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RESEARCH ARTICLE

DETERMINANTS OF IMMUNOLOGICAL RECOVERY OF HIV/AIDS PATIENTS UNDER ANTIRETROVIRAL TREATMENT

***Zelalem Getahun Dessie**

Department of Statistics, College of Science, Bahir Dar University, Bahir Dar, Ethiopia

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ABSTRACT

CD4 counts are one of the factors used to measure disease progression in HIV-positive individuals. CD4 counts vary in individuals and across populations due to a variety of demographic, environmental, immunological and genetic factors that probably persist throughout the course of HIV infection. The purpose of this study is to examine factors affecting immunological recovery of a patient under ART treatment. A sample of 710 patients has been taken from a hospital record at Bahir-Dar Felege-Hiwot Referral Hospital, Bahir Dar, Ethiopia from June 2006 to August 2013. Kaplan-Meier estimation method and Cox regression model were applied. From the Kaplan-Meier, female patients, baseline CD4 count>200cell/µl, TB negative, total lymphocyte count≥1200 cell/$mm^{3,}$ and baseline weight≥60kg has contributed to a shortened time to immunological recovery at 5% significant level. From Cox regression model result, male patient (adjusted HR=0.535), lower CD4 count of ≤200cell/µl (adjusted HR=0.59), lower lymphocyte count of <1200 cells/mm^3 (adjusted HR=0.59), patients who have severe anemia (adjusted HR=0.42) and lower baseline weight of <60kg (adjusted HR=0.964) were significantly associated to longer time to immunological recovery at 5% significant level. Negative tuberculosis Patients (adjusted HR=1.44) was significantly associated to shortened time to immunological recovery at 5% significant level. In conclusion, the findings of this study shows that sex, TB status, anemia status, baseline CD4 counts, baseline lymphocyte counts, and baseline weight are major factors related to immunological recovery of AIDS patient. I recommend that physicians need to be cautious about the baseline health status of a patient, as it may affect his/her time to immunological recovery.

1. INTRODUCTION

Acquired Immune Deficiency Syndrome (AIDS) which is caused by the Human Immunodeficiency Virus (HIV) has been the major problem worldwide. The rate of spread of the HIV/AIDS epidemic has reached a shocking level. The expansion of the epidemic has now become a burning issue globally and this is particularly so more important in developing countries. The disease being one without any cure is still accountable for economic, social and health crises in many developing countries. On a global scale, the HIV epidemic has stabilized, although with unacceptably high levels of new HIV infections and AIDS deaths. An estimated 34 million people worldwide were living with HIV in 2011 among which 23,500,000 million are living in sub-Saharan Africa (UNAIDS, 2013). Ethiopia is one of the countries hardest hit by HIV/AIDS epidemic. Because the country is the second most populous nation in sub-Saharan Africa with a population of over 79 million, it has a very large number of HIV/AIDS infected people. An estimated of 790,000 were living with HIV in 2011 (UNAIDS, 2013).

***Corresponding author:** Zelalem Getahun Dessie, Department of Statistics, College of Science, Bahir Dar University, Bahir Dar, Ethiopia.*

Almost 31 years have now elapsed since the virus was first reported (Barre-sonousssi *et al.*, 1983). During these years HIV infection has changed from a fatal condition to a manageable chronic illness mainly due to the development of antiretroviral therapy (ART). The goal this therapy is to improve survival; to reduce HIV associated morbidity and mortality, to increase the quality of life, to restore immune function and to achieve maximal and sustained suppression of viral replication (OARAC, 2008). Patients enrolling into ART programmes with very low CD4 cell counts have heightened risk of morbidity and mortality both before and during the initial months of ART (Stephen *et al*., 2006). Moreover, advanced pre-treatment immunodeficiency is also reported to be associated with diminished capacity for restoration of CD4 cell counts and CD4 cell functional responses during ART (Moore *et al*., 2005). This raises the concern that many patients entering ART programmes in sub-Saharan Africa particularly Ethiopia may have limited potential for immune recovery.

Although the current HIV/AIDS surveillance estimates indicate some encouraging signs in that the epidemic is stabilizing, the observed changes are not sufficient enough compared to the desired goals of the response against the epidemic. It is believed that, in resource poor countries like Ethiopia the

immunological recovery time of patients on ART depends on a variety of factors, which may also vary greatly with economic, demographic, behavioral risk and health factors. In other words, even if ARV treatment has shown significant clinical importance by meeting the goal of therapy, we are still facing a number of deaths that can otherwise be avoided by appropriate interventions on certain socio-economic, demographic, behavioral risk and health factors. Therefore, this study is motivated to investigate the major factors that affect survival time and time taken to an increase of 100 CD4 cells over the baseline after starting of ART of AIDS patients. The questions we want to address here is: Which factors have major effects on time to immunological recovery of a patient?

2. Sampling Procedure

The target populations for this study were patients under the follow up of ART at Felege-Hiwot Referal Hospital, Bahir Dar, Ethiopia from June 2006 to August 2013. The sampling frame consists of 9800 HIV/AIDS patients who have visited the hospital since the initiation of ART. The study may consider all HIV infected patients under ART whose age is $\geq$15 years regardless of their treatment category during the study period in Felege-Hiwot Referral Hospital, Bahir Dar, Ethiopia. However, the study excluded those patients on ART with age less than 15 years, whose diagnosis year was missing and those patients who do not have at least two follow-up CD4 measures. A systematic random sampling method is adopted for selecting a representative sample of the patients based on their ART unique identification number. The sample size used in the current study is estimated to be n = 710 with the population size N= 9800.

3. Data Analysis

The data was coded, entered and cleaned and then analyzed using SPSS version 20 and STATA 12 software. Kaplan-Meier survival curves were used to estimate median time to immunological recovery. Cox regression hazard models were used to determine major factors that affect time to immunological recovery. Scaled schoenfeld residual plots were used to cheek the validity of the Cox proportionality assumptions. Score test and partial likelihood ratio test were used to cheek goodness of fit for the Cox regression model. We fitted a Cox regression model that included all variables which were statistically significant at single covariate analysis.

3. RESULTS AND DISCUSSION

3.1 Descriptive Statistics

There were 710 patients in the cohort study out of which 462 (65.1%) attained immunological recovery and 248(34.9%) were censored. The proportion of female patients achieving immunological recovery accounted a larger proportion in the sample (about 60.4%) compared to male patients (39.6%). Similarly, the proportion of achieving immunological recovery for a patient whose age less than 40 accounted a larger proportion in the sample (about 82.3%) compared to patients whose age is greater than 40 (17.7%). Chi-square test shows that the status of immunological recovery of a patient is significantly associated with sex, baseline CD4 count, TB status, baseline WBC count, alcohol use and baseline weight (p-value < .005). The information presented above is summarized in Table 3.1.

Table 3.1. Summary Results of Immunological Recovery vs Socio-demographic and Health Variables

Variables	Number of Patients achieving immunological recovery (%)	Number of Censored (%)	Total (%)	Chi-Square P-value
Sex				
Female	279(60.4)	124(50.0)	403(56.8)	0.008*
Male	183(39.6)	124(50.0)	307(43.2)	
Age				
<40	380(82.3)	194(78.2)	574(80.8)	0.194
≥40	82(17.7)	54(21.8)	136(19.2)	
Baseline CD4 count				
≤200 cell/µl	237(51.0)	182(73.4)	419(59.0)	0.000*
>200 cell/µl	225(48.7)	66(26.6)	291(41.0)	
TB Status				
Negative	362(78.4)	163(65.4)	525(73.9)	0.000*
Positive	100(21.6)	85(34.3)	185(26.1)	
WHO Clinical Stage				
Stage I	161(34.8)	79(31.9)	239(33.7)	0.062
Stage II	101(21.9)	45(18.1)	146(20.2)	
Stage III	129(27.9)	66(26.6)	195(27.5)	
Stage IV	71(15.4)	58(23.4)	130(18.3)	
Baseline lymphocyte				
<1200 cells/mm^3	120(26.1)	134(54.3)	254(36.0)	0.000*
≥1200 cells/mm^3	339(73.9)	113(45.7)	452(64.0)	
Anemia status				
Normal	372(80.5)	127(51.2)	499(70.3)	0.000*
Sever/Moderate	90(19.5)	121(48.8)	211(29.7)	
Alcohol Use				
No	282(64.1)	124(52.1)	406(59.9)	0.002*
Yes	158(35.9)	114(47.9)	272(40.1)	
Base line Weight				
<60kg	362(78.4)	238(96.0)	600(84.5)	0.000*
≥60kg	100(21.6)	10(4.0)	110(15.5)	

(*) The association is a significant at α=0.05

3.2 Comparison of Immunological Recovery Time

In order to investigate if there is significant difference between immunological recovery times of a patient by gender, Kaplan-Meier survivor estimates for the two gender groups are plotted in Figure 1.1(a) in appendix . This Figure shows that females had shortened median recovery time compared with men. The log-rank test in Table 3.2 showed that there is significant difference between male and female with respect to immunological recovery time. Similarly, baseline CD4 count>200cell/µl, TB negative, total lymphocyte count≥1200 cell/$mm^{3,}$ and baseline weight≥60kg has contributed to a shorter time to immunological recovery. A low baseline CD4 count≤200cell/µl, TB positive, patient in WHO stage IV and anemia patient significantly contributed to longer time to immunological recovery at 5% significant level. The information presented above is summarized in Table 4.2 and Figure 3.1 in Appendix 1 below.

3.3 Bivariate and Multivariate Analysis

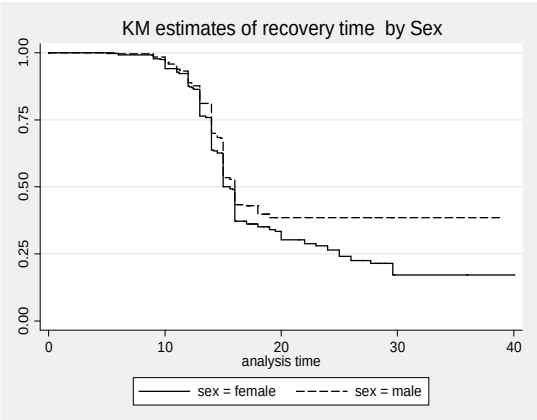
Bivariate Analysis

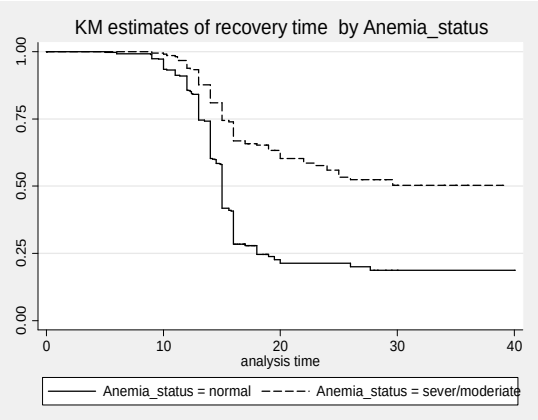
The relationship between each covariates and recovery time of AIDS patients is presented in Table 3.3. As can be seen from this Table, time to immunological recovery is significantly related with TB status, alcohol use, baseline CD4 count, anemia status, sex, baseline lymphocyte count, baseline weight and WHO clinical stage. The time to attain immunological recovery shortened among patients with baseline CD4 count>200cell/µl, TB negative, total lymphocyte count≥1200 cell/$mm^{3,}$ and those whose baseline weight≥60kg. A low baseline CD4 count≤200cell/µl, TB positive, patient in WHO stage IV and anemia patient significantly associated to longer time to immunological recovery at 5% of significant level.

Table 3.2. Comparison of immunological recovery for different socio-demographic and health variables

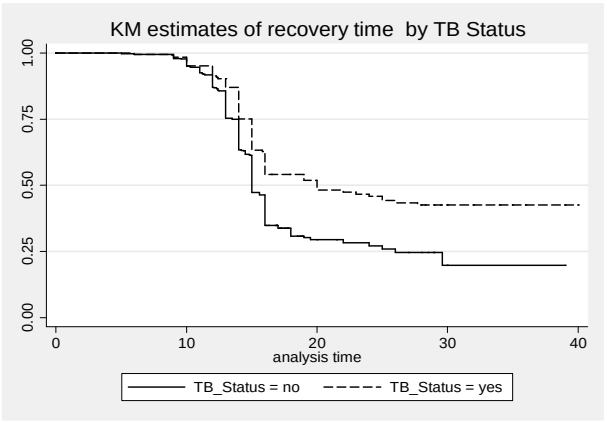
Variables	Median immunological recovery time	95% CI for Median Time	Log-Rank P-value
Sex			
Female	15.5	15.4-15.8	0.010*
Male	16.2	15.7-16.3	
Age			
<40	15.6	15.7-16.3	0.120
≥40	16.0	15.4-15.8	
Baseline CD4 count			
≤200 cell/µl	15.0	14.7-15.3	0.000*
>200 cell/µl	18.0	16.8-19.3	
TB Status			
Negative	15.0	14.8-15.2	0.000*
Positive	20.0	16.3-23.7	
WHO Clinical Stage			
Stage I	16.0	15.7-16.2	
Stage II	15.0	14.6-15.4	0.019*
Stage III	16.0	15.5-16.5	
Stage IV	20.0	14.5-25.5	
Baseline lymphocyte Counts			
<1200 cells/mm^3	25.0	16.3-25.7	0.000*
≥1200 cells/mm^3	15.0	14.9-15.0	
Anemia Status			
Normal	19.3	18.2-20.5	0.000*
Sever/mild/moderate	28.0	26.3-29.7	
Alcohol Use			
No	15.0	14.9-15.0	0.000*
Yes	16.0	14.5-17.5	
Base line Weight			
<60kg	13.0	12.4-13.6	0.000*
≥60kg	16.0	15.8-16.2	

(*) The deference is a significant at α=0.05

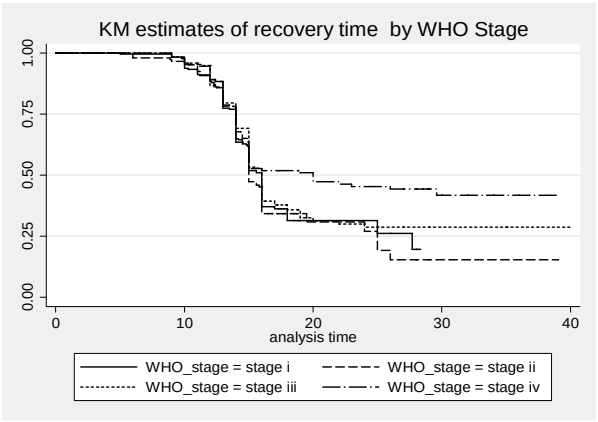




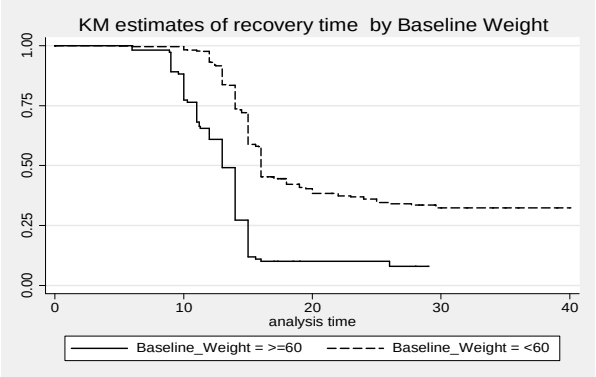
a) KM estimates of recovery time for the variable Sex **b) KM estimates of recovery time for variable of Anemia Status**



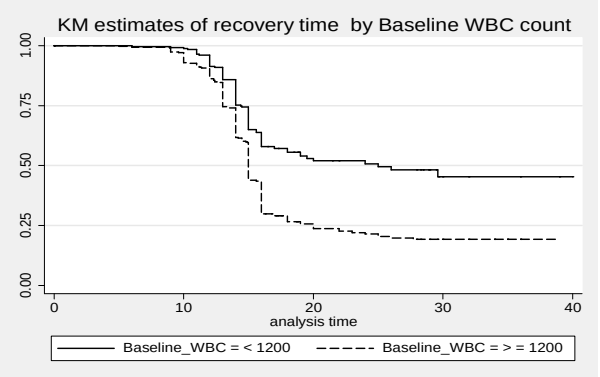
c) KM estimates of recovery time for variable of TB Status



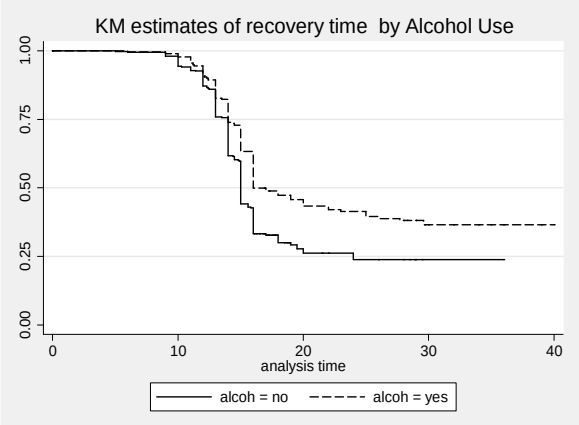
d) KM estimates of recovery time for variable of WHO Stage.



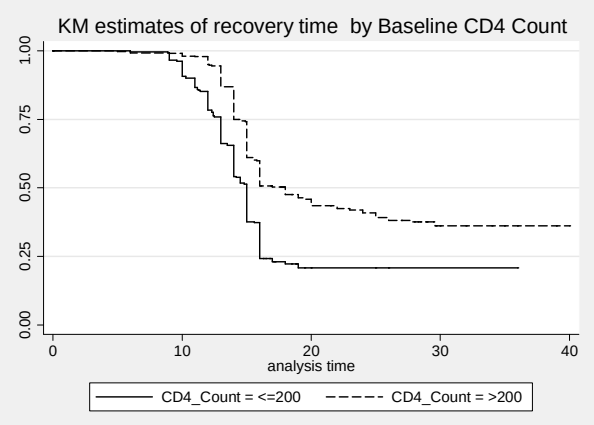
e) KM estimates of recovery time for variable of Baseline Weight



f) KM estimates of recovery time for variable of Baseline WBC Count



g) KM estimates of recovery time for variable of Baseline Alcohol Use



h) KM estimates of recovery time for variable of Baseline Baseline CD4 Count

Figure 3.1. Kaplan Meier time to Immunological Recovery estimates for categorical variables

Multivariate Analysis

One problem of single covariate approach is that it ignores the possibility that a collection of variables, each of which is weakly associated with the outcome, can become an important predictor of the outcome when taken together. It is for this reason, p-value of 0.25 was used for selection of variables that were candidates for the multi covariate analysis from single covariate findings. After adjusting other covariates, the hazard of attaining immunological recovery for female patients is about 23% higher than for male patients (adjusted HR=1.23, CI= 1.00-1.48).

A baseline CD4 count ≤200cell/µl was found to be associated with a longer median time to immunological recovery. The hazard of attaining immunological recovery 59% lower when comparing a patient with a baseline CD4 count ≥200cell/µl (adjusted HR=0.59, CI=0.48-0.71). Similarly, the hazard of attaining immunological recovery for TB negative patients was about 44% higher than TB positive patients (adjusted HR=1.44, CI=1.11-1.85). Anemia is the other covariate which has a significant impact on time to immunological recovery, the hazard of attaining immunological recovery for a patients who have severe anemia was about 42% lower than those patients who are normal(adjusted HR=0.42, CI=0.32-0.53). On the other hand, the hazard of attaining immunological recovery for a patient with a total lymphocyte count <1200 cells/mm3 is about 47 % lower than a patient with a total lymphocyte count of ≥ 1200 cells/mm^3 (adjusted HR=0.47, CI=0.38-0.59). Moreover, the hazard of attaining immunological recovery for a patient with baseline weight<60kg was about 30% lower than a patient with baseline weight≥60kg (adjusted HR=0.30, CI=0.24-0.38). The information presented above is summarized in Table 3.3.

Assessment of Model Adequacy

The plot of the scaled schoenfeld in Figure 3.2 in shows that the residuals are random without any systematic pattern and the smoothed plot looks straight line without any departure from the horizontal line. Thus, there is no violation of proportional hazards assumption. The results of the likelihood ratio test (chi-square=263.28, p< .000) and Score test (chi-square=279.19, p< .000) also suggests that model is in good fit, i.e. significant at 5% level of significance. Thus, all in all we can say that our model fits the data very well.

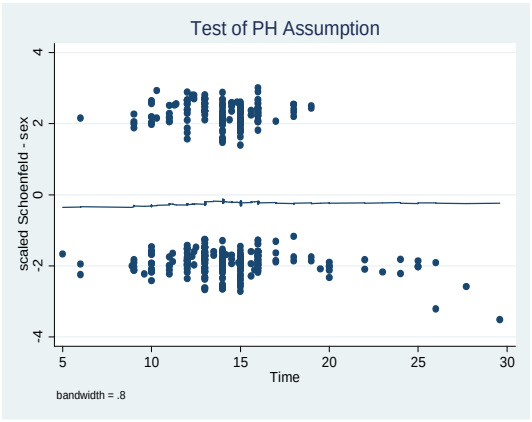
3.4 DISCUSSION

This study tries to estimate and compare the immunological recovery times with a given patients groups and to determine a major predictive factor on the immunological recovery times of AIDS patients. From the estimates, we found that time to immunological recovery is significantly related with TB status, alcohol intake, baseline CD4 count, anemia status, sex, baseline lymphocyte count, baseline weight and WHO clinical stage. From the Cox's proportional hazard model, we found that TB status, baseline CD4 counts, anemia status, sex, baseline lymphocyte counts and baseline weight jointly served as predictive factors on the time to immunological recovery of AIDS patients. A baseline total lymphocyte count ≥ 1200 cells/mm3 was found to be associated with a short median time to immunological recovery. The hazard of attaining immunological recovery for a patient with a total lymphocyte count <1200 cells/mm3 is about 47 % lower than a patient with a total lymphocyte count of ≥ 1200 cells/mm^3. Some studies have confirmed the significant association between a total lymphocyte count of < 1200 cells/mm3 and subsequent poor

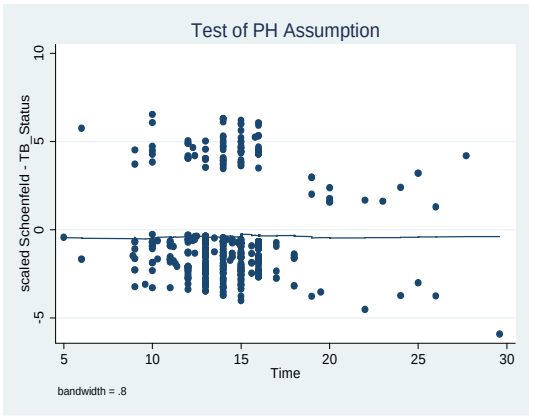
Table 3.3. Single Covariate and Multiple Covariates Analysis for different socio-economic health and demographic variables that affects time to immunological recovery

Variables	Crudes HR (95%CI for its HR)	Crude HR P-value	Adjusted HR (95%CI for its HR)	Adjusted HR P-value
Sex				
Female	1.26(1.04,1.51)	0.017*	1.23(1.00, 1.48)	0.047*
Male	1			
Baseline CD4 count				
≤200 cell/µl	0.50(0.41, 0.60)	0.000*	0.59(0.48, 0.71)	0.000*
>200 cell/µl	1			
TB Status				
Negative	1.69(1.35, 2.12)	0.000*	1.44(1.11, 1.85)	0.005*
Positive	1			
Baseline lymphocyte Counts				
<1200 cells/mm^3	0.49(0.40, 0.61)	0.000*	0.47(0.38, 0.59)	0.000*
≥1200 cells/mm^3	1			
Anemia status				
Sever/ Moderate	0.36(0.29, 0.47)	0.000*	0.42(0.32, 0.53)	0.000*
Normal	1			
Base line Weight				
<60kg	0.31(0.25, 0.39)	0.000*	0.30(0.24, 0.38)	0.000*
≥60kg	1		1	
WHO Clinical Stage				
Stage I	1.48(1.11, 1.96)	0.007*	0.84(0.61, 1.16)	0.297
Stage II	1.52(1.11, 2.06)	0.008*	0.79(0.56, 1.12)	0.189
Stage III	1.34(1.00, 1.80)	0.049*	1.06(0.77, 1.45)	0.726
Stage IV	1		1	
Alcohol intake				
No	1.54(1.26, 1.88)	0.000*	1.17(0.95, 1.44)	0.142
Yes	1		1	
Age				
≤40	0.87(0.68,1.10)	0.234	0.88(0.68, 1.13)	0.313
>40	1		1	

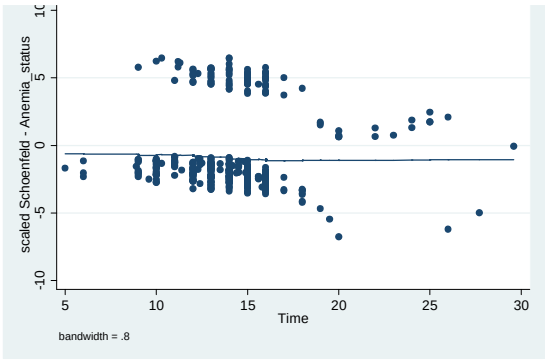
(*) HR is a significant at α=0.05



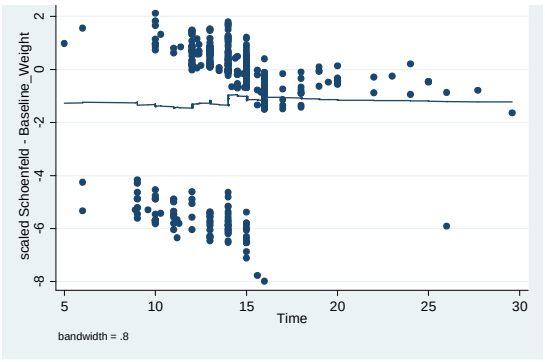
b) The plot of Scaled Schoenfeld residual for variable sex to check the validity of the PH Assumption



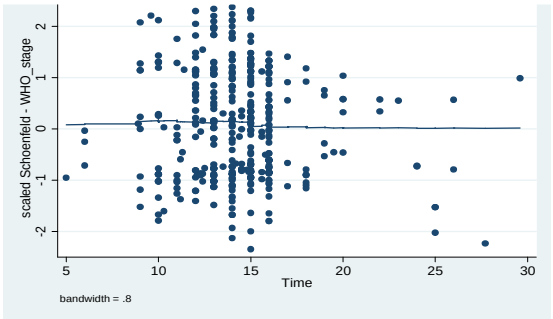
a) The plot of Scaled Schoenfeld residual for variable TB Status to check the validity of the PH Assumption



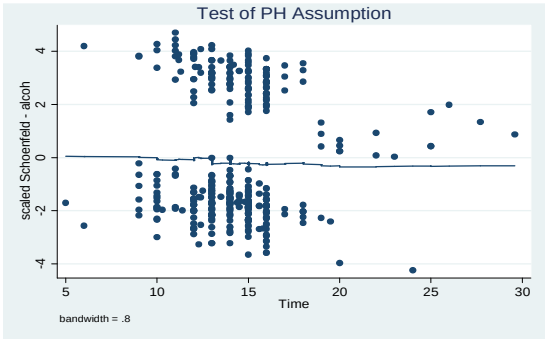
c) The plot of Scaled Schoenfeld residual for variable Anemia Status to check the validity of the PH Assumption



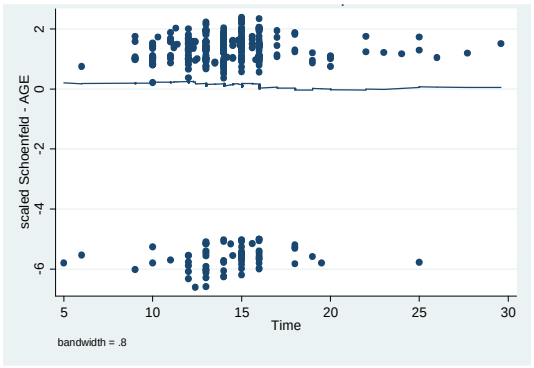
f) The plot of Scaled Schoenfeld residual for variable Baseline weight to check the validity of the PH Assumption



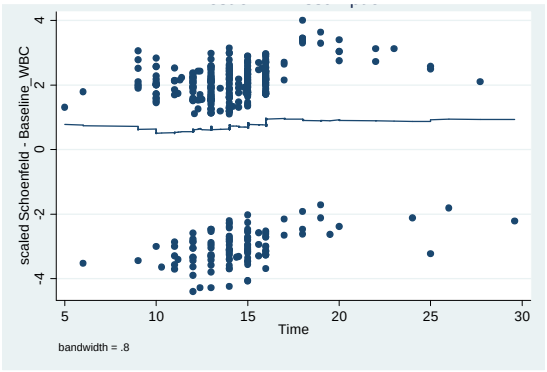
d) The plot of Scaled Schoenfeld residual for variable WHO Stage to check the validity of the PH Assumption



g) The plot of Scaled Schoenfeld residual for variable Alcohol Use to check the validity of the PH Assumption



e) The plot of Scaled Schoenfeld residual for variable Age to check the validity of the PH Assumption



h) The plot of Scaled Schoenfeld residual for variable Baseline WBC to check the validity of the PH Assumption

Figure 3.2. Plots of scaled schoenfield residuals against transformed time for each covariate in Cox Proportional Hazards Model fit AIDS patients

immunological recovery, disease progression or mortality (Lau *et al*., 2005; Brian *et al*., 2009). In this study, sex was an important predictor of time to immunological recovery of patients. The hazard of attaining immunological recovery for female patients is about 77% higher than for male patients. This result confirms the earlier findings reported by Patterson *et al*. (2007), Lorna et *al*. (2011), Kumarasamy *et al*. (2008), Moges *et al.* (2013) and Puthanakit *et al.* (2012). In contrast, two studies from Uganda and Ghana sex has no effect on median time to immunological recovery (Brian *et al*., 2009; Lorna *et al*., 2011). Similarly, tuberculosis has been the stronger predictor of time to immunological recovery of AIDS patient. The hazard of attaining immunological recovery for TB negative patients was about 56% higher than TB positive patients. This result is compatible with Desta (2011) in Ethiopia study, Stephen *et al*. (2007) in South Africa study and Dias *et al*. (2007) in Portugal study. In contrast, one study from South Africa TB status has no effect on time to immunological recovery of patients (Julg *et al*., 2011).

Anemia has also been the most serious HIV related disease complication which increases the risk of death. The hazard of attaining immunological recovery for patients who have severe anemia was about 42% lower than those patients who are normal. This result is in accordance with the study from England (Moyle, 2002) and from USA (Patrick, 2002) showing anemia is the most predictive of immunological recovery of AIDS patient. Other determinants that favored a good immunological recovery process after ART initiation was a baseline CD4 count (> 200 cell/µl). The hazard of attaining immunological recovery for a patient with a baseline CD4 count <200 cell/µl is about 59% lower than a patient with a baseline CD4 count of ≥ 200 cell/µl. the current study is consistent with other studies where immunological recovery is largely dependent on baseline CD4 count and thus the timing of ART initiation is important in order to maximize the CD4+ T-cell response to therapy (Barin *et al*., 2009; Egger *et al*., 2009; Lawn *et al*., 2006; Moges *et al*., 2013; Antonella *et al*., 2010).

Baseline weights determine one's resistance to different opportunistic diseases. Thus, the larger their number/value, the lower the danger of being at risk of HIV death. The outcomes of this study support this fact as the hazard of attaining immunological recovery are high for those with higher baseline weight. This result is in accordance with the study from USA (Mair *et al*., 2007). In this study, old age was not associated with median time to immunological recovery. This result is compatible Barin *et al*. (2009) from Ugandan. On the contrary, one study from South Africa age was an important predictor of time to immunological recovery of patients (Stephen *et al*., 2006).

4. Conclusion and Recommendation

In conclusion, the major factors that affects the immunological recovery times of HIV/AIDS patients were sex, TB status, anemia status, baseline CD4 counts, baseline lymphocyte counts, and baseline Weight. Female patients had shortened time to immunological recovery as compared to men patients. Similarly, patients with poor health indicators like TB and anemia positive case, small baseline CD4 counts and small baseline lymphocyte counts were less likely to attain shorter immunological recovery. Patients, whose baseline weight greater than 60kg, had shortened time to immunological recovery. The demand of ART service in Ethiopia is given due attention by government and non-government organizations. As a consequence, ART clinics are now widespread in all the corners of the country. Patients are being treated in the ART clinics to extend their lives. But in parallel with this, due to many reasons, patients are still dying under ART follow up. Since the results of the study underlined risk factor (alcohol use) as important predictors of immunological recovery times of the patient, physicians are expected to work hard to bring about behavioral changes. According to the results of this study, the main predictive factors for time to immunological recovery of AIDS patients are more of clinical variables. So, health workers should be cautious when a patient has lower CD4 counts, lower weight, lower lymphocyte counts, and is TB or anemia positive.

5. Ethical considerations

The Ethical Committee of the Bahir Dar University approved the protocol for this study. Letter of approval were given to the HIV/AIDS clinics and agreement were signed with researcher and college research office.

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