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COMPARATIVE ANALYSIS OF SURVIVAL AND GROWTH MODEL APPROACH WITH RELATION TO CD4 COUNT IN HIV- POSITIVE PREGNANT WOMEN

BASAVARAJAIAH D. M, B. NARASIMAHAMURTHY & B. LEELAVATHY

National Institute of Epidemiology, Indian Council of Medical Research, Chennai, Tamil Nadu, India

ABSTRACT

Several authors have compared survival rates across different CD4 categories after patients were initiated on HAART. However, these studies focused on survival differences in these patients over a period 1-5years while on HAART. There are a large proportion of patients who are still alive on therapy since the inception of HAART in the late 2004.Low CD4+ T lymphocyte counts in HIV +Ve pregnant women are likely to be associated with a variety of factors, including many viral infections, bacterial infections, parasitic infections, sepsis, tuberculosis, coccidioidomycosis, burns, trauma, intravenous injections of foreign proteins, malnutrition, over-exertion, multiple pregnancies, corticosteroid use. In HIV some positive pregnant women on HAART, declining CD4 Count may be because of temporal changes which gets corrected over a period of time.

This paper presents a brief review of several studies documenting low CD4 counts in people who are experiencing such decline in CD4 count[4]; explained through Mathematical and statistical models that can serve as tools for understanding the temporal changes of CD4 count in HIV +Ve pregnant women. HIV/AIDS patients, over 18 years of age group, who were started on HAART during April 2004 to March-2010, had their retrospective cohort data collected from different government hospitals of Karnataka state. Survival, Growth models were employed to find out the rate of improvement of CD4 count in type-I HIV infected pregnant women. A total of 202 PLHIV pregnant women had received HAART during the study period .Among them, the mean age was 23.26±7.18 years, 75.46% had HIV infected spouses, and mean treatment follow up time from HAART initiation to onset of pregnancy was 57.0 months .Most of the patients were compliant with good treatment adherence.

The cumulative survival rate after initiation of HAART was 0.95 in survival analysis ($P \leq 0.05$, R^2=79.82%) and 0.98 in growth model($P \leq 0.05$R2=81.36%). HIV Positive pregnant women with CD4 Count>350 µ/Dl at HAART initiation were likely to have achieved better survival rate. The rate of CD4 count decline is often much more rapid in patients where, HAART was initiated at CD4 Count <250µ/dL with clinical WHO stage-IV.Growth model can easily calculate the rate of survival; it is a best model for forecasting the mortality rate.

KEYWORDS: HAART, CD4, HIV, Growth Models, WHO, PLHIV

INTRODUCTION

A common methodology employed in the field of epidemiology is survival analysis. Survival analysis, sometimes referred to as duration analysis, analyzes the time to failure, where ‘failure’ signifies a single discrete event (Gutierrez, 2007). In the present study, the final events is lost to follow up (LFU), missed investigation treatment stop (MIS) and death. Survival analysis commonly uses panel and cohort surveys with repeated interviews on a sample of interest (Jenkins 2005). Unlike logit and probit models, the dependant variable is the “waiting time until the occurrence of a well-defined event” (Rodríguez, 2007). A unique element of a survival analysis model is that it is able to retain observations for which

the event has not occurred and then take the effects of these observations into account statistically (Reed et al., 1994). In the context of HAART treatment in NACP'S programme, survival analysis is a helpful tool for determining the duration of time an individual is likely to survive with certain health symptoms and other demographic features like Physical health and clinical characteristics. Epidemiological studies have applied survival analysis to examine the time of survival until death. Reed et al. (1994) used survival analysis to examine gay men with AIDS and how well realistic acceptance or knowledge of the disease predicts the duration of survival.

The authors assessed the efficacy of ART treatment in those who had a "low –CD4 Count at the time of Rx (<250 µ/dL" realistic acceptance) and those who had a "high- CD4 Count at the time of Rx (>250 µ/dL" realistic acceptance). Similarly, Zangerle et al. (1995) used survival analysis to determine the effect of clinical and demographic factors on survival among 901 AIDS cases in Austria. He concluded that there are considerable differences in survival time between different HIV-risk groups (intravenous drug users, heterosexual contact, and homosexual contact).

In a more recent study in Brazil, Braga et al. (2007) used survival analysis to look at the effects of gender differences on survival in HIV/AIDS cohorts. Conditioned on the fact that men and women have equal and free access to ARTs and other drugs that alleviate the mortal effects of HIV/AIDS, they found survival rates to be dramatically different between males and females (holding all other variables constant), one specification being females were shown to be a good predictors of shorter survival.

Zhou and Kumarasamy (2005) also employed survival analysis in Asia and the Pacific region to predict short-term disease progression among HIV-infected patients, half of whom were receiving antiretroviral treatment and the other half who remained as a control group. They reported that, compared to patients receiving antiretroviral treatment, patients not on treatment had a higher rate of disease progression. While all of these studies differ in their employment of survival analysis, they drew notable conclusions about the length of time a person with certain characteristics survives with a particular disease.

Aims: The main aim is to comparatively analyze survival and growth models at HAART inception with low CD4 count in pregnant women and to determine which model certainly predicts the survival Setting and design: A sample size was calculated by using Co hen's d table, the desired sample size was 202 (α =0.05β=0.70).A total of 202 HIV infected pregnant womens who are on HAART over 18 years of age group, who had started HAART during April 2004 to March 2010,the retrospective data collected from Government hospital ,clinical and laboratory data were collected

EQUATION

A total of 202 HIV infected Pregnant womens who are on HAART over 18 years of age group, who had started HAART during April 2004 March-2010, the retrospective cohort data were collected from different government hospitals of Karnataka state. Clinical and laboratory data were collected .Survival and Growth statistical models were employed to fit progression.

This study uses survival analysis, or 'time to event analysis,' where the focus is on analyzing the time leading up to an event. For this analysis, the event is defined as death, lost to follow up, missed treatment (Exclusion criterion) . There are two specific elements of survival analysis data, censoring and non-normality, The purpose of using survival analysis for this study is to follow subjects over 5 years and to observe at which point of time they experience death.

"Survival Analysis" generally refers to statistical analysis for **time to event** data. The outcome variable of interest is time to event, usually called **failure time** or **survival time** or **lifetime**. For example,

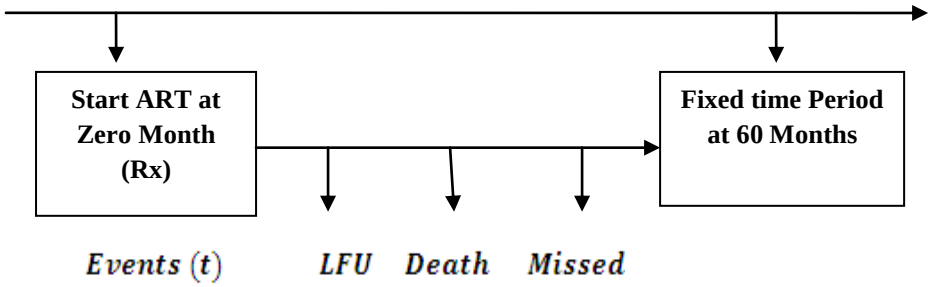
- Time from start of treatment to a failure event
- Time from birth to death = life time
- Time from HIV-infection to AIDS
- Time from birth to onset of a disease = onset age.

The distribution of survival time is usually described or characterized by three functions:

Survival Function

S(t) = P (an individual survival longer than t)

= P(T > t)



$$S(t) = 1 - P(an\ Individual\ die\ before\ fixed\ time).$$

$$S(t) = 1 - F(t).$$

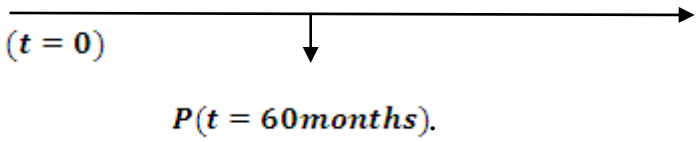
Model Concept

The distribution of survival time is usually described or characterized by three functions.

Survival Function

S(5) = P(an HIV Patients survival longer than 60 months)

= P(T > 60months)



S(60) = 1 – P(an HIV Patients die before 60 Months)

= 1 – F(60 months)

Estimation of S(t)

$$\hat{S}(t) = \frac{No.of\ patients\ survival\ longer\ than\ "t"}{Total\ No.of\ patients\ in\ co\ hort}$$ (If the obervation are no censored)

Probability Density Function

$$f(t) = lim\Delta t \to 0 \quad \frac{P(an\ Individual\ dying\ in\ the\ interval\ \ t,t+\Delta t,}{\Delta t}$$

$$f(t) = \frac{-ds(t)}{dt} = (The\ slope\ of\ the\ survival\ \ function)$$

$$\hat{f}\ (t) = \frac{No.of\ patients\ dying\ in\ the\ interval\ begining\ at\ the\ time\ of\ "t"}{Total\ no.of\ patients\ X\ Interval\ width}$$

Hazard Function(Hz)

$$\boldsymbol{h}(t) = lim\Delta t \to 0\ \frac{1}{\Delta t} P(An\ Individual\ \ die\ in\ the\ time\ interval(\ t,t+\Delta t).$$

$$\boldsymbol{h}(t) = lim\Delta t \to 0\ \frac{1}{\Delta t} P((\ t < T <\ t+\Delta t)/\mathrm{T} > t.$$

$$= \frac{f(t)}{1-f(t)} = \frac{f(t)}{S(t)}$$

Estimation of h(t)

$$\widehat{h}\ (t) = \frac{No\ of\ die\ in(t,\Delta t)}{No.of\ alive\ at\ t*\Delta t}$$

$$= \frac{No.of\ die\ in(t,\Delta t)/Totalpts}{\Delta t * (No.ofpatients\ at\ t)/Totalpts}$$

COMPOUND GROWTH RATE MODEL(CGR)

A number of studies pertaining to HIV research growth rate have been carried out.The important functional forms were employed to study the growth rates like linear ,exponential and logrithmic forms .However, many of the studies have used the geometric forms (Compountd growth rate) which is given by well known method used for the variation of CD4 count before Rx start (ART) and after one year of completion of the treatment.

However,the Compound growth rate is given by $Y = AB^t$,where "Y" is variable under the study , "B"represents the regression coefficient and it is $(\mathbf{1} + \boldsymbol{CGR})$, "**CGR**" is the compound growth rate and "t" is time period for assessment of CD4 conut at different time intervals .

This model can also be used to estimate the rate of RNA plasma viral load increase.The rate of increase of CD4 count over a period of time is calculated by using this equation.

$$\boldsymbol{CGR = \frac{b}{\bar{y}} X100, Incase\ of\ Increase\ of\ CD4\ Count\ CGR = (Antilog\ B - 1)X100,}$$

y: $Represents\ the\ time\ period\ for\ the\ assessment\ of\ CD4\ Count\ at\ Six\ Months, 12months,$

$24months, etc.,$

$a, A: Constant\ values$

$b, B: Co\ efficient\ of\ regression$

$CGR: Growth\ rate,$

$\overline{y}$ =Mean of CD4 Count.

TABLES AND FIGURES

In order to capture variations in survival time, this study uses a sample made of individuals recruited for cohort in 2005, and who were interviewed IID (In-depth interview and discussion) in 2011 or recorded to have died between 2005 and2011.

Table 1: Descriptive Statistics of CD4 Count and Clinical Parmeters after Intiation of HAART

N=202

SL.	Variable	Female Mean±SD	P-Value
1.	Age (Year)	23.26±7.18 (202)	0.029*
2.	Base line CD4	116.36±56.46 (202)	0.492Ns
3	CD4-at the end of six month	302.01±152.28 (196)	0.036*
4.	CD4-at the end of one year cohort	372.28±96.73 (195)	0.006**
5.	CD4-at the end of Two year cohort	379.36±65.39 (193)	0.021*
6.	CD4-at the end of Three year cohort	410.00±49.50 (191)	0.085*
7.	CD4-at the end of fourth year cohort	445.00±41.29 (187)	0.011*
8.	CD4-at the end of fifth year cohort	451.00±36.98 (185)	0.003*

II	WHO-Clinical Stage		
A	Stage-I	Nil	
B	Stage-II	8(1.60%)	0. 531^{ns}
C	Stage-III	85 (17.10%)	0.422^{ns}
D	Stage-IV	109 (21.93%)	0.488^{ns}
E	Working- Assessment Up to fifth year	157(31.58%)	0.067*
F	Ambulatory - Assessment Up to fifth year	20(4.02%)	0.176^{ns}
G	Bed ridden- Assessment Up to fifth year	09(1.81%)	0.402^{ns}
G	Death	16(3.24%)	0.033*
III.	**HIV-TB Co-Infection**		
A	Yes	18(7.24%)	0.203^{ns}
B	No	184(37.02%)	0.891^{ns}
IV.	**Mean Duration of Rx Start to end of the Fifth Cohort**		
A	Mean Days	1738±48.93 (186)	0.002**

***,** Significant @P≤0.05 &0.01.**

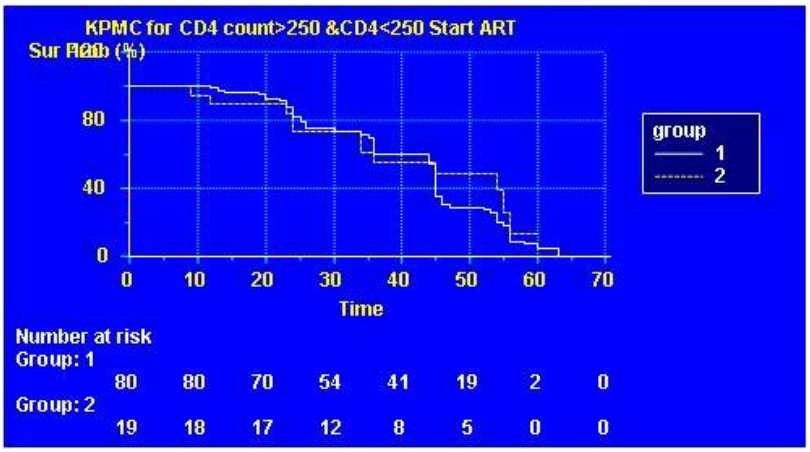


Figure 1: Kaplan-Meier Survival Curve and its 95% Confidence Interval for Patients Initiating Therapy from Different CD4 Category

Table 2: Survivability of Different CD4 Category with HAART Duration

Survival Time	Survival Proportion	Standard Error	Survival Proportion	Standard Error
9	-	-	0.947	0.0512
12	0.987	0.0124	0.895	0.0704
13	0.975	0.0175	-	-
14	0.962	0.0212	-	-
18	-	-	-	-
19	0.950	0.0245	-	-
20	0.924	0.0298	-	-
22	0.911	0.0322	-	-
23	0.871	0.0381	0.842	0.0837
24	0.818	0.0440	0.737	0.101
25	0.792	0.0464	-	-
26	0.751	0.0496	-	-
30	0.738	0.0504	-	-
34	0.711	0.0522	0.614	0.116
35	0.697	0.0529	-	-
36	0.599	0.0569	0.553	0.119
38	-	-	-	-
40	-	-	-	-
44	0.541	0.0584	-	-
45	0.351	0.0569	0.484	0.123
46	0.305	0.0553	-	-
47	0.290	0.0546	-	-
48	-	-	-	-
52	0.275	0.0538	-	-
53	0.259	0.0529	-	-
54	0.198	0.0485	0.387	0.131
55	0.183	0.0471	0.258	0.137
56	0.0915	0.0354	0.129	0.114
58	0.0732	0.0327	-	-
60	0.0488	0.0295	-	-
63	0.000	0.000	-	-
	Comparison of survival curves (Logrank test)			

Table 3: Survival Rate on HAART Patients Determined by Using Growth Model

SL.	Components	Co-efficient	SE	R^2 (%)	Survival Growth or Rate	P-Value
01.	Intercept(Year)	4.217	0.080	45.64%	0.652^{ns}	P≥0.05
	Rx start (HAART) <250 CD4 cell count(µ/dL)	0.072	0.007			
02.	Intercept(Year)	9.38	0.065	89.75%	0.980^{**}	P≤0.05
	Rx start(HAART) >250 CD4 cell count(µ/dL)	0.077	0.004			

**,Significant at 0.05 level.

MODEL PROOF

The average age of the patient was 23.26±7.18 years, mean base line CD4 count before start HAART was lower than the National guidelines; it was recorded as 116.36±56.46 µ/dL, after one year of completion of HAART, mean CD4 count had increased , CD4-at six month(302.01±152.28 µ/dL),CD4-at one year (372.28±96.73 µ/dL),CD4-at Two year (379.36±65.39 µ/dL),CD4-at Three year (410.00±49.5 µ/dL 0),CD4-at fourth year (445.00±41.29 µ/dL) and CD4-at fifth year (451.00±36.98 µ/dL).WHO Clinical staging was assessed based on national guidelines ,WHO stage II 8(1.60%), Stage-III 85 (17.10%)& Stage-IV 109 (21.93%- statistically non significant- P>0.05,P=0.488).clinical and physical assessment was made by chorobanch scale, the PLHIVS who were in Working condition was- 157(31.58%) P<0.05, Ambulatory-20 (4.02%)P>0.05, Bed ridden-09(1.81%) P>0.05 and Death -16 (3.24%) P<0.05, TB HIV co infection-7.24% P>0.05.Mean duration of HAART initiation at end of the study was 1738±48.93 days with P<0.002, statistically significant.

In order to analyze the relative risk of an individual surviving, the data described above were converted into survival data by establishing the two time variables (start, which is age in2004; and end, which is age at death or age in 2010); and the failure variable (=1 if dead). After setting the data to survival analysis mode, there were 488 total failures, with the average entry age of 23 years (time 0:2004) and the average exit age of 30 years (time 1: 2010). From2004, the average survival time for an individual is about 05 years. Overall, 16 individuals were reported dead by 2004.

Before running a Cox proportional hazards model, the Kaplan- Meier curve was estimated for two groups ie., low CD4count <250µ/Dl and higher CD4 count >250µ/dL (see Figure 1). The curve showed no significant difference in survival probability between two groups. Results from the statistical test confirmed that there was no statistical significance for CD4 count in survival probabilities (logrank test *p= 0.20*).

Similarly, the Kaplan- Meier Survival curve was predicted for previously married individuals (divorced, widowed, or separated) relative to individuals who have either never married or married, the curve showed that there is a significant difference between the two groups of individuals (logrank test *p=0.000).*

The Kaplan-Meier model is useful for understanding the differences in survival time for individual exogenous variables. To capture the effects of multiple variables on survival time, the study also uses a Cox proportional hazards model. Cox proportional hazards ratio for the risk of death of an individual with certain OI symptoms are presented in Graph (2) in three different specifications. In the first specification, the effect of the four chronic symptoms on survival time is evaluated. Persistent weight-loss is the only chronic symptom that is reported as statistically significant, where the risk of disease progression to death is 16 percent greater than those who do not report having chronic weight-loss.

Although not statistically significant, individuals reporting the other three chronic symptoms are predicted to have a greater risk of death, relative to those individuals who do not report a chronic illness.

Controlling for other biological and demographic exogenous variables, the second and third specifications show that there are other factors that contribute to a shorter survival time. In the third specification, individuals experiencing persistent weight-loss have a 23 percent greater risk of death, compared to individuals who do not experience this chronic illness.

The variable duration of chronic illnesses and OIS was also statistically significant. As hypothesized, individuals who reported having a chronic illness of less than a year were likely to live longer. In the analysis, individuals who experienced a chronic illness between 53 and 104 weeks (1-2 years) presented a 64 percent greater risk of death than individuals who experience some chronic symptom between 0 and 26 weeks (6 months).

women who reported between 157 and 209 weeks of illness (3-4 years) have a 94 percent greater risk of death compared to the baseline group was shown to have no statistical significance or effect on the estimated risk of survival for individuals reporting a chronic illness compared to those who do not report an illness. The quality of the diagnosis cannot be measured in this variable. As a result, a doctor's diagnosis for a chronic illness has little effect on the estimated risk of death. Age was only statistically significant for one group of individuals (HAART Start >250 CD4 µ/Dl): 21-26-year-olds had lower risk group and survived more.

Individuals aged 26-35 years old were found to have a 61 percent greater risk of progression to death compared to the baseline age group(HAART Start <250 CD4 µ/Dl). There is a trend of increased risk of progression to death as age increases (63 percent greater risk for individuals 18-25 years old and 87 percent greater risk for individuals 26-34 years old). Estimated hazard ratios for other age categories are not statistically significant and, therefore, are not presented in the table.

CONCLUSIONS

While the use of the cohort data containing demographic and biological information allows for the analysis of survival time, Survivability models have many limitations. First, the variables used to capture the chronic health symptoms are very limited in scope. There is no medical examination or in-depth analysis of each symptom. Further, these data reley heavily on the individual's ability to consistently self-report the chronic and OI symptoms they have been experiencing and for how long.

If the data are reported inconsistently, the results in this analysis are likely to be biased. Second, in the Growth analysis, of the CD4 was evaluated for chronic symptoms, in this study, chronic weight-loss alone were statistically significant and the strongest predictor of risk of death. There are a number of exogenous factors that could be biasing the hazard ratio on the chronic weight-loss variable. Some of these factors include: poor nutrition, acute or chronic illness, or a disease inherent to the family. Most of the patients well compiled with treatment adherence.

The cumulative survival rate after initiation of HAART was 0.98, 0.89 respectively ($P \leq 0.05$, $R^2=79.82\%$). HAART with CD4 Count>350 µ/dL was likely to have achieved better survival rate. The CD4 count is also important immunological marker for HIV patients, the rate of CD4 count decline is often much more rapid if inception of HAART is at CD4 <250µ/dL with clinical WHO stage-IV.Growth model can easily calculate the rate of survivability; it is a best model for forecasting the survival rate.

- One of the implications of our study is that, this is a user-friendly model and can be designed to ensure the efficient and accurate estimation of survival rate.
- Growth Model can be helpful for physician and researcher for taking clinical decisions.
- The findings of these models are strengthened by the relatively homogeneous as well as heterogeneous study population.
- (While fitting up of Survival and Growth model, the method of growth analysis provides good estimates of survival rate,R- square 81.25% with proportion of survival growth0.95

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