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Modelling the Efficacy of Antiretroviral Treatment in HIV Patients: Case of Dr George Mukhari Academic Hospital in Tshwane, Gauteng Province, South Africa

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Abstract: This paper used survival analysis to evaluate the efficacy of antiretroviral (ARV) treatment in HIV patients and also to determine if ARVs reduces the risk of HIV/AIDS. Secondary data were collected from files archived in Tshepang Clinic in Dr George Mukhari Academic Hospital in Tshwane, Gauteng Province of South Africa. Survival time was regressed on influential variables that affect survival. The statistical data analysis was conducted using STATA. Both descriptive and inferential statistics were used in the analysis of data. Of the 318 patients tested, 292 (92%) were alive after treatment and 26 (8%) had died. Survival time was regressed on influential variables (gender, age, education level, marital status, township, CD4 count and viral load) affecting survival. The epidemiological measure of effect was the hazard ratio. At the 5% level of significance, significant hazard ratios were characterized by hazard ratios that are significantly different from "1", $p<0.05$ and 95% Confidence Interval (CI). The combination of Regimen 1 and 2 of ARVs had a positive and significant impact on the lives of patients around the hospital's jurisdiction. The Cox Proportional Hazards Model was identified as the most suitable for the Tshepang data. An equation and models are provided.

Keywords: Log Rank, Treatment Efficacy, Regimen, Survival

Introduction

Survival analysis estimates the probability of survival, relapse, death or any event that occurs over time in a cohort under investigation for a particular outcome (Cleves, 2004; Hosmer *et al*., 2008). It is relevant in clinical studies evaluating the efficacy of treatments, and commonly deals with the relapse rates. The World Health Organisation (WHO, 2006) states that in African randomized clinical trials, several single-dose ARV regimens administered on pregnant women around the time of delivery of babies have verified a short-term efficacy to prevent mother-to-child transmission of HIV-1, as estimated at age 6-8 weeks of life. HIV/AIDS causes death (Dohertey and Colvin, 2004). According to Dedicoat (2002), millions of lives are lost due to HIV/AIDS infection in the developing countries of which almost 30 million are from the Sub-Saharan region. The impact of the AIDS epidemic is reflected in the dramatic change in South Africa's mortality rates. The overall number of annual deaths increased sharply (almost doubled) from 1997 when 316559 people died, to 2006 when 607184 people died. The rise is in young adults, the age group most affected by AIDS, who are particularly shouldering the burden of the increasing mortality rate (Ojikvth and Zheng, 2008). In 2006, 41% of deaths were attributed to 25-49 year olds, up from 29% in 1997, a strong indicator that AIDS is a major factor in the overall rising number of deaths (PCP, 2011).

Problem Statement

Dr George Mukhari Academic Hospital, through its Tshepang Clinic, provides ARV Treatment (ART) to HIV/AIDS patients. The efficacy of ARV treatment in these patients seems favourable, but this has not been verified. The extent of benefit of the ARVs to the patients receiving them is not clear. There is a question of whether ART is associated with survival or not. The study models the treatment for the hospital.

Science Publications

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Motivation for the Study

Statistical interest is to determine the optimal time to start ART Socially, patients from all surrounding clinics of the hospital, including Wisani, Ramogodi, Ga-Rankuwa, Hebron, Erasmus and Klipgat clinic as well as neighbouring provinces like Limpopo, Mpumalanga and North West can benefit from such a study. Economically, the hospital and in return, the government's department of health stands to benefit in the sense that once ART is effective, fewer patients would be required to visit the hospitals as they will take their treatment closer to home. Survival analysis, a scientific or statistical tool is used to inspect these ideas by employing statistical techniques.

Materials and Methods

The study population was described by baseline characteristics at the time of starting the ART. These characteristics include data on:

- Demographic factors (gender, age, education, marital status, township)
- Factors that describe the stage of the disease (CD4 cell count and viral load)
- Factors describing the level of the ARV (regimen) taken
- Factors that indicate the number of days the patient has been on ART

Information on ART was dichotomised into levels '1' and '2' while on censoring it was dichotomised into living or dead. When comparing these baseline data, Pearson's chi-square test was used.

Study Design

This was a retrospective cohort study, evaluating patients from 01 January 2007 to 31 December 2010 from the HIV/AIDS Tshepang Clinic of the hospital. It caters for young (18-54 years) and old (55 years and above), and all race groups. Blood samples are drawn from patients and send to the laboratory for screening first using the serologic ELISA test. Because ELISA often generates some false positive results, a positive ELISA test must always be followed by a confirmatory Western blot test (Losinaa, 2008). The ideal diagnosis marker of HIV infection should be easily and reproducibly measurable in all individuals with the disease. Furthermore, it should worsen with progression of the disease and improve with positive responses to therapy CD4+ T-cells are the primary targets of HIV infection. Depletion of CD4+ T-cells is the immunologic hallmark of HIV disease progression. Measurement of CD4+ T-cell should be an excellent marker of disease progression, and it also yields information regarding the degree of immunodeficiency; quantification of HIV RNA in plasma obtains the information related to the rate of severity of immune deficiency.

Carpenter *et al.* (1998) noted that current recommendations regarding the initiation and maintenance of ART rely on the two best laboratory markers for HIV disease progression, the CD4+ T-cell count and the HIV viral load. According to Zhang (2008), some investigations have demonstrated that the CD4+ T-cell count is a powerful predictor of the short-term risk of developing an AIDS-defining disease. CD4+ T-cell counts frequently increase in response to antiretroviral therapy.

Sampling

The study population comprise of all HIV-infected patients. The clinic caters for all young (18-54 years) and old (55 years and above) HIV patients from all race groups who are exposed to ART. Since this is a retrospective study, archival files and electronic records of HIV patients with a catchment area that caters for an estimated population of about a million inhabitants will be accessed. Collett (2003) points out that there is the crucial issue of the number of patients that are required for such studies. If too few patients are recruited, there may be insufficient information available in the data to enable a treatment difference to be pronounced significant. On the other hand, it is unethical to waste resources in studies that are unnecessarily large. In order to calculate the actual number of patients that are required in a survival study, there is a need to consider the probability of death over the duration of a study. Patients are recruited over an accrual period of length *a*. After recruitment is complete, there is an additional follow-up period of length *f*. The total duration of a study will therefore be of length $a + f$. If f is small, or even zero, there will need to be correspondingly more patients recruited in order to achieve a specific number of deaths. Once the probability of a patient dying in the study has been evaluated, the required number of patients will be found from:

$$n = \frac{d}{P(death)} \tag{1}$$

where, d is the required number of deaths found from:

$$d = \frac{4\left(z_{\frac{\alpha}{2}} + z_{\beta}\right)^2}{\theta^2_R} \tag{2}$$

where, $z_{\frac{\alpha}{2}}$ and z_{β} are the upper $\frac{\alpha}{2}$ and upper β-points respectively, of the standard normal distribution. It is convenient to write $c(\alpha,\beta) = \left(z_{\frac{\alpha}{2}} + z_{\beta}\right)^2$ in Equation 2, giving:

$$d = \frac{4c(\alpha,\beta)}{\theta^2{}_R} \quad (3)$$

Deriving the required number of patients starts with the general result from the distribution theory that the marginal probability of a patient dying during the course of a study can be obtained from the joint probability of death and entry to the study at time *t* using:

$$P(death) = \int_0^a P(death \ \& \ entry \ at \ timet)dx \quad (4)$$

The joint probability can in turn be found from the result:

$$\begin{aligned} &P(death \,\&\, entry@time\ t) \\ &= P(death / entry@t)P(entry@time\ t) \end{aligned} \quad (5)$$

Using Epi-Info version 3.5 (a statistical software package for medical data analysis) on a population size of an estimated one million (1,000000) inhabitants, with an expected frequency of 50% (frequency of obtaining positive results), a 80% power and a 95% Confidence Interval (C.I.), an estimated sample size of 384 was obtained as the sample for use in this study.

Survival Analysis

Survival analysis will be employed to model and predict the patient's clinical disease progression after diagnosis. For HIV/AIDS patients, relative survival is estimated as the ratio of observed survival of the HIV/AIDS patients (where all deaths are considered as events) to the expected survival of the general population, matched to the patients with respect to the main factors (age, race, sex, calendar year) and assumed to be free of HIV infection (Lohse and Hansen, 2007).

The mean residual life is a measurement of the remaining life expectancy of a subject at time *t,* which is the remaining survival time given the subject surviving up to *t* (Dawson and Trapp, 2004; Qin and Zhao, 2007). Since relative survival analysis can be used to identify the determinant factors of HIV/AIDS clinical progression, it has been taken as a reliable approach to estimate the efficacy of prophylaxis and treatment strategies of HIV-infected subjects. The observed survival probabilities of AIDS patients will be calculated using the Kaplan-Meier method for the corresponding data sets. The expected survival probability will be obtained by merging the population data and mortality data sets sorted by age, sex, race/ethnicity and calendar year.

Experimental Study

Data for analysis will be retrieved from the patients' clinic files. Attempts will be made to obtain the overall count of HIV/AIDS patients in the Dr George Mukhari Academic Hospital's jurisdiction. Once an estimate or count is obtained, it will be determined as to the number of patients (i.e., the extent) are using the service (i.e., how many collect ARVs). On this, the lengths they have obtained the services will be recorded to stratify the patients, and the level of recovery measured from medical records. On the group that do not use the service, it will be important to determine reasons for not using the treatment.

Experimental Set-Up

The original raw data set used in this study was provided on a yearly basis in a form of a table given as Appendix, covering the years 2007 to 2011. Organization of this data was done using frequency tables and bar graphs. Data consists of three hundred and eighteen (318) HIV/AIDS infected cases or observations with twenty four (24) variables that were selected for the study.

STATA version 12 (Stata Corp, Texas, USA) and SPSS version 21(IBM SPSS, New York, USA) statistical software packages, mainly because of availability and training obtained by the researcher, were used to perform the initial analysis of the data.

Experimental Results

The section is divided into various sections to pattern an order used in reporting the results. The study variables are exposed at the beginning. Then the level of survival, given as the number of people who survived due to ART, is shown in tables and graphs. This exposes the number who died while on treatment. In addition, the section presentation displays the patients in terms of gender, age, education level, and location.

The presentation also covers the CD4 count of the patients, viral loads, the Kaplan-Meier graph survival estimates, log-rank test equality of survival, survival probability, Hazard function for estimating mortality rate, years of admission to ART, marital status of patients, life-table estimator, and the Cox regression to model survival of HIV patients undergoing ART at the Tshepang clinic.

Table 1 indicates the number of days ART was administered to the patients. The highest number of days for patients to take on ARVs was more than 1800 (>60 months/5 years) and this was experienced by eight patients making up 2.5%. The least number of days of ARV administering was less than 180 days (<6 months) and that was administered to 37 patients (11.6%). Between 360-540 days (12-18 months) was taken by 53 patients (16.7%) and this was the highest number of patients recorded.

Figure 1 represents the number of days of ARV taking by all patients. The number of days on ARV is the days taken by each patient to be on ART from the date of admission to the last day or year of this study (2011). In Fig. 2, number of patients decrease when the CD4 count values increase. Figure 3 indicates that survival of patients on ARV lessens after many days on treatment.

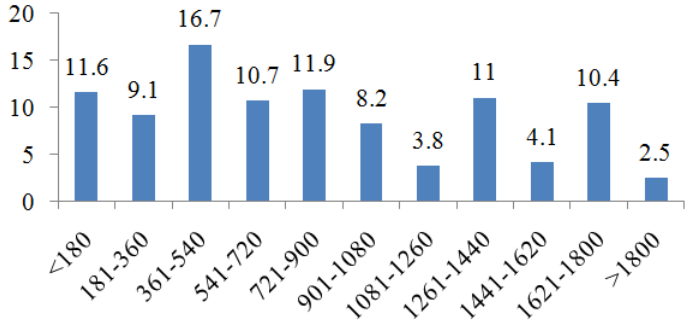

Fig. 1. Number of days on ARV (%)

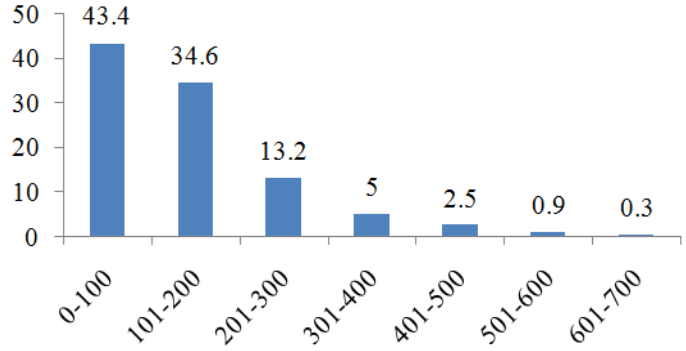

Fig. 2. CD4 counts of patients

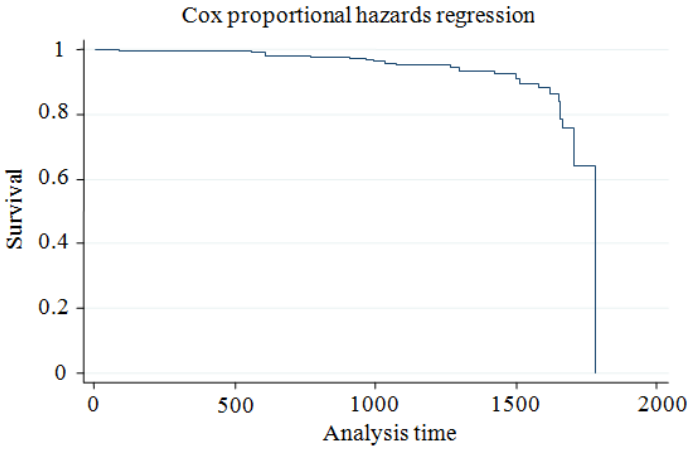

Fig. 3. Cox survival curve

Table 2 below shows that 26 (8.2%) patients had died and 292 (91.8%) had survived in the period of the study. Of the 292 who were living, females were 204 (69.9%) against 13 (20.1%) males. Of the 26 dead, females and males were equal at 13 each.

In Table 3, the chi-square test showed a significant statistical difference between males and females ($P<0.05$).

Table 4 shows that single patients (234/318) dominated other categories at about 73.6% appearance, followed by 64 (20.1%) married, 14 (4.4%) divorced and six (1.9%) widowed were the least.

Table 5 shows that the highest observed CD4 count is one (0.31%) patient with a CD4 count of over 601. This was followed by three (0.9%) patients with CD4 counts between 501 and 600; then eight (2.5%) with CD4 counts from 401 to 500; 16 (5.0%) with CD4 counts of 301-400; 42 (13.2%) with CD4 counts of 201-300; 110 (34.4%) with CD4 counts of 101-200; and 138 (34.6%) with CD4 counts of 0 to 100.

Table 1. Number of days on ARV

Number of days on ARV	Frequency	Percent days
<180	37	11.6
181-360	29	9.1
361-540	53	16.7
541-720	34	10.7
721-900	38	11.9
901-1080	26	8.2
1081-1260	12	3.8
1261-1440	35	11.0
1441-1620	13	4.1
1621-1800	33	10.4
>1800	8	2.5

Table 2. Cross tabulation of gender

		Living/dead		
		Dead	Living	Total
Gender	Male	13	88	101
	Female	13	204	217
Total		26	292	318

Table 3. Chi-square tests

	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson chi-square	4.346[a]	1	0.037		
Continuity Correction[b]	3.478	1	0.062		
Likelihood ratio	4.071	1	0.044		
Fisher's exact test				0.047	0.034
Linear-by-linear assoc.	4.332	1	0.037		
N of valid cases	318				

Table 4. Marital status

Marital status	Frequency	Percent
Divorced	14	4.40
Married	64	20.13
Single	234	73.58
Widowed	6	1.89

Table 5. CD4 frequency table

CD4 Count	Frequency	Percent
0-100	138	43.4
101-200	110	34.6
201-300	42	13.2
301-400	16	5.0
401-500	8	2.5
501-600	3	0.9
601-700	1	0.3

Table 6. Viral loads

Viral load	Frequency	Percent
<1000	219	68.9
1001-50000	56	17.6
>50000	43	13.5

Table 6 shows 43 (13.5%) patients with viral loads of over 50 000; 56 (17.6%) had viral load between 1001 and 50 000; and 29 (68.9%) had viral load count below 1000.

Table 7. The log-rank test

Log-rank test for equality of survivor functions

Group	Events observed	Events expected
0	0	20.09
1	26	5.91
Total	26	26.00

chi2(1) = 105.26
Pr>chi2 = 0.0000

The null hypothesis of no difference in survival functions is H_0: The two survivor functions are equal. "Events observed" that refers to the number of failures observed (0) for the first group and 26 for the second group. "Expected" refers to the number events expected if the two groups had the same survivor function. Figure 7 shows expected value of 20.09 for the first group and 5.91 for the second group. The observed values are different from the expected values to produce a highly significant chi-squared value ($p<0.05$). The log-rank test rejects the null hypothesis at the 5% significance level that the survivor functions of the two groups are the same. The survival curve is also used.

Figure 3 is the estimated baseline survivor function. The Cox approach is the most widely used regression model in survival analysis (Forthofer *et al*., 2007). The probability of survival is 1 at time $t = 0$ and drops to zero as the number of days elapses to maximum of 1781.

According to Cox (1972), the Cox proportional hazards regression model gives the hazard rate for the i^{th} subject in the data as $h(t|x_i) = h_0(t)\exp(x_i\beta_x)$, where the regression coefficients, β_x, are to be estimated from the data and $h_o(t) = constant$. The model includes the variables: Gender (G), age (A), marital status (M), education level (E), township (T), CD4 count and Viral Load (VL). The model emerging from Table 8 is thus:

$$H(t / ARV) = h_0(T)e^R,$$
$$R = 0.679G + 1.033A + 0.361M + 1.084E,$$
$$+0.844T + 0.999CD4 + VL$$

$$ARV = \begin{cases} 1 & if\ subject\ is\ alive \\ 0 & if\ subject\ is\ dead \end{cases}$$

Since $p>0.05$ for gender, age, education, township, CD4 count and viral load, there is thus no significant statistical difference amongst these variables with regard to the predictor variable (days on ARV). Hence, they are all insignificant. The only significant variable is marital status with $p<0.05$. This value also falls outside the 95% confidence interval of 0.161 to 0.809. Thus there is a significant difference between this variable and the days on ARV. That also implies that there is no significant association between ARV regimen and marital status.

Table 8. Cox regression model

_t	Haz. Ratio	Std. Err.	z	P>|z|	[95% Conf. Interval]	
Gender2	0.6791803	0.2879292	-0.91	0.361	0.2958897	1.558979
Age	1.032749	0.0259595	1.28	0.200	0.9831025	1.084903
Marital2	3615232	0.1486429	-2.47	0.013	0.1614947	0.8093083
Education2	1.084283	0.0966501	0.91	0.364	0.9104767	1.291268
Township2	0.8435348	0.0977518	-1.47	0.142	0.6721447	1.058628
Cd4	0.9987908	0.0023613	-0.51	0.609	0.9941735	1.00343
Viral	1	5.54e-08	-0.20	0.845	0.9999999	1

.stcox gender2 age marital2 education2 township2 cd4 viral
failure _d: delta
analysis time _t: days_arv
Iteration 0: log likelihood = -103.46664
Iteration 1: log likelihood = -96.947004
Iteration 2: log likelihood = -96.696118
Iteration 3: log likelihood = -96.694567
Iteration 4: log likelihood = -96.694567
Refining estimates:
Iteration 0: log likelihood = -96.694567
Cox regression -- no ties
No. of subjects = 312 Number of obs = 312
No. of failures = 26
Time at risk = 249675
LR chi2(7) = 13.54
Log likelihood = -96.694567 Prob > chi2 = 0.0599

Discussion

A five year period 2007 to 2011 was used. The year 2010 had the highest number of patients (88 or 28%). This was followed by 2009 with 65 (20%) and 2007 recorded the least number (50 or 16%) of these patients.

The peak admitted in 2010 could have been due to that South Africa hosted a World Cup soccer event. It is probably because people indulged in sexual activities that led to contraction of sexually transmitted diseases which includes HIV.

ARVs were administered to patients for over 1800 days accounting for 2.5% of the total number of patients. Most patients (16.7%) took between 360-540 days. Of the 318 patients on ARV, 292 (91.82%) survived while 26 (8.18%) died.

Most of the patients used First Line ARV regimen drugs that include Stavudine (D4T), Lamivudine (3TC) and Esdorneverapine. These regimens accounted for 94% of all administered ARVs as compared to Second Line regimen that includes D4T, 3TC and alluvia which accounted for 5.7% of all treatments.

Of the dead, males and females recorded the same number (13 each). Of the living, males were 88 (30%) and females were 204 (70%). The Pearson's Chi-square test shows a significant statistical relationship between the living/dead against gender ($p<0.05$).

Recommendations

Clinics should:

- Visit communities to offer the various forms of help in treating HIV
- Assist referred patients to interpret the Tshepang clinic's recommendations
- Follow up on patients taking ARV treatment
- Have a contact person on behalf of the patients, who can support the patients and give feedback about the patients

Schools should:

- Allocate sessions to educate learners about sexual topics, focusing on issues of HIV/AIDS
- Invite and host health experts to educate community members using school resources
- Encourage learners to conduct themselves in preventive ways
- Education departments should sponsor, or co-sponsor with health departments proactive campaigns for awareness about HIV/AIDS, CD4 counts, ARVs and the level of death from AIDS

Health departments should:

- Sponsor NGOs willing to account and be monitored on the work towards HIV/AIDS and use of ARVs
- Provide training to more officials in all areas, including remote rural areas, to provide ARVs and HIV/AIDS Care and Counselling
- Establish more service facilities at the local level

Conclusion

The Cox Proportional Hazards model was the most suitable method for data analysis as it enabled us to obtain

the Kaplan-Meier survival probability curves, the log-rank tests, the probability plots and the life tables. Survival time ($h(t/ARV)$ was regressed on influential variables (gender, age, education level, marital status, township, CD4 count and viral load) that affect survival based on the Cox Proportional Hazards model. At the 5% level of significance, significant hazard ratios were characterised by hazard ratios that are significantly different from "1", $P<0.05$ and 95% Confidence Interval (CI).

ARVs were found to be effective in the treatment of HIV/AIDS patients. Of the total three hundred and eighteen (318) tested, two hundred and ninety two (292) were alive after treatment (92%) as compared to twenty six (26) that died (8%). ARVs have improved the survival rate of HIV/AIDS patients significantly over the said period of study as the mortality rates dropped tremendously. If ARVs had been initiated much earlier than 2007, most lives could have probably been saved within the communities of the hospital. Some may have improved unnoticed as most patients become lost due non-follow up or are simply not taking any initiative of returning to the hospital for check-ups.

Most users of ARVs survived longer. The problems with ARV use is that when the low CD4 counts are not realised earlier, treatment may fail to start due to a patient considered to have reached terminal stages, or may start using them late but with no effect. Hence, treatment should start when ARVs can still be effective. Monitoring of the patients under treatment did not take place, and thus it was not easy to know if the collected ARVs were used correctly. Discussions also showed that communities that are poor could not utilize ARVs properly because of scarcity, but that where they used them, their life was extended in the same way as the rich ones. This showed that use of ARVs does not depend on differences in people using them.

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Author's Contributions

Madimetja Marcus Motshwane: Conducted the study and developed the models.

Solly Matshonisa Seeletse: Assisted in data collection, suggested alternative methods/models and developed this paper for AJAS.

Ethics

The protocol was observed and the university has allowed the distribution of this work and also committed to fund any publication resulting from it.

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