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Accelerated Failure Time Model for Determination of Effectiveness of Antiretroviral Therapy at General Hospital Adikpo, Benue State, Nigeria

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Abstract

The introduction of antiretroviral therapy (ART) has markedly improved the clinical outcomes of individuals living with HIV, transforming the infection from a fatal illness to a manageable chronic condition. Central to HIV management is the CD4 count, a critical biomarker that reflects immune system status and informs clinical decisions regarding ART initiation and the management of opportunistic infections. Reaching a CD4 threshold of ≥500 cells/mm³ is widely considered a key indicator of immune reconstitution and long-term treatment success. However, there remains limited guidance for patients and clinicians on the expected timeline or probability of reaching this milestone, highlighting the need for robust statistical models to support evidence-based treatment planning. This study employed a retrospective cohort design using data from 400 HIV-positive patients who initiated ART at General Hospital Adikpo, Benue State, Nigeria, between 2012 and 2022. Inclusion criteria required that patients begin treatment with a CD4 count <500 cells/mm³. Over the study period, 54% of patients (216) achieved a CD4 count ≥500 cells/mm³, while 46% (184) did not. The Anderson-Darling (test statistic: 0.3660) and Chi-square (test statistic: 12.73) tests confirmed that the lognormal accelerated failure time (AFT) model was an appropriate fit for estimating the time to immune recovery. The analysis revealed that the rate of CD4 improvement was highest in the initial years following ART initiation, with diminishing returns over time. The median time to achieve the CD4 threshold was five years. Key predictors of successful immune reconstitution included baseline CD4 count, patient age, and tuberculosis (TB) status ($p < 0.05$). These findings reinforce the critical importance of early HIV detection, timely initiation of ART, and integrated TB management in improving long-term immunological outcomes.

Keywords: Lognormal; AFT Model; Failure Time; Hazard Rate; CD4 Count; HIV; ART Outcomes

INTRODUCTION

HIV/AIDS has continued to be one of the major universal public health challenges as there has been no known cure since its inception decades ago. Recent statistics indicate that over 600,000 people have died of the disease globally, about 630,000 people died from HIV-related causes in 2023, while about 5 million people are currently living with HIV in the Sub-Sahara Africa, accounting for nearly 15% of new cases globally (UNAIDS 2024). Of the people living with the virus globally, about 2 million (6.1%) are from Nigeria. Notwithstanding the changes in administration and policies, Nigeria is positioned to 'wipe out' the virus within a few decades as many HIV-positive patients continue to enroll on the life saving medication known as Active Antiretroviral Therapy (AART) which increases the lifespan of such patients (NACA 2012). About 1.7 million people are currently on ART in Nigeria (Be-in-the-know, 2024). This has over the years, helped in check-mating the effect of the virus on infected persons thereby increasing life expectancy of people living with HIV/AIDS (PLWHA) (Obeagu et al., 2022). Antiretroviral therapy (ART) is a groundbreaking medical intervention designed to suppress the viral load in HIV/AIDS patients, and a notable phenomenon has emerged within the population undergoing this life-saving treatment. The World Health Organization (WHO) has established a pivotal milestone in the management of ART patients, marking a point of reference against which stability is assessed. This pivotal threshold is the attainment of a CD4 count that reaches a minimum of 500 cells per cubic millimeter (500cells/mm^3) which signifies a state of immunological health and resilience that indicates a patient's capacity to manage the virus effectively.

However, many individuals embarking on this therapeutic journey have limited knowledge of when or how they might eventually exit from it. But given the significance of this CD4 count milestone, this research intends to use this threshold as a theoretical exit point for patients on ART. We decided to explore and estimate the timeline within which patients can realistically aspire to reach this crucial threshold using survival analysis model.

Survival analysis involves statistical methods designed to handle incomplete information about the time until a specific event occurs (Chakraborty, 2018). Widely used in fields such as engineering, biology, medicine, and social sciences (Abhaya & Chandra, 2021), it focuses on understanding the time it takes for an event of interest to happen.

An event refers to an outcome of scientific interest, such as death, disease diagnosis, marriage, or graduation (Ho & Silva, 2006). Historically, death was the primary focus of survival analysis, giving the field its name. However, as the methodology developed, it expanded to include other events like falling in love, wedding, or completing treatment milestones (Zhang et al., 2013).

Central to survival analysis is the concept of time-to-event, which measures the time from a defined starting point (e.g., diagnosis or treatment initiation) to the occurrence of the event. Often called survival time, this measure remains applicable even when the event is unrelated to death (Aalen et al., 2008). For this study, the time starts from the initial CD4 count and ends when the CD4 count reaches ≥500 cells/mm^3.

The median survival time is a commonly reported statistic, representing the point at which 50% of individuals have experienced the event. It is preferred over the mean due to skewed survival time distributions, which often include a few long-term survivors (Ben-Aharon et al., 2019).

A unique aspect of survival analysis is the handling of censored data, which arises when survival times are incomplete. This occurs if an event does not happen during the study period, participants are lost to follow-up, or they withdraw for other reasons such as death if it is not the event of interest (Nasejje, 2013). Censoring creates partially observed data, which requires specialized statistical methods since standard techniques are inadequate. Other studies include works by Deeks et al., (2013), Gupta (2020), Chen 2011, Lifson (2010), Simoni et al., (2006), Alon (2020), Jaya et al., (2014), and Jie (2022).

METHODS

The Survival Function and its Estimation

Let T be a random variable representing the survival time. By definition, the survival function is the probability that the survival time is greater than or equal to t.

$$S(t)=P(T \geq t),\ t \geq 0. \tag{1}$$

For a discrete T, let $0 \leq t_1 < t_2 < \ldots,$ be the ordered values of T, and let $P(T = t_i) = f(t_i)$, i=1, 2…., be the probability mass function. Then,

$$\begin{aligned} S(t) &= \sum_{t_i \geq t} f(t_j) \\ &= \sum f(t_j) I(t_j \geq t), \end{aligned}$$

$$I(t_j \geq t) = \begin{cases} 0\, if\ t_j < t \\ 1\, if\ t_j \geq t \end{cases} \tag{2}$$

Where $I(t_j \geq t)$ is the indicator function.

If T is continuous,

$$S(t)=\exp\left[-\int_t^{\infty} h(u)du\right], \tag{3}$$

Where $h(u)$ is the probability density function.

Lognormal Distribution Model

The probability density function (PDF) of a lognormal distribution is:

$$f(t;\mu,\sigma,\theta)=\frac{1}{(t_i-\theta)\sigma\sqrt{2\pi}} e^{-\frac{(\ln(t_i-\theta)-\mu)^2}{2\sigma^2}},\ 0 < t < \infty. \tag{4}$$

where:

μ is the location parameter (the mean of the log-transformed variable), σ is the scale parameter (the variance of the log-transformed variable), θ is the threshold parameter (shape), and t is the observed data.

The survival function is given by

$$S(t)=1-F(t)=1-\Phi\left[\frac{In(t-\theta)-\mu}{\sigma}\right], \tag{5}$$

where

$$F(t)=\int_0^t \frac{1}{\sigma t\sqrt{2\pi}}\exp\left(-\frac{1}{2\sigma^2}[Int-In\theta]\right)dt=\Phi\left[\frac{Int-In\theta}{\sigma}\right]$$ and $\Phi(z)$ denotes the standard normal cumulative distribution function.

The hazard function $h(t)$ is given by

$$h(t)=\frac{f(t)}{S(t)}=\frac{\left[\frac{1}{t\sigma\sqrt{2\pi}}\exp\left(-\frac{[Int-In\theta]^2}{2\sigma^2}\right)\right]}{1-\Phi\left[\frac{Int-In\theta}{\sigma}\right]} \tag{6}$$

Maximum Likelihood Estimators (MLE) of Model Parameters μ, σ and θ.

We used the maximum likelihood function to estimate our model parameters μ, σ and θ.

The likelihood function is given by

$$L(\mu,\sigma,\theta)=\prod_{i=1}^{n}\frac{1}{(t_i-\theta)\sigma\sqrt{2\pi}}e^{\left(-\frac{(\ln(t_i-\theta)-\mu)^2}{2\sigma^2}\right)} \tag{7}$$

Taking the natural logarithm of the likelihood function and simplifying, we obtain:

$$\ell(\mu,\sigma,\theta)=-n\ln(\sigma)-\sum_{i=1}^{n}\ln(t_i-\theta)-\frac{n}{2}\ln(2\pi)-\frac{1}{2\sigma^2}\sum_{i=1}^{n}(\ln(t_i-\theta)-\mu)^2 \tag{8}$$

To find the MLEs for μ, σ and θ, we take partial derivatives of the log-likelihood function with respect to each parameter and set the derivatives to zero and then use Minitab software to generate their estimates.

$$\partial\ell(\mu,\sigma,\theta)=0 \tag{9}$$

Lognormal Accelerated Failure Time Model (AFT)

The lognormal model given in equation (5) can only be used to make a general inference on the characteristics of our study population without making reference to a particular patient or their covariates. To account for this, AFT model was used to incorporate patients' covariates in order to assess their impact on survival time.

The general log-linear representation of AFT model for i[th] individual is given as:

$$\log(T_i)=\beta_0+\beta_1x_1+\beta_2x_2+\ldots+\beta_kx_k+\sigma\varepsilon_i \tag{10}$$

For i= 1, 2,…,k.

where:

$\log(T_i)$ represents the log-transformed survival time

β_0 is the intercept

$x_1, x_2,..., x_k$ are the explanatory variables with the coefficients $\beta_1, \beta_2,..., \beta_k$.

ε_i is the residual in the log-transformed survival times, which follows a particular distribution.

σ is the scale parameter.

Using covariates considered for this study, the accelerated failure time model can be formulated as

$$\log(T_i) = \beta_0 + \beta_1 x_1 + \beta_2 x_2 + \beta_3 x_3 + \beta_4 x_4 + \beta_5 x_5 + \sigma\varepsilon_i \tag{11}$$

$$T_i = e^{\log(T_i)} \tag{12}$$

where $\beta_0, \beta_1,..., \beta_k$ and σ are the parameters, x_1, x_2, x_3, x_4, x_5 are the values of covariates, ε is a random variable that is independently and identically distributed. A 95% confidence interval was considered as $\hat{\beta}_i - Z_{1-\alpha/2} SE(\hat{\beta}_I)$ to $\hat{\beta}_i + Z_{1-\alpha/2} SE(\hat{\beta}_i)$

Covariates considered in this research are:

X_1= gender, X_2= age, X_3= TBstatus, X_4= initial CD4 count, and X_5= weight.

Evaluating the Lognormal Model Fit

In order to select the parametric distribution which suits the failure time data, the Anderson-Darling (AD) test and Chisquare was adopted to carry out goodness of fit test. The AD test statistic is given as:

$$AD = \left[\sum_i \tfrac{1-2i}{n}\left\{\ln\left(1-\exp\left(-Z_{(i)}\right)\right) - Z_{(n+1-i)}\right\} - n\right] \tag{13}$$

And

$$AD^* = \left(1 + 0.2/\sqrt{n}\right) AD$$

where

$Z_{(i)} = \left[X_{(i)} / \theta^{*}\right]^{\beta^{*}}$ and the asterisks (AD*) represents the estimators of the lognormal parameters (Neamvonk and Phuenaree 2023). The Chisquare test statistic is stated as:

$$\chi_0^2 = \sum_j^c \frac{(O_j - E_j)^2}{E_j} \sim \chi_{c-k-1}^2 \qquad (14)$$

where

$O_j =$ Observed frequencies, and $E_j =$ Expected frequencies. The decision is such that H_0 is rejected if $\chi_0^2 > \chi_{c-k-1}^{2(\alpha)}$; where α is the level of significance.

Hypotheses

H_0 : The failure time follows lognormal distribution

H_1 : The failure time does not follow lognormal distribution

We reject H_0 if $P_{value} < 0.05$ or the test statistic is greater than the critical value at α level of significance.

Study Design and Data Collection

The study applied the most suitable Accelerated Failure Time (AFT) model to evaluate the effectiveness of Antiretroviral Therapy (ART) at General Hospital Adikpo, Benue State, Nigeria. A retrospective cohort of HIV/AIDS patients enrolled for ART at the hospital between 2012 and 2022 was analyzed, with data collected semi-annually over a ten-year period from the hospital's HIV/AIDS registers. A total of 400 patients were selected for the study. Inclusion criteria required that participants have an initial CD4 count less than 500 cells/mm^3 upon starting ART. The dataset includes variables such as gender, age, tuberculosis (TB) status, initial CD4 count, weight, and the time taken to reach a CD4 count ≥500 cells/mm^3.

RESULTS AND DISCUSION

Descriptive Statistics

Table 1 presents the descriptive statistics of the response and continuous predictor variables. The survival period of HIV/AIDS patients on ART ranges from 1 to 9 years, with a mean of 4.77 years (±3.08). This represents the time taken to transition to a CD4 count ≥ 500 cells/mm³, regardless of initial status. The average patient age is 35 years (±10), ranging from 16 to 65 years. The initial CD4 counts were all below 500 cells/mm³, with a mean of 221.68 (±121.29), reflecting poor immunological status before treatment. The average weight of patients is 62.50 kg (±16.36).

Table 2 summarizes categorical variables. Males comprised 68.3% (273), and females 31.7% (137) of the sample. TB-positive patients accounted for 35.8%, while 64.2% were TB-negative. Patients with CD4 counts < 500 cells/mm³ at the study's end were censored, as the event of interest was transitioning to CD4 count ≥ 500 cells/mm³. By the study's conclusion, 54% (216) reached this threshold, while 46% (184) had not.

Table 1: Description of Response and Continuous Predictor Variables

Variable Type	Variable Name	Min	Max	Mean	SD
Response Variable	Survival Time in years	1	9	4.77	3.08
Predictor Covariates	Age of Patients	16	65	34.61	10.32
	Initial CD4 Count	0	499	221.68	121.29
	Weight of Patient	35	90	62.50	16.36

Table 2: Description of Categorical Predictor Variables for HIV/AIDS Patients at General Hospital Adikpo.

Variable	Category	Frequency	Percentage
Gender	Male	273	68.3
	Female	137	31.7
TB Status	Positive	27	35.8
	Negative	143	64.2
Censored	(0) CD4 Count <500	184	46
	(1 CD4 Count >= 500	216	54

Goodness-of-Fit Test

In order to select the appropriate theoretical distribution which fits the response variable two techniques were adopted to test the fitness of the data to Lognormal distributions as presented in Section 2.6. Results in Table 3, shows that the Anderson-Darling test statistic (0.3660) is less than the critical value (2.5018) at 0.05 level of significance. Similarly, Chi-square tests statistic (12.73) for Lognormal distribution is less than the critical value (15.507) at 0.05 level of significance. Hence, the null hypothesis that the response variable T is Lognormal is accepted. Based on the decisions reached from the two goodness-of-fit techniques, the Lognormal distribution was adopted as the appropriate theoretical distribution for the survival time of HIV/AIDS patients under study.

Table 3: Goodness of Fit Test for Lognormal Distribution

Distribution	Type of Test	Level of Significance	Test Statistic	Critical Value	Decision
Lognormal	Anderson-Darling	0.05	0.366	2.5018	Accept H_0
	Chi-Squared	0.05	12.73	15.507	Accept H_0

Survival and Hazard Rate Analysis

Figure 1 illustrates the survival plot with a 95% confidence interval for the Lognormal distribution. The graph's downward slope indicates that the probability of patient survival decreases over time before stabilizing. This suggests that during the initial years of therapy, the proportion of patients with CD4 count below 500 cells/mm³ was high. However, as therapy progresses, this proportion declines due to its effectiveness in helping patients achieve the CD4 count threshold of ≥ 500 cells/mm³.

Figure 2 displays the cumulative survival probabilities for ART successes recorded at the hospital. The upward slope indicates that the probability of patients reaching the CD4 count threshold increases over time, highlighting the therapy's efficacy in promoting immunological recovery.

Figure 3 presents the hazard rate plot for the Lognormal distribution. It shows that the rate at which patients achieve a CD4 count ≥ 500 cells/mm³ is higher in the early years of ART initiation but declines over time. This aligns with the variability in patient-specific factors influencing their response to treatment and the time required to reach the threshold (Park et al., 2018).

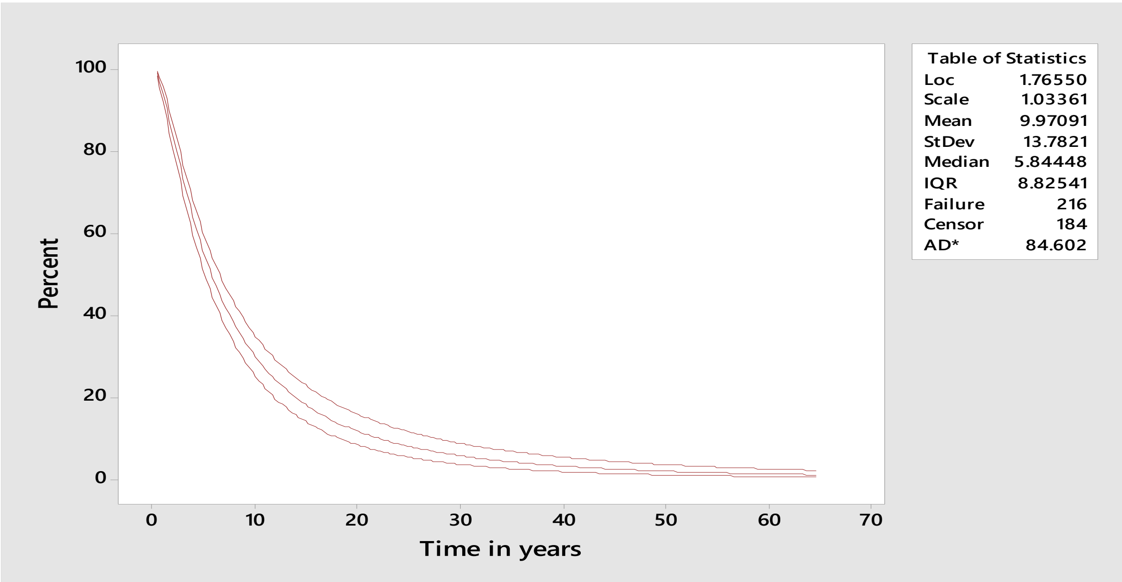

Figure 1: Lognormal Survival plots for HIV/AIDS Patients at General Hospital Adikpo

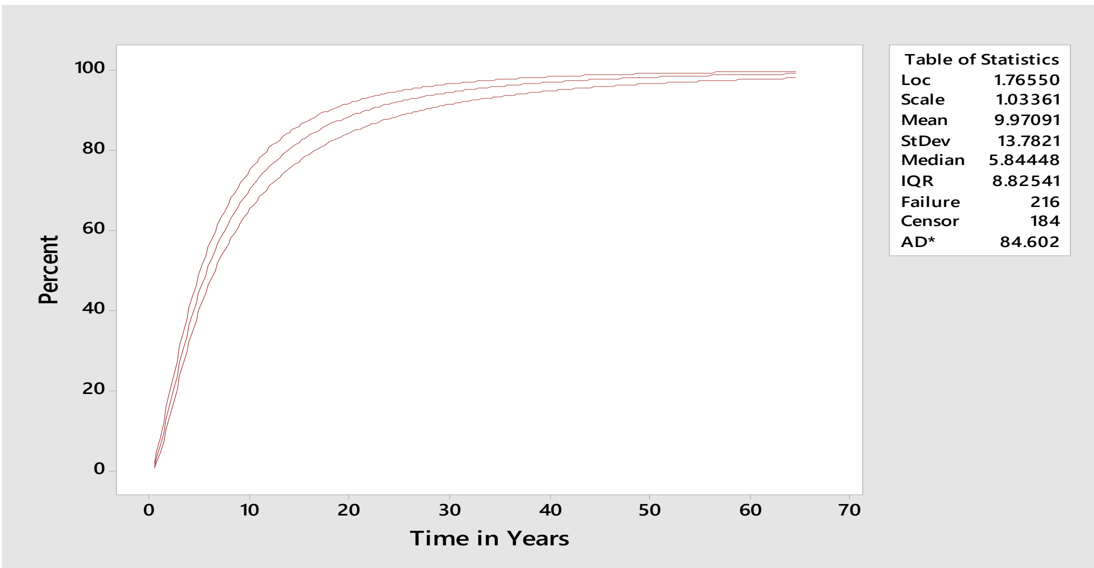

Figure 2: Lognormal Cumulative Failure plot for HIV/AIDS Patients at General Hospital Adikpo

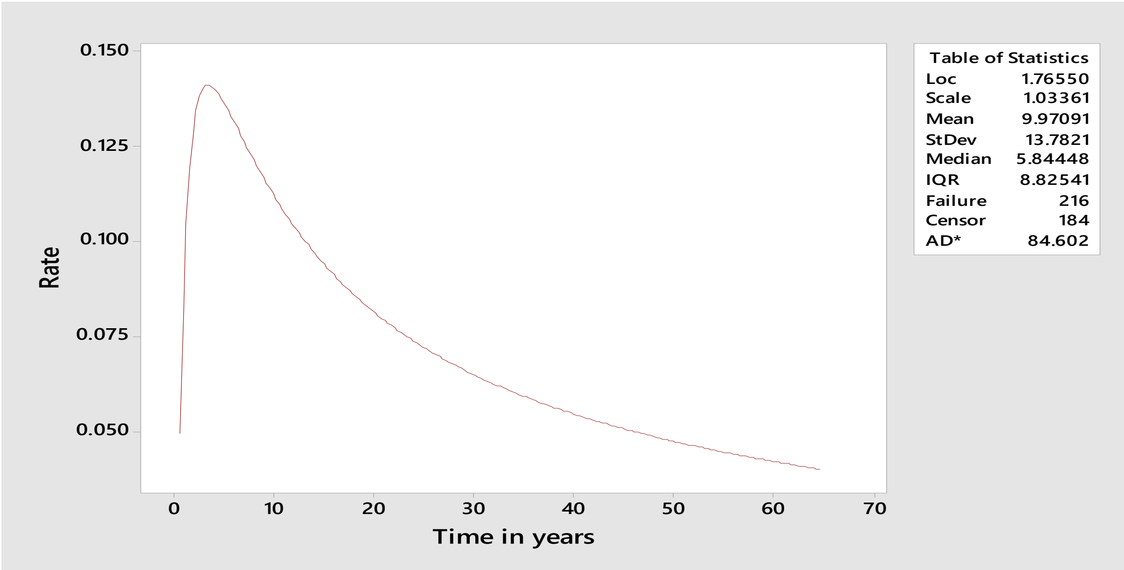

Figure 3: Lognormal Hazard Plot for HIV/AIDS Patients at General Hospital Adikpo

Table 4 presents probability estimates from the survival data, showing the proportion of HIV/AIDS patients under ART who had not yet achieved a CD4 count ≥ 500 cells/mm³ at various times. Within two years of therapy, approximately 85% of patients had not reached the threshold. However, this proportion decreased significantly over time, reflecting the effectiveness of ART. For example, by five years, 46% of patients had reached the threshold, increasing to over 60% within eight years, as shown in Table 5. The average time to reach the threshold, as indicated in Table 8, is 9 years, further demonstrating the therapy's efficacy.

Table 6 highlights the hazard rates, which represent the rate at which patients achieve the CD4 threshold at a given time while remaining on therapy. At the study's onset, over 10% of patients reached the threshold. The hazard rate gradually declined over time, indicating that as more patients reached the WHO-recommended stability threshold (CD4 count ≥ 500 cells/mm³), the study population diminished, reflecting the therapy's effectiveness.

Regression Analysis

To identify significant covariates influencing patient outcomes, accelerated failure time analysis was conducted, with results summarized in Table 7. The lognormal regression model identified initial CD4 count, TB status, and patient age as significant predictors of achieving CD4 count ≥ 500 cells/mm³ at the 0.05 significance level.

Initial CD4 count and TB status had negative coefficients, indicating they significantly reduced the time required to reach the threshold, while age had a positive coefficient, suggesting it increased the time to achieve stability on therapy.

These findings align with prior research, which highlighted opportunistic infections and the clinical stage of HIV as key predictors of survival time for HIV/AIDS patients (Nigussie et al., 2020; Belay & Derebe, 2022).

Table 7: Regression Results of Lognormal AFT Model for HIV/AIDS Patients on ART at General Hospital Adikpo

Predictor	Coefficient	Standard Error	Z	P	95.0% Lower	CI Upper
Intercept	1.8323	0.3013	6.08	0.000	1.2417	2.4229
Age	0.0101	0.0052	1.95	0.051	-0.0001	0.0202
InitialCD4	-0.0021	0.0004	-4.87	0.000**	-0.0029	-0.0013
Weight	0.0030	0.0031	0.97	0.330	-0.0031	0.0092
Tb_Status	-0.4757	0.1061	-4.48	0.000**	-0.6837	-0.2677
Gender	0.0689	0.1137	0.61	0.544	-0.1540	0.2917
Scale	0.9053	0.0450			0.8211	0.9980

**Significance

Fitting the Lognormal AFT Model

Given the regression results in Table 6 and equation (15), the fitted lognormal AFT model is

$$\begin{aligned} T_i &= e^{\log(T_i)} \\ &= e^{\beta_0+\beta_1 x_1+\beta_2 x_2+\beta_3 x_3+\beta_4 x_4+\beta_5 x_5+\sigma\varepsilon_i} \\ \hat{T}_i &= e^{(1.8323+0.0689x_1+0.0101x_2-0.4757x_3-0.0021x_4+0.0030x_5)} \end{aligned} \quad (16)$$

Equation (16) can be used to estimate the time taken for a patient to reach a CD4 count ≥500cells/mm^3 given their covariates (gender, age, TBstatus, CD4 count at entry and weight).

CONCLUSION

In this study, a survival analysis of the people living with HIV/AIDS on antiretroviral therapy at General Hospital Adikpo, Benue State Nigeria was carried out using accelerated failure time model. By the end of the study, 216 patients (representing 54%) had reached a CD4≥500cells/mm^3 while on ART. Using appropriate parametric survival model, the survival and hazard rates of the patients were obtained. Covariates which significantly affected the survival of patients were also isolated using Accelerated Failure Time model analysis.

The following conclusions are drawn from the study: For patients on ART at General Hospital Adikpo, the probability of a patient attaining normality threshold increases until it becomes constant over time. In other words, the rate at which HIV/AIDS patients under ART attained CD4 count ≥ 500cells/mm^3 irrespective of the initial CD4 count increases as time increase. Precisely, the rate at which HIV/AIDS patients under ART attained CD4 count ≥ 500cells/mm^3 increases in the early years of patients' commencement of ART but declines as time goes on. Also, 50% of the patients were noticed to have reached the threshold within 5 years (median time) of commencement of ART. The study further revealed that initial CD4 count, TB status and age of patients have significant influence on patients' attainment of CD4 count ≥ 500cells/mm^3 at 0.05 level of significance. The antiretroviral therapy at General Hospital Adikpo is thereby adjudged to be effective with 9 years as average time to attain the WHO threshold of CD4 count ≥ 500cells/mm^3 based on our findings.

Recommendations

The following recommendations are made with reference to our findings:

1. That people should screen regularly for HIV so as to avoid late diagnosis.
2. Antiretroviral therapy should be initiated as soon as one is tested positive to HIV/AIDS
3. People living with HIV/AIDS should be routinely screened for opportunistic infections.
4. People living with HIV/AIDS should be properly educated to avoid lifestyles that can further expose them to opportunistic infections.
5. People living with HIV/AIDS who have opportunistic infections should be given more care in other to enhance their survival rate.
6. Researchers should explore other risk factors which have the likelihood of influencing the survival of people living with HIV/AIDS.

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