International Journal of Mathematics and Physical Sciences Research ISSN 2348-5736 (Online)
Vol. 5, Issue 1, pp: (73-76), Month: April - September 2017, Available at: www.researchpublish.com

Estimation of Waiting Times for the Three Transient States of HIV Infection in Kenya

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Abstract: **The methods that were employed in this project analyzed HIV data. The aim was to evaluate the evolution of HIV positive patients to bring out some significant factors associated with this pathology. Many clinical situations can be described in terms of the conditions that individuals can be in (states), how they can move among such states (transitions), and how likely such moves are (transition probabilities). State transition models were therefore best suited to analyze this decision problem. Transition probabilities from states 1, 2, and 3 into state 4 increased as time progressed. The estimated total length of stay in state 1 was longer than state 2 and 3 respectively.**

Keywords: **Transient state, HIV Infection, and Waiting Time.**

1. INTRODUCTION

Survival analysis is the study of the time to some event, usually failure time. This ranges from machine failure, heart attack, death, onset of a disease, or birth of a child. Distribution of the survival times, sometimes called event times or "failure" times, is studied, but most often it is the effect of explanatory variables on the survival that is the focus. Some individuals will not reach a failure before the end of the study, may leave the study early, or be lost to follow up. In these cases, they will be right censored. However, in practice the disease evolution or progression can be broken up into a finite number of intermediate states, which may offer a greater understanding and clarity of the evolution of disease than a pure survival analysis model would provide. The objects studied in survival and event history analysis are stochastic phenomena developing over time. It is therefore natural to use the highly developed theory of stochastic processes especially in event history analysis. Some specific examples are treated: Markov models and staged models. Many chronic diseases have a natural interpretation in terms of staged progression.

2. STATEMENT OF THE PROBLEM

Standard survival analysis techniques like Kaplan Meier survival curves and Cox regression models can be used when one wishes to study the time until a specified event occurs. However, this does not describe a sequence of events and fails to utilize all the information that longitudinal data can provide if multiple events are studied. Markov processes posses a potential solution to the modeling of a sequence of events with the use of longitudinal data. State transition models are favourable to the modeling of diseases when a disease can be grouped into a set of mutually exclusive health states. Previous researchers in Kenya have mainly applied Markov processes to manpower systems. Because of this a study of the survival of HIV positive patients in Kenya is needed to understand the disease progression.

3. LITERATURE REVIEW

In 2002, Jackson constructed a library for Multi-state modeling with R called *msm*. The *msm* user manual has since been revised severally with the latest being version 1.2, May 2013.The multi-state Markov model is a useful way of describing a process in which an individual moves through a series of states in continuous time. The *msm* package for R allows a general multi-state model to be fitted to longitudinal data. Data often consist of observations of the process at arbitrary times, so that the exact times when the state changes are unobserved. For example, the progression of chronic diseases is

often described by stages of severity, and the state of the patient may only be known at doctor or hospital visits. Features of *msm* include the ability to model data with a variety of observation schemes, including censored states. Possible observation schemes include:Fixed: Each patient is observed at fixed intervals specified in advance.Random: The sampling times vary randomly, independently of the current state of the disease.Doctor's care: More severely ill patients are monitored more closely. The next sampling time ischosen on the basis of the current disease state.Patient self-selection. A patient may decide to visit the doctor on occasions when they are in apoor condition. The *msm* package for R developed by Jackson is an important and widely used tool in the use of Markov processes in the disease modeling.

4. RESEARCH METHODOLOGY

Longitudinal data for monitoring disease progression are often incomplete in some way. Usually patients are seen at intermittent follow-up visits, at which monitoring information is collected, but information from the periods between visits is not available. Often the exact time of disease onset is unknown. Thus, the changes of state in a staged model usually occur at unknown times. Also a subject may only be followed up for a portion of their disease history. A fixed observation schedule may be specified in advance, but in practice times of visits may vary due to patient and hospital pressures. Observations may be censored. For example, at the end of a study a patient may be known only to be alive, and in an unknown state. This entails a discussion of important and key properties of continuous time homogeneous Markov models. These basic concepts are key to understanding staged models. To fit a staged model to data, we estimate the transition intensity matrix, Q . We concentrate on Markov models here. The Markov assumption is that the future only depends on the current state. That is $q_{ij}[t, z(t), F_t]$ is independent of F_t , the observation history F_t of the process up to the time preceding *t*. The *msm* package for R allows a general staged model to be fitted to longitudinal data.

5. FINDINGS

Table 1 Mean sojourn time in transient states

State	Estimate (years)	Standard Error	95% C.I
State 1	0.9481815	0.12236478	(0.7362786, 1.2210707)
State 2	0.4077935	0.04119168	(0.3345488, 0.4970741)
State3	0.6312653	0.08854050	(0.4795385, 0.8309988)

The interpretation of the mean sojourn times in states 1,2, and 3 are that an average stay in the CD4 count states are 0.95, 0.41, and 0.63 years respectively. Thus we see that a typical patient just entering a CD4 count between 350 and 499, can be expected to spend around 0.41 years (five months) at that level before transiting to either a higher or lower level of CD4 count. In the presence of reverse transitions, it is of interest to estimate the total length of stay in each transient state. These estimates are presented in table 2.

Table 2 Estimated total length of stay in transient states

State	Total length of stay (years)
State 1	11.043944
State 2	9.783447
State 3	8.361754
State 4	Inf

Table 2 gives the forecasted total length of time spent in each transient state. Each patient is forecasted to spend 11.04 years in the well state, 9.8 years in the mild state and 8.4 years in the advanced state.

6. CONCLUSION AND RECOMMENDATION

Transition probabilities from states 1, 2, and 3 increases as time increases. For example $p_{24}(1)$ = 0.03098 (0.02297, 0.07481) while $p_{24}(7) = 0.2173(0.1683, 0.3987)$). We are therefore justified to conclude that; Data from the health centre also indicates that, as time increases the number of patients occupying transient states 1, 2, and 3 decreases and the

number of patients being absorbed increase. Each patient is forecasted to spend 11.04 years in the well state, 9.8 years in the mild state and 8.4 years in the advanced state. This result confirms the accuracy of the Markov model to disease modeling.

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