C.M., Pradeep Mishra and Uttam Singh), Department of Biostatistics, Sanjay Gandhi Postgraduate Institute of Medical Research, Lucknow, India. (2002), 232-243.
- [2] Anderson, R.M., Blythe, S.P., Gupta, S., and Konings, E. The transmission dynamics of the human immunodeficiency virus type 1 in the male homosexual community in the United Kingdom: The influence of changes in sexual behavior. *Phil. Trans. Roy. Soc. Lond. B*, **325** (1989), 45-98.
- [3] Anderson, R.M., Medley, G.F., May, R.M. and Johnson, A.M. A preliminary study of the transmission dynamics of the human immunodeficiency (HIV), the causative agent of AIDS, *IMA Journal of Mathematics Applied in Meidcine and Biology*, **3**, (1986), 229-263.
- [4] Auger, I., Thomas, P., Gruttola, V.D., Morse, D., Moore, D., Williams, R., Truman, B. and Lawrence, C.E. Incubation periods for pediatric AIDS patients. *Nature*, **336** (1988), 575-577.
- [5] Bacchetti, P., Segal, M., and Jewell, N.P. Backcalculation of HIV infection rates, *Statistical Science*, **8**, (1993), 82-119.
- [6] Becker, N.G. and Marschner, I.C. A method for estimating the age-specific relative risk of HIV infection from AIDS incidence data. *Biometrika*, **80**, (1993), 165-178.
- [7] Boldson, J.L., Jensen, J.L., Sogarrd, J. And Sorensen, M. On the incubation time distirbution and the Danish AIDS data. *Journal of Royal Statistical Society, Series A*, **151**, (1988), 42-43.
- [8] Brookmeyer, R. Reconstruction and future trends of the AIDS epidemic in the United States. *Science*, **253**, (1991), 37-42.
- [9] Brookmeyer, R. AIDS, Epidemics and Statistics. *Biometrics*, **52**, (1996), 781-796.
- [10] Brookmeyer, R. and Gail, M.H. Minimum size of the acquired immunodeficiency syndrome (AIDS) epidemic in the United States. *Lancet*, **2** (1986), 1320-1322.
- [11] Brookmeyer, R. and Gail, M.H. A method for obtaining short-term projections and lower bounds on the size of the AIDS epidemic. *Journal of the American Statistical Association*, **83**, (1988), 301-308.
- [12] Brookmeyer, R. and Gail, M.H. *AIDS epidemiology: A quantitative approach*. Oxford University Press, Oxford (1994).
- [13] Brookmeyer, R. and Goedert, J.J. Censoring in an epidemic with an application to hemophilia-associated AIDS. *Biometrics*, **45** (1989), 325-335.
- [14] Brookmeyer, R. and Liao, J. Statistical modeling of the AIDS spread for forecasting health care need. *Biometrics*, **46** (1990), 1151-1163.
- [15] Chiarotti, F., Palombi, M., Schinaia, N., Ghirardini, A. and Bellocco, R. Median time from seroconversion to AIDS in Italian HIV positive hemophiliacs: different parametric estimates. *Statistics in* (1994).

-
- [16] Hethcote, H.W., Van Ark, J.W., and Longini, I.A. A simulation model of AIDS in San Francisco: I. Model formulation and parameter estimation. *Math Biosciences*, **106**, (1991), 203-222.
- [17] Isham, V. Estimation of the incidence of HIV infection. *Spec. Phil.* (1989).
- [18] Jewell, N.P. Some statistical issues in studies of the epidemiology of AIDS. *Statistics in Medicine*, **9**, (1990), 1387-1416.
- [19] Kalbfleisch, J.D. and Lawless, J.F. Inference based on retrospective ascertainment. An analysis of data on transfusion related ADIS. *Journal of the American Statistical Association*, **84**, (1989), 360-372.
- [20] Lawless, J.F. Inference in the generalized gamma and log-gamma distribution. *Thechnometrics*, **22**, (1980), 409-419.
- [21] Lawless, J. and Sun, J. A comprehensive backcalculation framework for the estimation and prediction of AIDS cases. In: "*AIDS epidemiology: Methodological issues*", (Eds. Jewell, N.P., Dietz, K. and Farewell, V.T.), (1992), 81-104.
- [22] Liao, J. and Brookmeyer, R. Empirical bayes approach to smoothing in backcalculation of HIV infection rates. *Biometrics*, **51**, (1995). 579-588.
- [23] Longini, I.M., Clark, W.S., Byers, R.H., Ward, J.W., Darrow, W.W., Lemp, G.H. and Hethcote, H.W. Statistical analysis of the stages of HIV infection using a Markov model. *Statistics in Medicine*, **8**, (1989), 831-843.
- [24] Lui, K.J., Lawrence, D.N., Morgan, W.M., Peterman, T.A., Hauerkos, H.W. and Bregman, D.J. A model-based approach for estimating the mean incubation period of transfusion associated acquired immunodeficiency syndrome. *Proc. Nat. Acad. Science, USA*, **83**, (1986), 3051-3055.
- [25] Mariotti, S. and Cascilio, R. Sources of uncertainty in estimating HIV infection rates by backcalculation: Application to Italian data. *Statistics in Medicine*, **15**, (1996), 2669-2687.
- [26] Medley, G.F., Anderson, R.M., Cox, D.R. and Billard, L. Incubation period of AIDS in patients infected via blood transfusion. *Nature*, **328**, (1987), 719-721.
- [27] Munoz, A. and Xu, J. Models for the incubation of AIDS and variations according to age and period. *Statistics in Medicine*, **15**, (1996), 2459-2473.
- [28] Rosenberg, P.S. and Gail, M.H. Uncertainty in estimates of HIV prevalence derived by Backcalculation. *Annals of Epidemiology*, **1**, (1990), 105-115.
- [29] Singh, K. and George, E.O. (1987). *Generalized log-logistic model for the survival data*, Technical Report. 87-3, Dept. of Mathematics, Central Michigan University, Michigan.
- [30] Singh, K., Lee, C.M.S. and George, E.O. On generalized log-logistic model for censored survival data. *Bimed. Journal*, **30**, (1988), 843-850.
- [31] Solomon, P.J. and Wilson, S.R. Accommodating change due to treatment in the method of back projection for estimating HIV infection incidence. *Biometrics*, **46**, (1990), 1165-1170.

- [32] Stacy, E.W. A generalization of the gamma distribution. *Annals of Mathematical Statistics*. **33**, (1962), 1187-1192.
- [33] Tan, W.Y. *Stochastic modeling of AIDS epidemiology and HIV pathogenesis*. World Scientific Publication, Singapore, (2000).
- [34] Tan, W.Y. and Byers, R.H. A stochastic model of the HIV epidemic and the HIV infection distribution in a homosexual population, *Math. Biosciences*, **113**, (1993), 115-143.
- [35] Tan, W.Y., Tang, S.C. and Lee, S.R. (1996). Characterization of the HIV incubation distribution and some comparative studies. *Statistics in Medicine*, **15**, 197-220.