A Bio-statistical Study for Exploring the Predictors of Survival in HIV Positive Patients after Initiation of ART (Antiretroviral Therapy) Treatment

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Smita Patgaonkar

Abstract

Life expectancy has increased for HIV positive patients since the treatment of (Antiretroviral Therapy) ART, but there is a strong need to better understand the characteristics of long-term survival in HIV-positive patients. Survival in HIV-positive patients receiving ART was examined in the present study. The main aim of this investigation was to describe the factors which cause changes in mortality of HIV positive patients. Sampling was done using a quota sampling method. Since data of fifty deceased patients was available, fifty living patients were selected randomly for comparison. HIV cases were further classified on the basis of gender with 25 males and 25 females in living and deceased patients respectively. Therefore from the recorded data, information was collected for 100 patients. Statistical models used were the Cox model for hazard analysis and the Kaplan-Meier model for estimating survival probability. The paper also gives an idea about the demographic profile of the overall samples collected.

Keywords: Antiretroviral Therapy, Cox model, Kaplan-Meier model.
Introduction

In HIV positive persons, the level of immunity decreases drastically if they do not receive drugs, if they miss a particular dose or if they are irregular in taking prescribed drugs. The lower the immunity greater are the chances of the infected person getting secondary opportunistic infections. India has managed to control HIV cases over the past five to six years by bringing in more patients under treatment and by starting counselling and testing centres across the country with many private laboratories apart from the government centres.

Estimates by National AIDS Control Organization (NACO, 2014) show that the number of patients surviving after taking ART (Antiretroviral Therapy) increased from 137958 (in 2013) to 219103 (in 2014). Thus, life expectancy has increased for HIV positive patients since the treatment of ART. However, there is a need to better understand the characteristics of long-term survival in HIV-positive patients. The main aim of this case study is to explore the factors which cause changes in mortality of HIV positive patients. Since there are adverse effects of ART, such as weight loss, skin rashes, asthma, tuberculosis and diabetes, the present study also focuses on investigating whether some of these adverse effects influence survival of HIV positive patients or not.

Materials and Methods

Study Setting and Participants

The present study was conducted in the ART Centre of a private hospital in Mumbai between 2010 and 2015. Data of a total 100 patients were collected consisting of 50 living patients and 50 deceased patients from the recorded data. The patients included in the study were those whose ART treatment started from the centre itself and those who had had at least one ART. Since the study period was fixed whereas the time of entry of patients into the study was not, the entry time for different patients was different. Core data variables studied included:

1. Sex.
2. Age.
3. Marital status.
4. Education.
5. Income.
6. Occupation.
7. Weight (baseline and latest).
8. CD4 count (baseline and latest).
9. Date of ART (first and latest).
10. Number of ARTs taken.
11. AIDS-defining illnesses.
12. Time (Date of registration to an event/ end of the study).
For the purpose of this study, immunologic classification of the disease was done using CD4 count, based on WHO criteria (WHO, 2015). As per this classification:

- Patients with CD4 ≥ 500 were classified as “not-significant”,
- 350–499 as “mild”,
- 200–349 as “advanced” and
- <200 as “severe”.

Classification was based on age as:

- 15-20 years,
- 20-30 years,
- 30-40 years,
- 40-50 years and
- ≥50 years.

Further classification was number of ARTs taken <5 and ≥5. The covariates considered were:

- Sex.
- Age.
- Baseline CD4 count.
- Latest CD4 count.
- Number of ART.
- Smoking habit.
- Infection.

Deaths were registered from hospital records. Since it was uncertain whether the patients outliving the study period would die and when, therefore such patients had to be censored. Censoring indicates that the event of interest did not occur during the study period (Walters, 2009). Patients who were living at the end of the study period were censored on September 1, 2015.

**Limitations**

The data collection had the following limitations:

1. The factor whether those patients on medication continued to take medicines regularly at home or not has not been taken into account.
2. These results are limited only to the ART center where the study has been done.
3. The study only emphasizes on the method which is used and not for the results.
4. Collected data are not firsthand meaning they have not been collected directly and therefore the results are based on secondary data.

**Statistical Analysis**

Data were collected and analysis was done with the help of SPSS statistical software.

Since the overall data depend on time, Kaplan-Meier model was used to estimate the survival period during ART care and log rank test to compare survival curves among different groups. The Cox proportional hazards model was used to identify independent predictors of mortality and to calculate hazard ratios of predictors.

This model was used because it is most appropriate for studying the relationships between the survival of patients and related variables. In other words, it analyses the effects of variables on survival. It gives an estimate of the efficacy of treatment in terms of survival after adjustment for other variables (Walters, 2009).

The survival time was calculated in months using the time interval between the date of commencing ART and (1) the date of event (death) or (2) date of censoring. Univariate Cox regression analysis was performed for studying baseline variables. In such types of studies, the event data are not normally distributed. The values on the ordinate axis (y) consisting of the dependant variable cannot be observed fully and may not have corresponding values of independent variable on the abscissa (x). This makes it difficult to use the normal linear regression model and that is the advantage of using Cox regression model in such studies, as the latter is not limited by the above requirements. In the present study, the following baseline variables: sex, age group, baseline WHO CD4 category, and Number of ARTs taken were studied.

**Results**

*Patients’ Information*

Of the total samples (100) studied (living and deceased), 50% were males and 50% were females. The overall study shows following results:

1) **Age group**

Nearly 45% patients belonged to the age-group of 30-40 years and 40% patients belonged to the age-group of 40-50 years. The median age of the patients was 39 years. Figure 1 shows the age profile distribution of patients included in the present study.
2) Type of dwelling

Figure 2 shows the distribution of patients in the present study based on different types of dwelling. It is seen that, 72% of the patients were from slum areas, 15% from apartments and 13% from hutments.

3) Marital status with respect to gender of the patient

It was observed in the present study that married males (42%) were greater in number than females (18%). It implies that married Indian women are more loyal to their husbands, thus their chances of getting infections are less as compared to males. On the other hand, widowed females (27%) were more compared to females having other marital status. This is most probably because widowed patients got infected from their husbands and their husbands died before them.
Figure 3 shows the marital status of patients in the present study with respect to gender.

**Figure 3. Marital Status of Patients in the Present Study with respect to Gender**

![Marital Status Graph](image)

4) **Education with respect to gender of the patient**

Among the study sample, 20% patients were illiterate, 13% were having primary education and 63% patients had secondary education. It shows that the patients who were illiterate or had only primary education were not aware of sex during their education years whereas those with secondary education were quite grown up to understand the implications of sex and yet may have indulged in unguarded sex. Figure 4 graphically represents the education level of the patients in the present study.

**Figure 4. Education Level of the Patients in the Present Study**

![Education Level Graph](image)
Mortality Rates

In the univariate analysis, sex, age group, baseline CD4 count and latest CD4 count were significantly associated with progression to death.

A) Mortality with respect to gender
The Median survival time for female patients was 56 months whereas for male patients it was 44 months. Initially, the probability of survival for female patients was less than that of male patients but in the middle part the male and female survival probability equalized; it remained steady thereafter and again in the long run the female survival probability was decreased. Table 1 shows the overall comparison of survival curves among patients. Figure 5 shows the survival of patients in the present study with respect to the ART period.

Table 1. Overall Comparison of Survival Curves

<table>
<thead>
<tr>
<th>Test</th>
<th>Chi-Square</th>
<th>Df</th>
<th>Sig.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Log Rank (Mantel-Cox)</td>
<td>.083</td>
<td>1</td>
<td>.773</td>
</tr>
<tr>
<td>Breslow (Generalized Wilcoxon)</td>
<td>7.563</td>
<td>1</td>
<td>.023</td>
</tr>
<tr>
<td>Tarone-Ware</td>
<td>.157</td>
<td>1</td>
<td>.692</td>
</tr>
</tbody>
</table>

Figure 5. Survival of Patients in the Present Study with respect to ART Period

B) Mortality with respect to age
As mentioned above, the patients studied were classified into different age groups and the percentage composition of deceased and
censored patients (those who were alive or having follow-up treatment) was calculated for each age group. For the group of patients aged less than 20 years, the deceased comprised 100% patients while censored patients were 0%. Similarly, for the age group of 20-30 years, 29% patients were deceased while 71% were censored. 44% patients were deceased while 56% were censored for the age group 30 - 40 years and for the age group of 40–50 years, 55% patients were deceased while 45% were censored. In the last age group of patients aged more than or equal to 50 years, 71% patients were deceased while 29% were censored. This Indicates that the percentage of the deceased patients is greater for the patients aged less than 20 years and for the patients greater than 50 years whereas the percentage of censored patients is greater for the patients aged between 20-40 years.

Table 2 and Figure 6 summarize the age characteristics of the patients in this study.

Table 2. Percentage Composition of Deceased and Censored Patients Studied

<table>
<thead>
<tr>
<th>Age Group of patient</th>
<th>Total N</th>
<th>Percentage of</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Deceased patients</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Censored patients</td>
</tr>
<tr>
<td>&lt;20</td>
<td>1</td>
<td>100</td>
</tr>
<tr>
<td>20-30</td>
<td>7</td>
<td>29</td>
</tr>
<tr>
<td>30-40</td>
<td>45</td>
<td>44</td>
</tr>
<tr>
<td>40-50</td>
<td>40</td>
<td>55</td>
</tr>
<tr>
<td>&gt;=50</td>
<td>7</td>
<td>71</td>
</tr>
<tr>
<td>Overall</td>
<td>100</td>
<td>50</td>
</tr>
</tbody>
</table>

Figure 6. Percentage Composition of Deceased and Censored Patients Studied

A) Mortality with respect to CD4 count
Progression to death was found to be higher among patients with baseline CD4 >500 and CD4 200-349 as compared with patients with CD4 350-499 and CD4<200. This is shown graphically in Figure 7.

**Figure 7.** Hazard Function for Baseline CD4 Count of Patients in the Present Study

![Graph showing the hazard function for baseline CD4 counts.](image)

**Figure 8.** Hazard Function for Latest CD4 Count of Patients in the Present Study

![Graph showing the hazard function for latest CD4 counts.](image)
Table 3. Hazard Rate Table

<table>
<thead>
<tr>
<th>CD4 count</th>
<th>B</th>
<th>SE</th>
<th>Wald</th>
<th>Df</th>
<th>Sig.</th>
<th>Exp(B)</th>
</tr>
</thead>
<tbody>
<tr>
<td>500 ≥</td>
<td>2.426</td>
<td>.665</td>
<td>19.279</td>
<td>3</td>
<td>.000</td>
<td>11.308</td>
</tr>
<tr>
<td>350-499</td>
<td>1.351</td>
<td>.590</td>
<td>13.284</td>
<td>1</td>
<td>.000</td>
<td>3.861</td>
</tr>
<tr>
<td>200-349</td>
<td>1.143</td>
<td>.346</td>
<td>10.928</td>
<td>1</td>
<td>.001</td>
<td>3.138</td>
</tr>
<tr>
<td>LatestCD4</td>
<td>-3.246</td>
<td>.574</td>
<td>31.937</td>
<td>1</td>
<td>.000</td>
<td>.039</td>
</tr>
<tr>
<td>350-499</td>
<td>-2.386</td>
<td>.599</td>
<td>15.892</td>
<td>1</td>
<td>.000</td>
<td>.092</td>
</tr>
<tr>
<td>200&lt;</td>
<td>-1.314</td>
<td>.364</td>
<td>13.024</td>
<td>1</td>
<td>.000</td>
<td>.269</td>
</tr>
</tbody>
</table>

It is observed from Figure 8 that the percentage of patients with latest CD4 >500 (31%) is increased as compared to baseline CD4 >500 (8%) and patients with latest CD4 <200 (28%) is decreased as compared to baseline CD4 <200 (57%). An improvement in CD4 count of the patients and a resultant overall increase in the probability of survival of the patients are observable from Figure 8 and Figure 9. It is evident from Table 3 that progression to death was 33% higher among patients with latest CD4 <200 as compared with patients with CD4 >500.

Figure 9. Distribution of Patients on the Basis of Baseline and Latest CD4 Counts

B) Mortality with respect to number of ARTs taken

There is a significant association between the number of ARTs taken (Group1: No. of ART≥5, Group2: No. of ART<5) and the progression of death. It can be said that at a 99% confidence level the risk of dying decreases by 24% if the number of ARTs taken is more than 5. This is shown in Tables 4 and 5.
Table 4. Omnibus Tests of Model Coefficients in Number of ART

<table>
<thead>
<tr>
<th>-2 Log Likelihood</th>
<th>Overall (score)</th>
<th>Change From Previous Step</th>
<th>Change From Previous Block</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Chi-square</td>
<td>df</td>
<td>Sig.</td>
</tr>
</tbody>
</table>

Table 5. Variables in Number of ART

<table>
<thead>
<tr>
<th>Variable</th>
<th>B</th>
<th>SE</th>
<th>Wald</th>
<th>df</th>
<th>Sig.</th>
<th>Exp(B)</th>
<th>95.0% CI for Exp(B)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.ART</td>
<td>-.278</td>
<td>.087</td>
<td>10.172</td>
<td>1</td>
<td>.001</td>
<td>.757</td>
<td>.639</td>
</tr>
</tbody>
</table>

C) Mortality with respect to smoking habit

There is a significant association between smoking habits and progression of death. Though the percentage of non-smokers (61%) is greater than smokers (39%), the risk of death is on the higher side in smoking patients as is evident from Figure 10.

Figure 10. Hazard Function for Smoking Habit of Patients in the Present Study

D) Mortality with respect to health problems

As is seen from Tables 6 and 7, there is a significant association between health problems, weight loss and progression of death.
Also, it can be said at 90% confidence level that in this case the risk of dying is 6 times more than other secondary infections.

Table 6. *Omnibus Tests of Model Coefficients*<sup>a</sup>*Weight Loss*

<table>
<thead>
<tr>
<th>-2 Log Likelihood</th>
<th>Overall (score)</th>
<th>Change From Previous Step</th>
<th>Change From Previous Block</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Chi-square</td>
<td>df</td>
<td>Sig.</td>
</tr>
<tr>
<td>418.220</td>
<td>7.588</td>
<td>1</td>
<td>.006</td>
</tr>
</tbody>
</table>

Table 7. *Variables in the Equation Weight Loss*

<table>
<thead>
<tr>
<th>Health.X1</th>
<th>B</th>
<th>SE</th>
<th>Wald</th>
<th>Df</th>
<th>Sig.</th>
<th>Exp(B)</th>
<th>95.0% CI for Exp(B)</th>
<th>Lower</th>
<th>Upper</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1.758</td>
<td>.723</td>
<td>5.915</td>
<td>1</td>
<td>.015</td>
<td><strong>5.800</strong></td>
<td>1.407</td>
<td>23.911</td>
<td></td>
</tr>
</tbody>
</table>

Conclusions

From the present study, it can be concluded that:

- Cox hazards model and regression analysis is the best method for studying survival and mortality rates in HIV patients;
- The incidence of HIV is more in the age group of 30 – 50 years;
- HIV is more prevalent in slum areas, clearly indicating that low standards of hygiene cause incidence of HIV in less affluent strata of the society, whereas the disease is not so widespread in conditions of better hygiene;
- The occurrence of HIV in married men is more than in married women which implies that women are more loyal to their spouses than males who engage in extra-marital sex;
- The percentage of HIV patients with a higher education is more which is surprising and which indicates that awareness about safe sex does not necessarily come with high education;
- Survival time for HIV patients with respect to gender is more in females than in males;
- Mortality of HIV patients is maximum in the age group of 30 – 50 years;
- The probability of survival of HIV patients is more in case of latest CD4 count of more than 500 while it is low in patients with latest CD4 count of less than 200;
- The number of Antiretroviral Therapies (ARTs) taken by HIV patients positively influences the chances of their survival;
- Smoking significantly increases the risk of death among HIV patients;
- Health problems (especially weight loss) augment the risk of death among HIV patients.
References

