Parametric Modeling of Survival Data Based on Human Immune Virus (HIV) Infected Adult Patients under Highly Active Antiretroviral Therapy (HAART): A Case of Zewditu Referral Hospital, Addis Ababa (AA), Ethiopia

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Abstract: In the present article our aim is to model the HIV infected adult patients' dataset. A retrospective cohort study was conducted in Zewditu Referral Hospital located in Addis Ababa, Ethiopia. Records of patients enrolled between September 2010 and August 2014 were reviewed continuously using patients'Antiretroviral Therapy (ART) unique identification numbers as reference. Kaplan-Meier survival curves and Log-Rank test were used to compare the survival experience of different category of patients. Then we attempted to model the above data with the help of four parametric models namely; Exponential, Weibull, Gompertz, and Log-logistic. All fitted models were compared separately by using AIC and log likelihood. The log-logistic model gave a better description of the time-to-death of HIV infected adult patients than the other models. Based on log-logistic model, age, weight, and functional status, TB screen, World Health Organization (WHO) clinical stage and educational level were found to be the most prognostic factors of time-to-death. Furthermore a high risk of death of patients was found to be associated with lower initial weight, WHO clinical stage IV, lower CD4 count, being ambulatory, bedridden, and TB screened and illiterate.

Keywords: Human immunodeficiency Virus, Acquired immune deficiency syndrome, Parametric Models, HAART, ARTCD.

1. INTRODUCTION

HIV, the agent that causes acquired immune deficiency syndrome (AIDS), is classified as members of the lent virus subfamily of retroviruses. There are two main types of HIV: HIV type 1 (HIV-1): the most prevalent throughout the world. HIV type 2 (HIV-2) is prevalent in West Africa. They both cause ADIS and the routes of transmission are the same. However, HIV-2 causes AIDS much more slowly than HIV-1 [1].

Africa is the region most affected by the spread of HIV/AIDS and within Africa, Sub-Saharan Africa has remained to be the most devastated by the epidemic. In 2007, Sub-Saharan Africa accounted for more than two thirds (68%) of all persons infected with HIV, and 72% of global AIDS deaths [2].

In Ethiopia the adult prevalence of HIV was estimated to be 1.5% in 2011. The total number of People Living with HIV/AIDS (PLHIV) in the same period was estimated to be 1,037,267 adults and 68,136 of them were children. Furthermore the number of deaths due to AIDS for the same period was estimated to be 58,290 for adults and 9,284 among children [2].

Several cohort studies and clinical trials have shown that the CD4 count is the strongest predictor of subsequent disease progression and survival [3]. Seid *et al*. (2014) found that gender, age, clinical stage, functional status and educational level to be significantly associated with defaulting. In addition, the results show that the patient's survival in the HAART treatment is associated with patient-specific CD4 fluctuations such that a patient with higher CD4 trend is less likely to default from the treatment. An individual with higher CD4 variability is more likely to default than an individual with smaller CD4 variability.

Seage GR, *et al.* (1997) showed that functional status and recent opportunistic diseases as the major predictors of survival time. A finding of a cross-sectional study based on 241 cases reported from nine domestic hospitals throughout mainland China was in agreement with the stated claim, concluded that HIV/Tuberculosis (TB) co-infection was related to high mortality even when HAART and/or drug therapy for TB was provided [6].

A retrospective survival time study of 790 HIV-infected patients in Singapore found that the patients of younger age and higher baseline CD4 cell count associated with a lower risk of progression to AIDS [7].

A survival study conducted in South Africa revealed that the advanced WHO clinical stage and low CD4 cell count as indicators of high mortality [8]. A similar study Malawi found that low body-mass index, WHO clinical

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stage IV, male gender, and baseline CD4 count lower than 50 cells/ml as determinants of death [9].

To determine the relationship between mortality risk and the CD4 cell response to ART, a cohort of 2,423 patients on ART and who had a median baseline CD4 105 cells/μl were observed for up to 5 years of ART in South Africa and found that CD4 cell counts were the variable most strongly associated with death [10].

Likelihood based criteria for model selection indicated that the Weibull model was the best fitting parametric model for predicting survival following both HIV and AIDS diagnoses [11].

Ponnuraja C. and Venkatesan P. (2010) using applied likelihood-based criteria for model selection, showed that the Gamma model was the best fitting parametric model for tuberculosis clinical trial data. Hayat *et al.* (2010), showed that the Gompertz model was more suitable, for breast cancer registry data from Ege university cancer research center.

The present study further evaluates the use of the CD4 count in assessing the clinical status of HIV-infected individuals, in making informed decisions regarding the initiation of antiretroviral therapy and in monitoring the success of such therapy by using statistical methodology.

Despite the availability of a large body of research evidence that addresses issues about HIV infected adult patients treated on HAART in Ethiopia, the level of understanding about predictor variables associated with mortality rate as a result of HIV infection is low. The present article compares the performance of four parametric models and identifies the prognostic factors for time-to-death of HIV infected adult patients treated on HAART using Zewditu Referral Hospital as case study area.

2. METHODOLOGY

2.1. Data

The data for this study is a longitudinal cohort follows up retrospective cohort design of HIV infected adult patients obtained from Zewditu Referral Hospital, Addis Ababa, Ethiopia. The ART clinic Zewditu Referral Hospital provides HIV/AIDS interventions including free diagnosis, treatment and monitoring. The center diagnoses new cases and monitors those on therapy. This study is based on a review of the patients' intake forms and follow-up cards of HIV patients on HAART. The patient's forms have been designed by FMOH for uniformity of use in the country so that those forms can be used to document almost all relevant clinical and laboratory variables.

We had taken all patients older than 15 years (i.e., both adolescents and adults) who received HAART in 2010. A total of 653 patients in the clinic who started HAART between September, 2010 and August, 2011 were included in the study. Patients were eligible for ART on the basis of the 2010 WHO guidelines (WHO clinical stage I/II disease with CD4 cell count below 350 cells/μL and WHO stage III/IV disease with CD4 cell count above 350 cells/μL). The patients were followed up until August 2014. However, the study used data on included 638 HIV infected adult patients for whom data for variables of interest are complete.

2.2. Variables of the Study

The response (dependent) variable is the survival time of HIV infected adult patients i.e the length of time from HAART start date until the date of death (or censor) measured in months. HIV infected adult patients, who stayed alive during the study time, transferred to other hospitals, lost and dropped before death, are considered as censored. This means that the type of the survival data is random right censored.

Explanatory variables which are assumed to influence the survival of HIV infected patients are: gender (male, female), age (<30, [30-39], [40-49], [>=50] years), weight (in Kg), CD4 cell count (in mm^3), functional status (working, ambulatory, and bedridden), TB screen (no, yes), OIs (no, yes), WHO clinical stage (stage I, stage II, stage III, and stage IV), educational level (no education, primary education, secondary and above). Predictor variables except CD4 cell count are taken as baseline values. CD4 count is recorded at every six month of visit time. In the analysis the first categories of all variables are considered as reference categories.

2.3. Survival Distributions

2.3.1. Notation

T denote a continuous non-negative random variable representing survival time, with probability density function (pdf) f(t) and cumulative distribution functions (cdf) F (t) = Pr {T≤ t}.We focus on the survival function S(T) = Pr {T >t}, the probability of being alive at t , and the hazard function λ (t) = f(t) / S(t) . Let $\Lambda(t) = \int_0^t \lambda(u)$ denote the cumulative (or integrated) hazard and recall that

S (t) = exp{- $\Lambda(t)$ }

2.3.2. (a) Weibull

The survival function for Weibull distribution is given by

$$S_T(t) = \exp(-\lambda t^{\alpha})$$

and the hazard rate is expressed by

$$h_T(t) = \lambda \alpha t^{\alpha-1}$$

To incorporate covariates **Z** (.) = { $Z_1(.), \ldots, Z_p(.)$} into the Weibull model , we use a linear model for log time

Y = μ + **γ′z** + σ W

where W has the standard extreme value distribution. This model leads to a proportional hazards model for X with a Weibull baseline hazard, that is

$$h_T(T/\mathbf{Z}) = (\lambda \alpha t^{\alpha-1}) \exp(\boldsymbol{\beta}'\mathbf{Z})$$

With α = 1/σ, λ = exp(-μ/σ) and β_j = - γ_j / σ , j = 1, 2, ..., p.

Using the accelerated failure –time representation of the Weibull regression model, the hazard rate for an individual with covariate vector **Z** is given by

$$h_T(t/\mathbf{Z}) = \exp(\boldsymbol{\theta}'\mathbf{Z})(\lambda \alpha t^{\alpha-1}) \exp(\boldsymbol{\beta}'\mathbf{Z})$$

The factor exp(**θ′ Z**) is called an acceleration factor.

(b) Log-Logistic

T has a log-logistic distribution iff

Y = log *T*=μ + σ W

where W has the standard logistic distribution, with pdf.

$$f_W(w) = \frac{e^w}{(1+e^w)^2}$$

and cdf $F_W(w) = \frac{e^w}{1+e^w}$

The survivor function is the complement

$$S_W(w) = \frac{1}{1+e^w}$$

Changing variables to *T* we find that the log-logistic survivor function is

$$S(t) = \frac{1}{1+(\lambda t)^p}$$

Where α = - log λ and p = 1/σ. Taking logs we obtain the (negative) integrated hazard, and differentiating w.r.t. t we find the hazard functions

$$\lambda(t) = \frac{\lambda p (\lambda t)^{p-1}}{1+(\lambda t)^p}$$

The second representation is obtained by replacing λ by exp(**β′ Z**). Here the conditional survival function for the time to event is given by

$$S_T(t/\mathbf{Z}) = \frac{1}{1+\lambda \exp(\boldsymbol{\beta}'\mathbf{Z}) t^p}$$

(c) Gompertz - Makeham distribution

The Gompertz distribution is characterized by the fact that the log of the hazard is linear in t, so

λ (t) = exp {α + β t)

and is thus closely related to the Weibull distribution where the log of the hazard is linear in log t. In fact, the Gompertz is a log-Weibull distribution.

3. RESULTS

The patients were followed up for a median period of 51 months. The minimum and maximum follow-up time was 3 and 59 months, respectively. Of all 638 HIV infected adult patients, 64(10%) died during the follow up period. The overall mean estimated survival time of patients under the study was 44 months

As shown in Table **1**, the actual mean of the CD4 count was increasing over time. This shows that after patients initiated to HAART the average CD4 count increased due to the positive effect of the therapy.

Table1: The Mean and Standard Deviation of HIV Infected Adult Patients Longitudinally Measured CD4 Count at each Visit Time in Zewditu Referral Hospital, AA, 2010

Time (month)	0	6	12	18	24	30	36	42	48	54	60
Mean (CD4)	154.7	160.0	190.0	255.3	310.3	351.5	381.3	416.5	444.8	452.7	465.4
Std.Dev(CD4)	108.8	110.3	110.1	114.0	127.5	124.3	133.3	130.1	131.4	118.8	123.6

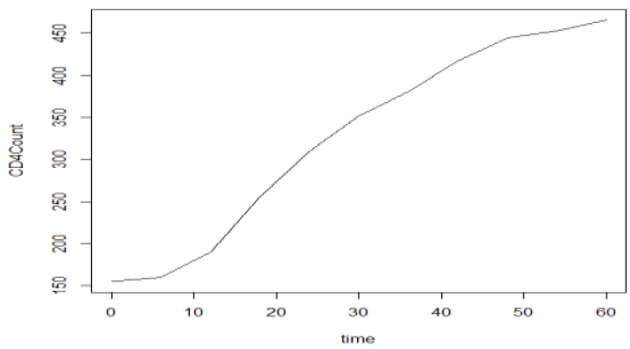

Figure 1: The average progression of actual CD4 count of HIV infected adult patients under HAART in Zewditu Referral Hospital, AA, 2010.

Figure **1** depicts that the mean CD4 count evolution shows an increase the patient's immune system or the progression of the disease declines over time (i.e. because CD4 count and HIV infection are negatively correlated).

3.1. Survival Function of Different Categorical Group of Covariates

Descriptive graphs of survivor function would be used for the purpose of comparing the event experiencing time of two or more groups and the survival quantities of covariates to describe survival experience. In order to get a closer look at estimate of the survival time we use the Kaplan-Meier and Nelson-Aalen estimation techniques. The estimated hazard function depicted in Figure **2** below shows that an increase in the hazard rate has direct relation with the increase in time.

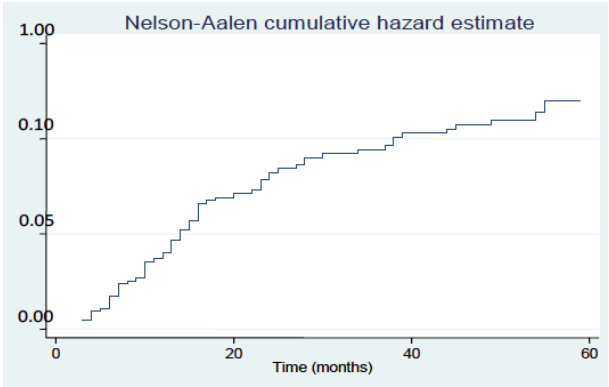

Figure 2: The Nelson-Aalen estimated cumulative hazard function of HIV infected adult patients under HAART in Zewditu Referral Hospital, AA, 2010.

Figure **3** is the estimate for overall Kaplan-Meier survivor function. It depicts that, relatively, a large number of the deaths occurred at the earlier months of HAART treatment, and a decrease over the follow up period.

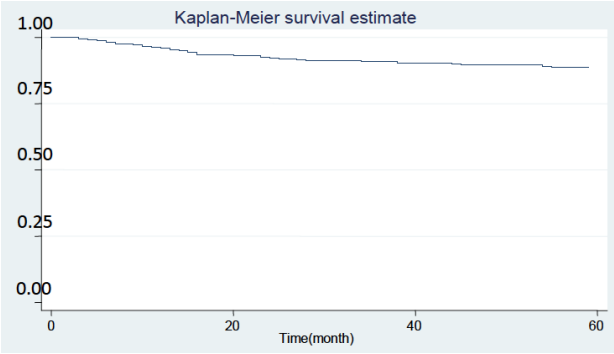

Figure 3: The plot of the overall estimate of Kaplan-Meier survivor function of HIV infected adult patients under HAART in Zewditu Referral Hospital, AA, 2010.

To check for significance differences among categories of factors of survivor functions, we employ the log-rank statistical test. Based on the log-rank test, there were no significant differences in survival experience between the various categories of gender, marital status, and religion. However, the log-rank test showed that the survival experience of HIV infected adult patients in different categories of age, functional status, TB screen, OIs, WHO clinical stage and educational level differ significantly (Table **4**).

Table 2: Results of the Log-Rank Test for each Categorical Variables of HIV Infected Adult Patients under HAART in Zewditu Referral Hospital, AA, 2010

Covariate/Factor	DF	Chi-square	p-value
Age	3	26.06	0.0000
Functional status	2	82.05	0.0000
TB screen	1	24.44	0.0000
OIs	1	6.96	0.0083
WHO clinical stage	3	68.92	0.0000
Gender	1	0.49	0.4855
Marital status	2	3.72	0.1558
Educational level	2	13.30	0.0013
Religion	2	0.47	0.7919

Using all the multivariable parametric models, the covariates age, CD4 count, functional status, TB screen, WHO clinical stage, and educational level were significant, indicating that they were the most important prognostic factors for the time-to-death from HIV infected adult patients data.

From Table **3**, we can see that the values of AIC and log likelihood of the four parametric models. In this case, we used AIC and log likelihood to compare the

models separately. The lowest value of AIC in combination with the largest value of log likelihood is a criterion to select a model. The AIC value of the log-logistic model i.e. 448.9452 is the smallest. The largest log likelihood value of the log logistic model is -209.4726. This indicates that the log-logistic model is the most efficient model to describe the HIV infected adult patient's dataset among the candidates parametric model.

Table 3: AIC and Log Likelihood of the Candidate Parametric Models

Model	AIC	Log likelihood
Exponential	452.2243	-212.1122
Weibull	454.2235	-212.1118
Gompertz	450.9601	-210.4801
Log-logistic	448.9452	-209.4726

Multivariable analysis based on log-logistic model shows that, all covariates were significant except some category of age and WHO clinical stage (Table **4**).

The 95% confidence intervals of the acceleration factor for all significant categories of the covariates do not include 1 at 5% level of significance. This shows that they were prognostic covariates for determining the time-to-death of HIV infected adults patients. The estimated coefficient of the parameters for patients who had TB screen was -1.125203. The sign of the coefficient is negative which implies that decreasing logged survival time. Hence, their death time will decrease by a factor $\hat{\phi}$=0.3245866 than the reference category (patients who had not TB screen) at 5 % level of significance.

The acceleration factor for functional status of HIV infected adult patients was 0.4531and 0.3308 for group of ambulatory and bedridden respectively using working groups as a reference category. This indicates that for ambulatory and bedridden groups survival is reduced by a factor $\hat{\phi}$=0.4531 and $\hat{\phi}$=0.3308, respectively, than the reference group at 5% level of significance. The coefficients of categorical variable age, shows the survival of age group [40-49] and >=50 years were reduced by a factor of ($\hat{\phi}$=0.220243) and ($\hat{\phi}$=0.1598542), respectively, by using age group younger than 30 years as a reference category.

The acceleration factors for those adult patients who had attended the primary and secondary and above educations were 2.7798 and 2.9006 respectively. This indicates that the two groups of primary and secondary and above were significantly prognostic factors for timing of time-to-death by using illiterate category as a reference. An acceleration factor of greater than 1 indicates prolonging the survival. Therefore, for patients who attended primary education death time was longer by a factor of $\hat{\phi}$=2.7798 than the reference group. For patients who attended secondary and above education was the factor 2.9006 relative to the reference group.

The acceleration factor and 95% CI of acceleration factor for WHO clinical stage of HIV infected adult patients who were in stage IV was 0.274140 and (0.08412, 0.89337), respectively, compared with patients in stage I as a reference category. This indicates patients with stage IV their survival was shrank by a factor of $\hat{\phi}$=0.274140 compared with patients who were in stage I.

For a 10 Kg change in weight the log of time is increased by 0.377, holding the remaining covariates constant. Similarly, for 100 cells/mm^3 change in CD4 count log of time is increased by 0.39, holding the remaining covariates constant. The value of the shape parameter in the log-logistic model is isρ=1.617352. Since this value is greater than unity the hazard function is unimodal.

The Cox- Snell residuals and q-q plot were used to check the adequacy of the models. The Cox- Snell residuals (together with their cumulative hazard function) had been obtained from fitting using the exponential, Weibull, Gompertz and log-logistic models to our data via maximum likelihood estimation.It can be seen that the plot of the cumulative hazard function against Cox-Snell residuals (Figure **4**) is closest to the 45^0 straight lines through the origin for log-logistic model when compared to exponential, Weibull and Gompertz models. This suggests that log-logistic model provided the best fit for the HIV infected adult patients under HAART dataset.

Figure **4a** Cox-Snell residuals obtained by fitting exponentia,6(b,c,and d)Weibull, Gompertz and log-logistic models for HIV infected adult patients under HAART dataset in Zewditu Referral hospital, AA, 2010.

A quantile-quantile or q-q plot is used to check if the accelerated failure time provided an adequate fit to the data from two different groups of the population. We shall graphically check the adequacy of the accelerated failure-time model by comparing the significantly

Table 4: Results of the Multivariable Analysis of log-Logistic model

Covariate/factor Variable	$\hat{\beta}_j$	s.e	$\hat{\phi}_j$	p-value	95 % CI for ϕ	
					LCL	UCL
Age in years						
<30	Ref.					
[30-39]	-0.7687	0.4992	0.4636379	0.124	0.17427	1.23346
[40-49]	-1.5130	0.5131	0.220243	0.003	0.08056	0.60212
>=50	-1.8335	0.5443	0.1598542	0.001	0.05501	0.46453
Weight	0.0377	0.0136	1.03842	0.006	1.01106	1.06647
Functional status						
Working	Ref.					
Ambulatory	-0.7917	0.3333	0.4530713	0.018	0.23576	0.87069
Bedridden	-1.1063	0.3635	0.3307922	0.002	0.16222	0.67455
TB screen						
No	Ref.					
Yes	-1.1252	0.3788	0.3245866	0.003	0.15446	0.68203
CD4 count	0.0039	0.0016	1.00386	0.019	1.00065	1.0071
WHO clinical stage						
WHO stage1	Ref.					
WHO stage2	0.2011	0.6886	1.222776	0.770	0.31706	4.71572
WHO stage3	-0.6246	0.5763	0.5354494	0.278	0.17303	1.65698
WHO stage4	-1.2941	0.6027	0.2741401	0.032	0.08412	0.89337
Educational level						
No education	Ref.					
Primary	1.0224	0.3768	2.779878	0.007	1.32813	5.81849
Secondary and above	1.0649	0.3552	2.900569	0.003	1.44599	5.81833
Intercept	5.1358	1.0687	170.0018	0.000	20.9286	1380.91
Log likelihood = -209.47258, AIC=448.9452, ρ = 1.617352						

$\hat{\beta}_j$ = coefficient estimate, s.e= standard error, $\hat{\phi}_j$ = acceleration factor estimate, 95% CI=Confidence Interval for acceleration factor, LCL=lower class limit, UCL= upper class limit, Ref=Reference, ρ = shape parameter, AIC= Akaike Information Criterion.

different age groups (HIV infected patients in the age group less than 30 years and 50 years and above), patients who were illiterate and patients who attended secondary and above groups. The plots in Figure **7** below appear to be approximately linear for both covariates (age group and educational level) with slopes equivalent to the acceleration factors 0.1598542 and 2.900569, respectively. The q-q plot approximates a 45^0 straight line through the origin indicating that the AFT model is appropriate model.

DISCUSSION

Univariate and multivariable survival models were employed to examine the factors that determine time-to-death. Factors/variables considered in the study were age, weight, functional status, OIs, TB screen, CD4 count, WHO clinical stage, educational level, gender, marital status, and religion. In all four models age, weight, functional status, WHO clinical stage, CD4 count and educational level were significant. Hence, these covariates were used in model comparisons.

The comparison of the four parametric models was done by using AIC criterion and log likelihood, where a model with smallest AIC and largest log likelihood will be taken to be the most appropriate. Accordingly, log-logistic model which had AIC value of 448.9452 and log likelihood -209.4726 was the most appropriate model to describe the HIV infected patient's dataset.

Multivariable analysis using the log-logistic model showed that age, weight, functional status, TB screen, CD4 count, WHO clinical stage and educational level were prognostic factors/variables for the time-to-death.

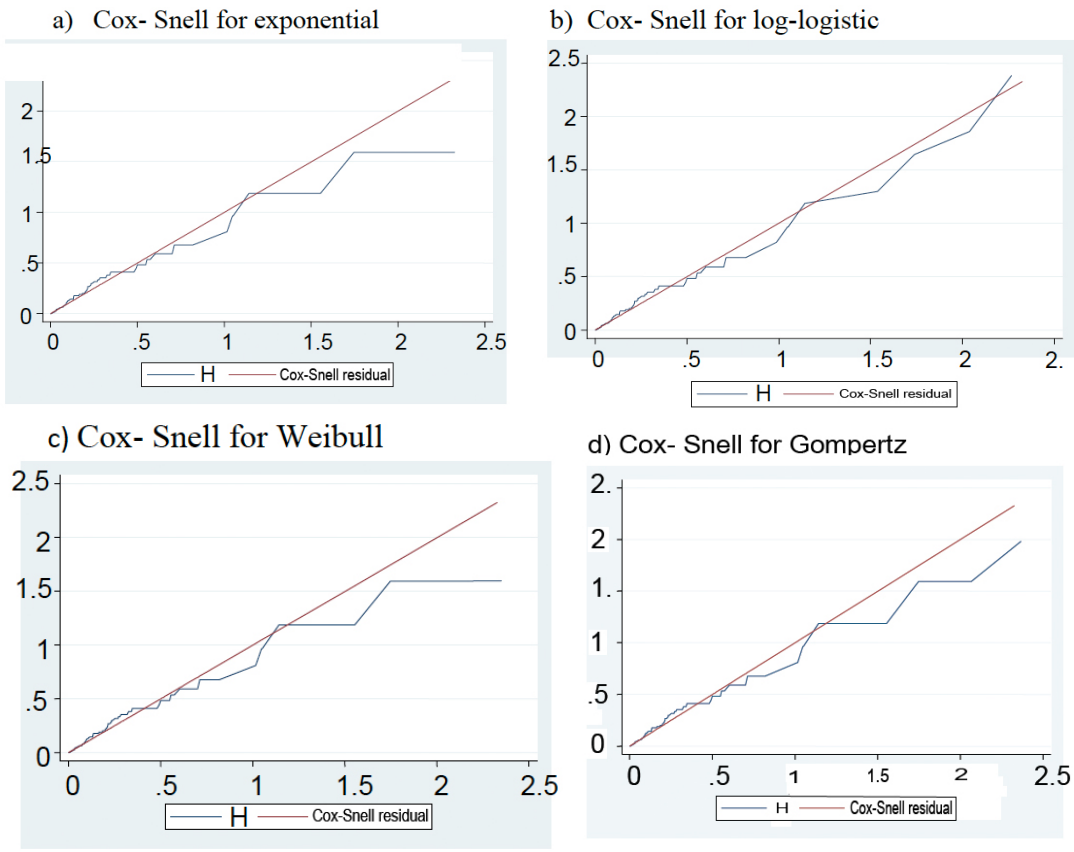

Figure 4: Cox-Snell residuals obtained by fitting exponential, Weibull, Gompertz and log-logistic models for HIV infected adult patients under HAART dataset in Zewditu Referral hospital, AA, 2010.

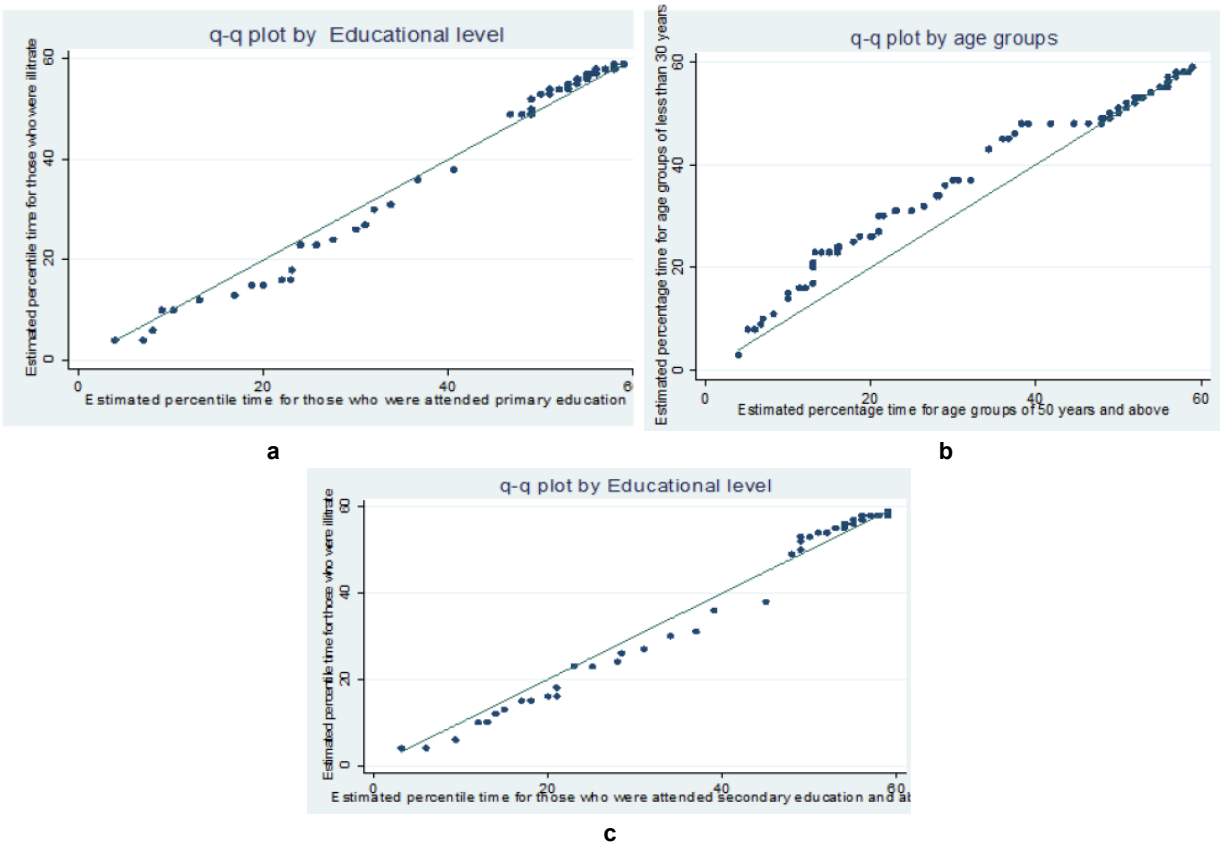

Figure 7: q-q plot to check the adequacy of the accelerated failure time model.

A study conducted by [7] suggested that both univariable and multivariable analyses showed that patients of younger age and higher baseline CD4 cell count were associated with a lower risk of progression to AIDS. Our finding showed that the age groups 40-49 and 50 years and above are associated with low chance of survival. HIV infected patients with higher baseline CD4 count had a better chance of survival. This finding agrees with studies by [4, 14, 15].

The findings of this study revealed that the TB screen had a significant effect on the time-to-death. It shortened time-to-death by a factor $\phi = 0.3245866$ compared to those with no TB screen the reference category. A study conducted by [6] concluded that HIV/TB co-infection was related to high mortality even when HAART and/or drug therapy for TB was provided. World Health Organization reported in 1999 that TB co-infection is the leading cause of mortality among those infected with HIV worldwide.

The result of this study suggested that WHO clinical stage, age and CD4 count were significant predictive factors of time-to-death i.e. HIV infected patients of older age, in WHO Clinical stage IV, and with low CD4 count had lower chance survive. This finding is in agreement with studies by [9].

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