Multistate Modelling Vertical Transmission and Determination of R_0 Using Transition Intensities

Idah Orowe, Patrick Weke, Joseph Ottieno and Nelson Onyango

School of Mathematics, University of Nairobi, Kenya

Abstract

In this paper multi-state modelling is used to determine the probability distribution of the different states of vertical transmission of HIV. We start with a healthy-infected-dead three state model which we then modify and extend to a four state healthy-infected-treated-Aids four state model. Using the matrix approach we calculate their respection transition probabilities and compare the two models using the basic reproduction number. In both models $R_0 < 1$ suggesting that this mode of transmission will eventually be contained.

Keywords: Multistate modelling, Markov process, transition intensities, transition probabilities, HIV, reproduction number, vertical transmission

1 Introduction

HIV model classifies the population into susceptibles (S) containing individuals who have not been infected with the virus, Exposed (E) individuals who are infected but in the latent stage, Infectives (I) containing individuals who are infected with the virus but have not yet developed AIDS symtoms and the AIDS cases (A) who are those individuals that have developed the disease. The progression is shown in Figure 1. All diseases are however subject to stochasticity in terms of the chance nature of transmission, and so in principle, a stochastic model is always more realistic than a deterministic one but since the relative magnitude of stochastic fluctuations reduces as the number of cases increases, therefore in large populations with a high level of disease

Susceptible

infected

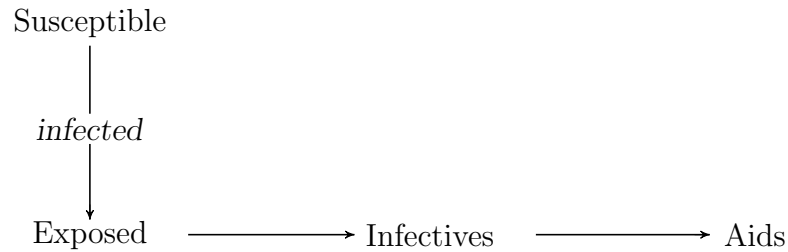Exposed $\longrightarrow$ Infectives $\longrightarrow$ Aids

Figure 1: Progression of HIV infection

incidence a deterministic model may be a good approximation.
Stochastic models are to be preferred when their analysis is possible, otherwise deterministic models should be used. Deterministic models can also serve as introductory models when studying new phenomena. They can also be used as introductory models when studying new phenomena. Both these two types of models play an important role in better understanding the mechanisms of disease spread.

The role played by chance in general is most important whenever the number of infectious individuals is relatively small which can be as a result of the population size being small, when an infectious disease has just invaded or when control measures are successfully applied.
In Mother-to-Child-Transmission (MTCT), also referred to as vertical transmission, the various controls and intervention methods available have greatly reduced HIV transmission in children and as such stochasticity is incorporated in modelling this mode of transmission.

The ultimate outcome of interest in the study of diseases is recovery or death. In addition a number of intermediate (transient) states exists. For these reasons, multi-state models (MSM) are extremely useful in understanding this process by considering the health condition and causes of death as criteria for defining states.

A multi-state model is defined as a model for a (continuous time) stochastic process (X(t), t$\in$ T) which at any time occupies a finite state space $S = \{1, 2 \cdots N\}$ and describe random movements of a subject among various states. In multistate process T=$[0, \tau]$, $\tau < \infty$ is a time interval and the value of the process at time t, the state occupied at that time.
In epidemics the states can describe conditions like healthy, infected and dead. The infected state can further be presented as a series of successively more severe stages of the disease. A change of state is called a transition, or an

event.

A mathematical model of two transient states was first proposed by Du Pasquier (1913). However it was Fix and Neyman (1951) who introduced the stochastic version and resolved many problems associated with the model.

Statistical model specifiction via transition intensities and likelihood inferences is introduced in the two state model for survival analysis, the competing risks and illness-death models and the models for bone marrow transplatation, [1].
In [2] the Markov assumption was used to show that probabilities and actuarial values can be calculated using a time-homogeneous Markov model and in the event that the Markov assumption is found to be inappropriate, the state space can be modified as an alternative to assuming a more general stochastic process.

Several other studies have also been carried out, both theoretical and experimental applying multistate models to estimate transition intensities in diseases (see, for example [6], [7], [10], [11], [12])
Most studies of diseases using multistate models have been restricted to non parametric approach such as Kaplan Meier estimator and Cox proportional hazard models. In this paper the emphasis is on birth death process and solving the Chapman-Kolmogorov differential equations using the generator matrix approach to obtain the transition matrix. Maximum likelihood estimator is used to estimate the transition intensities which are then used in calculating R_0.

2   Formulation of Model

We modify the Susceptibe Exposed Infectious Recovery (SEIR) model into a Suscptible Infected Treatment Aids (SITA) model. The modification involves taking the exposed and infectious stages as one state and calling it the Infected state and introducing a new state called the treatment stage. The Aids stage is assumed to be the removal stage. We consider a population size N with constant inflow of susceptible at rate bN and various categories of the population designated as $S(t), I(t), T(t)$ and $A(t)$.
It is assumed that susceptible children gets infected by their HIV positive mothers either in-utero, intrapartum or postpartum at the rate β. It is also assumed that some of those infected move to the treatment class at a rate of ϕ and then proceed to the AIDS class at a rate α. Those in the AIDS class also join the treated class at the rate ω. The stages, rates and order of the process is shown in the diagram below:

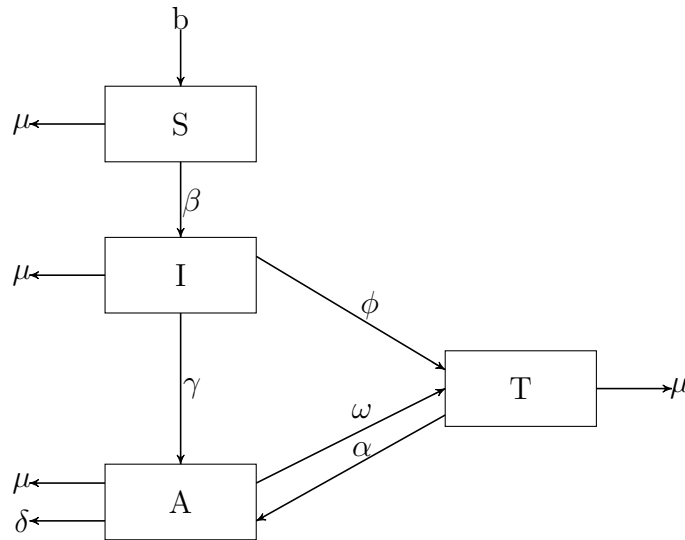This model enables us establish the key parameters in each stage.

Figure 2: HIV Transition model where all parameters are defined in table 1

The three parameters γ, α and δ determine the lifespan of HIV positive children (from acquisition of HIV to AIDS) and thus plays an important role on their survival.

The differential equations describing this system as presented are given as:

$$
\begin{aligned}
\frac{dS}{dt} &= b - \mu S - \beta SI \\
\frac{dI}{dt} &= \beta SI - \gamma I - \mu I - \Phi I \\
\frac{dT}{dt} &= \Phi I - \alpha T - \mu T + \omega A \\
\frac{dA}{dt} &= \gamma I + \alpha T - \omega A - \mu A - \delta A
\end{aligned}
\tag{1}
$$

where $S(t), I(t), T(t)$ and $R(t)$ are the numbers in these classes, so that $S(t) + I(t) + T(t) + R(t) = N$

The Table 1 given below shows all the parameters used in the model.

Table 1: Parameters of the MTCT model

Symbol	Description of Variable	Estimate
b	Natural birth rate	0.03
μ	Natural mortality rate	0.09
β	Rate of newborns infected with HIV	0.15
ϕ	Fraction of infected who get treatment	0.31
γ	Rate of movement from infected to AIDS	0.015
ω	Rate at which AIDS group get treatment	0.105
α	Rate at which treated group develops full blown AIDS	0.07
δ	AIDS induced death	0.18
N	That total number of children exposed to HIV positive mothers	1000

We use Figure 2 to form a four state model for MTCT given. Since there is still no cure for HIV, treatment doesn't lead to recovery and a treated individual is still infected. An infected individual is however able to move from the more severe State 3 to the less severe State 2 due to therapeutic interventions which are able to drastically improve the health status of the individual. The four
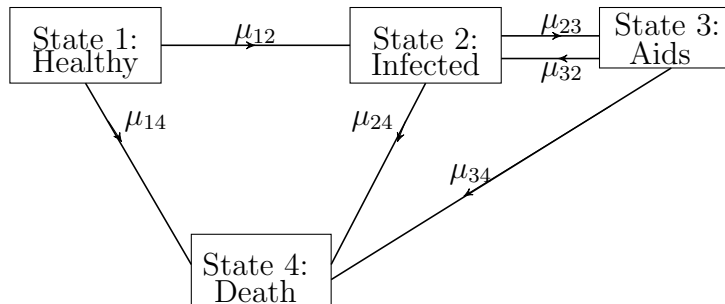

Figure 3: A Summarized Multistate Model for MTCT

state model in Figure 3 forms the Chapman-Kolmogorov equations;

$$P_{ij}(s, t+h) = \sum_{k=1}^{4} P_{ik}(s,t) P_{kj}(t, t+h)$$

from which we may derive the following transition probabilities

$$
\begin{aligned}
P_{11}(s, t+h) &= \sum_{k=1}^{4} P_{1k}(s,t)P_{k1}(t,t+h) \\
&= P_{11}(s,t)P_{11}(t,t+h) + P_{12}(s,t)P_{21}(t,t+h) \\
&\quad + P_{13}(s,t)P_{31}(t,t+h) + P_{14}(s,t)P_{41}(t,t+h) \\
&= P_{11}(s,t)((1-(\mu_{12}+\mu_{14}))h + o(h)) + P_{12}(s,t)\cdot 0 \\
&\quad + P_{13}(s,t)\cdot 0 + P_{14}(s,t)\cdot 0
\end{aligned}
$$

$$
P_{11}'(s,t) = -P_{11}(s,t)(\mu_{12}+\mu_{14}) \tag{2}
$$

This is the transition probability of not remaining in state 1.

$$
\begin{aligned}
P_{12}(s, t+h) &= \sum_{k=1}^{4} P_{1k}(s,t)P_{k2}(t,t+h) \\
&= P_{11}(s,t)P_{12}(t,t+h) + P_{12}(s,t)P_{22}(t,t+h) \\
&\quad + P_{13}(s,t)P_{32}(t,t+h) + P_{14}(s,t)P_{42}(t,t+h) \\
&= P_{11}(s,t)((\mu_{12}h + o(h)) + P_{12}(s,t)(1-(\mu_{23}+\mu_{24})h + o(h)) \\
&\quad + P_{13}(s,t)(\mu_{32}h + o(h)) + P_{14}(s,t)\cdot 0
\end{aligned}
$$

$$
P_{12}'(s,t) = P_{11}(s,t)\mu_{12} - P_{12}(s,t)(\mu_{23}+\mu_{24}) + P_{13}(s,t)\mu_{32} \tag{3}
$$

This gives the transition probability of moving from state 1 to State 2.

$$
\begin{aligned}
P_{13}(s, t+h) &= \sum_{k=1}^{4} P_{1k}(s,t)P_{k3}(t,t+h) \\
&= P_{11}(s,t)P_{13}(t,t+h) + P_{12}(s,t)P_{23}(t,t+h) \\
&\quad + P_{13}(s,t)P_{33}(t,t+h) + P_{14}(s,t)P_{43}(t,t+h) \\
&= P_{11}(s,t)\cdot 0 + P_{12}(s,t)(\mu_{23}h + o(h)) \\
&\quad + P_{13}(s,t)(1-(\mu_{32}+\mu_{34})h + o(h)) + P_{14}(s,t)\cdot 0
\end{aligned}
$$

$$
P_{13}'(s,t) = P_{12}(s,t)\mu_{23} - P_{13}(s,t)(\mu_{32}+\mu_{34}) \tag{4}
$$

Similarly (4) is the transition probability of moving from State 1 to State 3.

$$
\begin{aligned}
P_{14}(s, t+h) &= \sum_{k=1}^{4} P_{1k}(s,t)P_{k3}(t,t+h) \\
&= P_{11}(s,t)P_{14}(t,t+h) + P_{12}(s,t)P_{24}(t,t+h) \\
&\quad + P_{13}(s,t)P_{34}(t,t+h) + P_{14}(s,t)P_{44}(t,t+h) \\
&= P_{11}(s,t)(\mu_{14}h + o(h)) + P_{12}(s,t)(\mu_{24}h + o(h)) \\
&\quad + P_{13}(s,t)(\mu_{34})h + o(h)) + P_{14}(s,t)(1 + o(h))
\end{aligned}
$$

$$P'_{14}(s,t) = P_{11}(s,t)\mu_{14} + P_{12}(s,t)\mu_{24} + P_{13}(s,t)\mu_{34} \tag{5}$$

where (5) is the transition probability of moving from State 1 to State 4 which is an absorbing state.

From the transition probabilities given in equations (2),(3),(4) and (5) we are able to get the transition matrix which is given by

$$Q = \begin{pmatrix} -(\mu_{12} + \mu_{14}) & \mu_{12} & 0 & \mu_{14} \\ 0 & -(\mu_{23} + \mu_{24}) & \mu_{23} & \mu_{24} \\ 0 & \mu_{32} & -(\mu_{32} + \mu_{34}) & \mu_{34} \\ 0 & 0 & 0 & 0 \end{pmatrix}.$$

2.1   Calculation of transition intensities

Define

- E_i as the waiting time of the ith individual in the Healthy state

- F_i as the waiting time of the ith individual in the Infected state

- G_i as the waiting time of the ith individual in the Aids st0ate

For the three state model, for each individual we can record the entire observation via two random variables

$$U^i = \begin{cases} 1, & \text{if the } i^{th} \text{ individual transit from State 1} \\ 0, & \text{if the } i^{th} \text{ individual remains in State 1} \end{cases}$$

$$V^i = \begin{cases} 1, & \text{if the } i^{th} \text{ individual transit from State 2} \\ 0, & \text{if } i^{th} \text{ individual remains in State 2} \end{cases}$$

Let $f_i(u_i, v_i, e_i, f_i)$ be the joint distribution of (U_i, V_i, E_i, F_i). If $(U_i, V_i = 0)$ no transition has been observed. If $(U_i, V_i = 1)$ then transition was observed at time $s + t + \Phi$ where $\Phi = e_i, f_i$

The joint density function is given by

$$f_i(u_i, v_i, e_i, f_i) = \begin{cases} hP_{s+t} & U_i = 0 \\ hP_{s+t} & V_i = 0 \\ e_i P_{s+t}(\mu_{12}(s+t+e_i) + \mu_{14}(s+t+e_i)) & U_i = 1 \\ f_i P_{s+t}(\mu_{23}(s+t+f_i) + \mu_{24}(s+t+f_i)) & V_i = 1 \end{cases}$$

where $0 < e_i < h.$ $0 < f_i < h.$

$$= \begin{cases} \exp\left[-\int_0^h (\mu_{12}(s+t) + \mu_{13}(s+t))\right] & U_i = 0 \\ \exp\left[-\int_0^h (\mu_{23}(s+t))\right] & V_i = 0 \\ \exp\left[-\int_0^{e_i} (\mu_{12}(s+t) + \mu_{13}(s+t))\mathrm{dt}\right](\mu_{12}(s+t+e_i) + \mu_{13}(s+t+e_i)) & U_i = 1 \\ \exp\left[-\int_0^{f_i} (\mu_{23}(s+t))\mathrm{dt}\right](\mu_{23}(s+t+f_i)) & V_i = 1 \end{cases}$$

$$= \begin{cases} \exp\left(-\int_0^{e_i} (\mu_{12}(s+t) + \mu_{13}(s+t))\mathrm{dt}\right)(\mu_{12}(s+t) + \mu_{13}(s+t))^{u_i} \\ \exp\left(-\int_0^{f_i} (\mu_{23}(s+t))\mathrm{dt}\right)(\mu_{23}(s+t))^{v_i} \end{cases}$$

Assuming $\mu_{12}(s+t), \mu_{13}(s+t), \mu_{23}(s+t)$ are constants $\mu_{12}, \mu_{13}, \mu_{23}$ respectively, we get

$$f(u_i, v_i, e_i, f_i) = \begin{cases} e^{-(\mu_{12}+\mu_{13})e_i}(\mu_{12} + \mu_{13})^{u_i} \\ e^{-(\mu_{23})f_i}(\mu_{23})^{v_i} \end{cases}$$

Getting the maximum likelihood estimators we have

$$\begin{aligned} L_n(\mu_{12}, \mu_{13}, \mu_{23}) &= \prod_{i=1}^n f(u_i, v_i, e_i, f_i) \\ &= \prod_{i=1}^n e^{-(\mu_{12}+\mu_{13})e_i}(\mu_{12} + \mu_{13})^{u_i} e^{-(\mu_{23})f_i}(\mu_{23})^{v_i} \\ &= e^{-(\mu_{12}+\mu_{13})\sum_{i=1}^n e_i}(\mu_{12} + \mu_{13})^{\sum_{i=1}^n u_i} e^{-(\mu_{23})\sum_{i=1}^n f_i}(\mu_{23})^{\sum_{i=1}^n v_i} \end{aligned}$$

Let $e = \sum_{i=1}^n e_i, u = \sum_{i=1}^n u_i, f = \sum_{i=1}^n f_i, v = \sum_{i=1}^n v_i,$

Therefore taking the natural logs we get

$$\mathrm{Log}L_n(\mu_{12}, \mu_{13}, \mu_{23}) = -(\mu_{12}+\mu_{13})e + u\mathrm{Log}(\mu_{12}+\mu_{13}) - (\mu_{23})f + v\mathrm{Log}(\mu_{23}) \quad (6)$$

To estimate the transition intensities we defferentiate equation (6) with respect the respective intensities $\mu_{12}, \mu_{13}, \mu_{23}$ which gives

$$\begin{aligned} \hat{\mu}_{12} &= \frac{u - \mu_{13}e}{e} \\ &= \frac{\sum_{i=1}^n u_i - \mu_{13}\sum_{i=1}^n e_i}{\sum_{i=1}^n e_i} \quad (7) \end{aligned}$$

$$\hat{\mu}_{13} = \frac{u - \mu_{12}e}{e}$$

$$= \frac{\sum_{i=1}^{n} u_i - \mu_{13} \sum_{i=1}^{n} e_i}{\sum_{i=1}^{n} e_i} \tag{8}$$

$$\hat{\mu}_{23} = \frac{v}{f}$$

$$= \frac{\sum_{i=1}^{n} v_i}{\sum_{i=1}^{n} f_i} \tag{9}$$

In the extended four state model for each individual we can record the entire observation via the six random variables as follows:

$$U_i = \begin{cases} 1, & \text{if the } i^{th} \text{ individual transit from State 1 to State 2} \\ 0, & \text{if the } i^{th} \text{ individual remains in State 1} \end{cases}$$

$$V_i = \begin{cases} 1, & \text{if the } i^{th} \text{ individual transit from State 1 to State 4} \\ 0, & \text{if } i^{th} \text{ individual remains in State 1} \end{cases}$$

$$W_i = \begin{cases} 1, & \text{if the } i^{th} \text{ individual transit from State 2 to State 3} \\ 0, & \text{if the } i^{th} \text{ individual remains in State 2} \end{cases}$$

$$X_i = \begin{cases} 1, & \text{if the } i^{th} \text{ individual transit from State 2 to State 4} \\ 0, & \text{if the } i^{th} \text{ individual remains in State 2} \end{cases}$$

$$Y_i = \begin{cases} 1, & \text{if the } i^{th} \text{ individual transit from State 3 to State 2} \\ 0, & \text{if the } i^{th} \text{ individual remains in State 3} \end{cases}$$

$$Z_i = \begin{cases} 1, & \text{if the } i^{th} \text{ individual transit from State 3 to State 4} \\ 0, & \text{if } i^{th} \text{ individual remains in State 3} \end{cases}$$

Let $f(e_i, f_i, g_i, u_i, v_i, w_i, x_i, y_i, z_i)$ be the joint distribution of $(E_i, F_i, G_i, U_i, V_i, W_i X_i, Y_i, Z_i)$. If $(U_i, V_i, W_i, X_i, Y_i, Z_i = 0)$, no transition has been observed and therefore there is no change in the status of the different disease states. If however $(U_i, V_i, W_i, X_i, Y_i, Z_i = 1)$ then transition was observed at $x + a_i + \Phi$ where $\Phi = e_i, f_i, g_i$

The joint density function is given by

$$f(\Phi) = \begin{cases} P_{ij}(x+a_i, x+b_i) & i=j & U_i = V_i = W_i = X_i = Y_i = Z_i = 0 \\ P_{12}(x+a_i, x+a_i+e_i)\mu_{12}(x+a_i+e_i) & U_i = 1 \\ P_{14}(x+a_i, x+a_i+ei)\mu_{14}(x+a_i+e_i) & V_i = 1 \\ P_{23}(x+a_i, x+a_i+f_i)\mu_{23}(x+a_i+f_i) & W_i = 1 \\ P_{24}(x+a_i, x+a_i+f_i)\mu_{24}(x+a_i+f_i) & X_i = 1 \\ P_{32}(x+a_i, x+a_i+g_i)\mu_{32}(x+a_i+g_i) & Y_i = 1 \\ P_{34}(x+a_i, x+a_i+g_i)\mu_{34}(x+a_i+g) & W_i = 1 \end{cases}$$

where $0 < e_i \le h$. $0 < f_i \le h$ and $0 < g_i \le h$.

$$f(\Phi) = \begin{cases} \exp\left[-\int_0^{e_i} \mu_{12}(x+a_i+t)dt\right] (\mu_{12}(x+a_i+e_i))^{u_i} & u_i = 0,1 \\ \exp\left[-\int_0^{e_i} \mu_{14}(x+a_i+t)dt\right] (\mu_{14}(x+a_i+e_i))^{v_i} & v_i = 0,1 \\ \exp\left[-\int_0^{f_i} \mu_{23}(x+a_i+t)dt\right] (\mu_{23}(x+a_i+f_i))^{w_i} & w_i = 0,1 \\ \exp\left[-\int_0^{f_i} \mu_{24}(x+a_i+t)dt\right] (\mu_{24}(x+a_i+f_i))^{x_i} & x_i = 0,1 \\ \exp\left[-\int_0^{g_i} \mu_{32}(x+a_i+t)dt\right] (\mu_{32}(x+a_i+g_i))^{y_i} & y_i = 0,1 \\ \exp\left[-\int_0^{g_i} \mu_{34}(x+a_i+t)dt\right] (\mu_{34}(x+a_i+g_i))^{z_i} & z_i = 0,1 \end{cases}$$

Assuming homogeneity, we get

$$f(e_i, f_i, g_i u_i, v_i, w_i, x_i, y_i, z_i,) = \begin{cases} e^{-\mu_{12}e_i}(\mu_{12})^{u_i}, & u_i = 0,1 \\ e^{-\mu_{14}e_i}(\mu_{14})^{v_i}, & v_i = 0,1 \\ e^{-\mu_{23}f_i}(\mu_{23})^{w_i}, & w_i = 0,1 \\ e^{-\mu_{24}f_i}(\mu_{24})^{x_i}, & x_i = 0,1 \\ e^{-\mu_{32}g_i}(\mu_{32})^{y_i}, & y_i = 0,1 \\ e^{-\mu_{32}g_i}(\mu_{34})^{z_i}, & z_i = 0,1 \end{cases}$$

In order to determine the maximum likelihood estimators we have

$$L_n(\mu_{12}, \mu_{14}, \mu_{23}, \mu_{24}, \mu_{32}, \mu_{34}) = \prod_{i=1}^{n} f(u_i, v_i, w_i, z_i, e_i, f_i, g_i)$$

$$= \prod_{i=1}^{n} e^{-(\mu_{12}+\mu_{14})e_i} (\mu_{12})^{u_i} (\mu_{14})^{v_i} e^{-(\mu_{23}+\mu_{24})f_i} (\mu_{23})^{w_i} (\mu_{24})^{x_i} e^{-(\mu_{32}+\mu_{34})g_i}$$
$$\times (\mu_{32})^{y_i} (\mu_{34})^{z_i}$$

$$= e^{-(\mu_{12}+\mu_{14})\sum_{i=1}^{n} e_i} \mu_{12}^{\sum_{i=1}^{n} u_i} \mu_{14}^{\sum_{i=1}^{n} v_i} e^{-(\mu_{23}+\mu_{24})\sum_{i=1}^{n} f_i} \mu_{23}^{\sum_{i=1}^{n} w_i} \mu_{24}^{\sum_{i=1}^{n} x_i}$$
$$\times e^{-(\mu_{32}+\mu_{34})\sum_{i=1}^{n} g_i} \mu_{32}^{\sum_{i=1}^{n} y_i} \mu_{34}^{\sum_{i=1}^{n} z_i}$$

Letting $e = \sum_{i=1}^{n} e_i, f = \sum_{i=1}^{n} f_i, g = \sum_{i=1}^{n} g_i, u = \sum_{i=1}^{n} u_i, v = \sum_{i=1}^{n} v_i,$

$w = \sum_{i=1}^{n} w_i, x = \sum_{i=1}^{n} x_i, y = \sum_{i=1}^{n} y_i, z = \sum_{i=1}^{n} z_i$

and taking the logs gives

$\log L_n(\mu_{12}, \mu_{14}, \mu_{23}, \mu_{24}, \mu_{32}, \mu_{34}) = -(\mu_{12}+\mu_{14})e - (\mu_{23}+\mu_{24})f - (\mu_{32}+\mu_{34})g + u\log\mu_{12} + v\log\mu_{14} + w\log\mu_{23} + x\log\mu_{24} + y\log\mu_{32} + z\log\mu_{34}$

To estimate μ_{12},

$$\frac{\partial}{\partial\mu_{12}}\log L_n(\mu_{12}, \mu_{14}, \mu_{23}, \mu_{24}, \mu_{32}, \mu_{34}) = -e + \frac{u}{\mu_{12}} = 0$$

$$\frac{u}{\mu_{12}} = e$$

$$\hat{\mu}_{12} = \frac{\sum_{i=1}^{n} u_i}{\sum_{i=1}^{n} e_i} \tag{10}$$

To estimate μ_{14},

$$\frac{\partial}{\partial\mu_{14}}\log L_n(\mu_{12}, \mu_{14}, \mu_{23}, \mu_{24}, \mu_{32}, \mu_{34}) = -e + \frac{v}{\mu_{14}} = 0$$

$$\frac{v}{\mu_{14}} = e$$

$$\hat{\mu}_{14} = \frac{\sum_{i=1}^{n} v_i}{\sum_{i=1}^{n} e_i} \tag{11}$$

To estimate μ_{23},

$$\frac{\partial}{\partial\mu_{23}}\log L_n(\mu_{23}, \mu_{14}, \mu_{23}, \mu_{24}, \mu_{32}, \mu_{34}) = -e + \frac{w}{\mu_{23}} = 0$$

$$\frac{w}{\mu_{23}} = f$$

$$\hat{\mu}_{23} = \frac{\sum_{i=1}^{n} w_i}{\sum_{i=1}^{n} f_i} \tag{12}$$

To estimate μ_{24},

$$\frac{\partial}{\partial \mu_{24}} \log L_n(\mu_{12}, \mu_{14}, \mu_{23}, \mu_{24}, \mu_{32}, \mu_{34}) = -e + \frac{x}{\mu_{12}} = 0$$

$$\frac{x}{\mu_{24}} = f$$

$$\hat{\mu}_{24} = \frac{\sum_{i=1}^{n} x_i}{\sum_{i=1}^{n} f_i} \tag{13}$$

To estimate μ_{32},

$$\frac{\partial}{\partial \mu_{32}} \log L_n(\mu_{12}, \mu_{14}, \mu_{23}, \mu_{24}, \mu_{32}, \mu_{34}) = -g + \frac{y}{\mu_{32}} = 0$$

$$\frac{y}{\mu_{32}} = g$$

$$\hat{\mu}_{32} = \frac{\sum_{i=1}^{n} y_i}{\sum_{i=1}^{n} g_i} \tag{14}$$

To estimate μ_{34},

$$\frac{\partial}{\partial \mu_{34}} \log$$

$$_n(\mu_{12}, \mu_{14}, \mu_{23}, \mu_{24}, \mu_{32}, \mu_{34}) = -g + \frac{z}{\mu_{34}} = 0$$

$$\frac{z}{\mu_{34}} = g$$

$$\hat{\mu}_{34} = \frac{\sum_{i=1}^{n} z_i}{\sum_{i=1}^{n} g_i} \tag{15}$$

To make sure that the solutions represents a maximum and not a minimum, the second derivative of the log-likelihood is calculated and evaluated at $\mu_{ij} = \hat{\mu}_{ij}$. Getting the second derivatives of (10),(11),(12),(13),(14) and (15) confirms that these estimates are indeed maximums.

2.1.1   Reproduction Number

We first consider the three state model with states in Figure 3 given as Healthy Infected and Dead. Individuals move from healthy to infected to dead. Individuals can also move from healthy to dead. The transition matrix Q is given below

$$Q = \begin{pmatrix} -(\mu_{12} + \mu_{13}) & \mu_{12} & \mu_{13} \\ 0 & -\mu_{23} & \mu_{23} \\ 0 & 0 & 0 \end{pmatrix} \tag{16}$$

In calcutating R_0 we only used the infected states and therefore from matrix (16) we form the matrix

$$J = \begin{pmatrix} \mu_{12} & \mu_{13} \\ -\mu_{23} & \mu_{23} \end{pmatrix}$$

In calculating R_0 we use the Next Generation Matrix method which involves partitioning matrix J into submatrices F and V where F is non negative new infection matrix abd V is composed of death, improved status and other transition.

$$J = F - V \tag{17}$$

and

$$K = FV^{-1} \tag{18}$$

$$K = \begin{pmatrix} \dfrac{\mu_{12}\mu_{23}}{\mu_{13}} & 0 \\ 0 & 0 \end{pmatrix} \tag{19}$$

Since the basic reproduction number is the dominant eigen value of matrix (19) then

$$R_o = \frac{\mu_{12}\mu_{23}}{\mu_{13}} \tag{20}$$

Similarly for the extented four state model represented in Figure 3, matrix (2) is used to calculating R_0. The matrix of the infected states is given as

$$J = \begin{pmatrix} \mu_{12} & 0 & \mu_{14} \\ -(\mu_{23} + \mu_{24}) & \mu_{23} & \mu_{24} \\ \mu_{32} & -(\mu_{32} + \mu_{34}) & \mu_{34} \end{pmatrix}.$$

Calculating using equation (18) gives

$$K = \begin{pmatrix} \mu_{12}(\mu_{23}\mu_{34} + \mu_{24}(\mu_{32} + \mu_{34})) & -\mu_{12}\mu_{14}(\mu_{32} + \mu_{34}) & \mu_{12}\mu_{14}\mu_{23} \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{pmatrix}$$

$$R_o = \mu_{12}(\mu_{23}\mu_{34} + \mu_{24}(\mu_{32} + \mu_{34})) \tag{21}$$

3 Application of Model

We use table 1 to get the estimates for the three state model and four state model as follows Sustituting the values from parameter table 2 into the three

Table 2: Parameters estimates for three state model

	Symbol		
	μ_{12}	μ_{13}	μ_{23}
Estimate	0.15	0.09	0.18

Table 3: Parameters estimates for four state model

	Symbol				
	μ_{12}	μ_{23}	μ_{24}	μ_{32}	μ_{34}
Estimate	0.15	0.015	0.09	0.00467	0.18

state model gives $R_0 = 0.3$
Using (21) and table (3) and substituting into the four state model gives
$R_0 = 0.003$

4 Conclusion

In this paper we have considered a three state and four state multistate model and obtained the estimates of the transition intensities by the use of maximum likelihood method. We established that we can use the Next Generation Matrix Method to determine the R_0 in models of different stateswhich and use this in comparing transitions.

Since both the R_0 for the models are less than one it indicates that vertical transmission will eventually not contribute to transmission of HIV. This could be due to the fact that a lot of emphasis is being but to eradicate this mode of transmission.

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