Statistical Analysis of Correlates of Adverse Drug Reactions among HIV Infected Children under ART: A Case Study at Hawassa University Referral Hospital, Hawassa, Ethiopia

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Abstract

The introduction of antiretroviral therapy (ART) has changed the landscape of HIV-related morbidity and mortality. However, adverse drug reactions (ADRs) associated with ART are a serious concern. The objective of this study was to identify and analyze correlates of the ADR of peripheral neuropathy (PN) among children under ART and to assess the relationship between clinical parameters and complete blood group count, renal function and liver enzyme tests. The data used for the study is secondary data which is taken from the follow-up charts of children taking ART at Hawassa University Referral Hospital (HURH) from 2007 to 2011. Multiple logistic regression and multivariate multiple linear regression have been used to address the objectives of the study. The results revealed that the likelihood of developing PN was higher for child patients whose age group was less than five years; whose CD4 count at the start of ART was less than 100 cells/ml and 100-250 cells/ml; and whose haemoglobin level was less than 7 mg/dl. Moreover, children under ART follow-up who used Stavudine (D4T) drug combination were found to be at a higher risk of PN as compared to those patients who used Zidovudine (AZT) - Efavirenz (EFV) drug combination. Multivariate multiple regression analysis revealed that creatinine (the most commonly used indicator of renal function/risk of chronic kidney disease) was significantly associated with baseline CD4 count (negatively) and baseline CD8 count (positively) of patients under ART. Thus, there should be selective targeting for children under ART who are under-five, who used Stavudine (D4T) ART regimen, with low baseline CD4 counts and lower amount of haemoglobin.

Keywords: *antiretroviral therapy, adverse drug reactions, peripheral neuropathy, logistic regression, multivariate multiple regression*

1. Introduction

1.1 Background

HIV/AIDS is an epidemic that affects every part of the globe. Globally there were an estimated 37.9 million people living with HIV (PLHIV), 1.7 million new infections and 770,000 AIDS-related deaths in 2018. New HIV infections declined in five of eight regions and AIDS deaths were declining in six of eight regions between 2010 and 2018. Over 54% of PLHIV reside in Eastern and Southern Africa and a further 15% reside in Asia and the Pacific (WHO, 2018).

Globally the number of children aged 14 years old and under living with HIV peaked in 2005 at approximately 2.1 million. This has since declined to 1.8 million in 2017 and further to 1.7 million in 2018. Globally (with similar trends at national levels), the number of new infections in children peaked around the early 2000s (globally at 420,000 new infections per year) followed by a rapid decline over the last decade. In 2017 an estimated 180,000 new children were infected with HIV. Almost two-thirds (63%) of children living with HIV are in sub-Saharan Africa. This number of children living with HIV is declining over time as fewer children are becoming infected due to successful prevention of mother-to-child transmission programmes. In children with HIV, transmission has typically occurred from the mother (mother-to-child-transmission) either during pregnancy or childbirth, or through breastfeeding (WHO, 2018).

A couple of decades ago, the chances of surviving more than ten years with HIV were slim. Today, thanks to antiretroviral therapy (ART), people with HIV/AIDS can expect to live long lives. ART is a mixture of antiviral drugs that are used to treat people infected with HIV. ART is an essential player in making progress against HIV/AIDS because it saves lives, allows people with HIV to live longer, and prevents new HIV infections (Roser and Ritchie, 2018).

Since the first version of ART was introduced in the late 1980s, the treatment has saved millions of lives. The number of PLHIV on ART increased from two million in 2005 to more than 23.3 million in 2018; an increase in ART coverage from less than 7% in 2005 to close to 62% in 2018. By the end of 2018, it was estimated that 79% of PLHIV globally knew their HIV status; among those who knew their HIV status, 78% were accessing ART; and, 86% of people accessing ART had suppressed viral loads (UNAIDS, 2018). There is considerable evidence to show that people who use ART are less likely to transmit HIV to another person. ART reduces the number of viral particles present in an HIV-positive individual and therefore, the likelihood of passing the virus to another person decreases (Williams et al., 2011).

The first evidence of HIV epidemic in Ethiopia was detected in 1984. Since then, AIDS has claimed the lives of millions and has left behind hundreds of thousands of orphans. The government of Ethiopia took several steps in preventing further disease spread by increasing accessibility to HIV care, treatment and support for PLHIV. Consequently, the annual number of HIV infected people showed declining trends since 2002. Over the past two decades HIV prevalence rate decreased from 3.3% in 2000 to 0.9% in 2017, and AIDS-related deaths from 83,000 deaths in 2000 to 15,600 in 2017. The 2016 EDHS showed that the HIV prevalence varies from region to region ranging from 0.1% in Somali to 4.8% in Gambella. According to HIV Related Estimates and Projections for Ethiopia by EPHI in 2018, the estimated number of PLHIV is 610,335, of which 56,515 are children and 379,251 are female. The number of people who are in need of ART is the same since 'Treat all' is adopted by Ethiopia since 2016 (FMOH, 2018). There have been successes in increasing ART coverage in all populations and locations. On the basis of the 2010-2014 strategic plan, ART coverage for adults (age 15+) has reached 76% but the coverage remains low (23.5%) for children (age<15) living with HIV (UNAIDS, 2018; CSA and ICF, 2018; FMOH, 2018; FMOH, 2017).

As stated above, the introduction of antiretroviral therapy (ART) was one of the most significant interventions that changed the landscape of HIV-related morbidity and mortality. ART substantially modified the natural history of HIV infection and changed it from an end of life event to a manageable chronic condition. Despite its benefits, however, ART is not without challenges. Adverse drug reactions (ADRs) associated with the use of antiretrovirals (ARVs) can rapidly reverse the gains of ART resulting in worse health outcomes and increased mortality. Acute toxicities may lead to dose interruption and discontinuation of therapy. Some studies have reported treatment discontinuation rates ranging from 4% to 46% related to neuropsychiatric adverse effects of ART. Treatment discontinuation and other forms of medication non-adherence associated with ADRs are significant risk factors for virologic failure. Failure of first-line ART regimens resulting from ADRs creates the need for more expensive and difficult-to-implement second-line regimens often unaffordable in most resource-constrained countries, which are largely donor dependent for their ART programs (Murphy et al., 2007; Khan et al., 2015; Prosperi et al., 2012).

Peripheral neuropathy (PN) is a common annoyance among human immunodeficiency virus (HIV)–infected patients receiving antiretroviral therapy (ART) in resource-limited settings (van Oosterhout et al., 2005). In sub-Saharan Africa it is the most common side effect leading to a change in regimen among patients receiving stavudine (D4T). Although D4T exposure is a known risk factor for PN among HIV-infected individuals receiving ART, other known risk factors may also contribute, including nutritional

deficiencies; toxic effects of anti–tuberculosis (TB) medications; alcoholism; diabetes; and HIV infection itself (Ferrari et al., 2006).

Mehta et al. (2011) assessed the potential risk factors on the incidence of PN at Bomu Medical Centre in Kenya. In univariate analysis, women were 9.6 times more likely to develop PN than men (P = .03). Stratifying hemoglobin levels decreased the hazard ratio from 9.6 to 7.40 (P = .05), with higher levels corresponding to a lower risk of PN. The study found no significant associations between incidence of PN and age, baseline CD4 count, weight, height, BMI, and WHO clinical stage. The study also did not find the expected association between development of PN and initiation of ART with a D4T-based regimen.

In contrast, a number of studies reported that low CD4 cell count, high viral load, ART regime containing NRTI plus PI and exposure to isoniazid (a potent bactericidal antibiotic used in the treatment of tuberculosis) over an extended period (e.g., more than six months) were independent predictors for PN (e.g., Peters et al., 2014). Evans et al. (2011) investigated the potential risk factors associated with PN based on data from the ACTG Longitudinal Linked Randomized Trials (ALLRT) in the U.S. using multiple logistic regression and logistic generalized estimating equation (GEE). The study revealed that the following variables were associated with higher odds of PN: older patient age, current CD4 200 or less compared to CD4 at least 501, taller height, black race compared to white race, and other race compared to white race.

The other potential risk factor for PN is the type of drugs used (ART regimen). Riddler et al. (1995) reported that the dose-limiting toxicity of Stavudine (D4T) is PN, which occurred in 15% of stavudine versus 6% of zidovudine-treated patients for 80 weeks in a randomized, blinded, phase III trial. Browne et al. (1993) also found that PN has occurred in 55% of patients treated with D4T.

Like many countries in the world, ADR is one of the major problems associated with the treatment of HIV patients in Ethiopia. Even though treating HIV patients with the use of ARVs is in progress since the late 1990's, a limited research work has been done in relation to ADR of the therapy. Thus, the general objective of this study was to identify and analyze correlates of commonly encountered ARV related adverse drug reaction, namely PN, among children under ART follow-up as well as to assess the relationship between clinical parameters and complete blood group count, renal function and liver enzyme tests.

1.2 Definition of technical terms

Peripheral neuropathy (PN) refers to the many conditions that involve damage to the peripheral nervous system. Its signals are documented persistent pain, numbness, tingling or burning sensation usually in the body's extremities (such as hands, feet and arms). Many medicines and substances may lead to development of neuropathy. These include drugs used to fight HIV/AIDS (antiretroviral medication) such as Didanosine, Emtricitabine, Stavudine (D4T), Zidovudine (AZT) and Emtricitabine-tenofovir.

A **complete blood count** is a test that counts the cells that make up the blood: red blood cells, white blood cells, and platelets.

Hematocrit (HCT) is the percentage by volume of red blood cells in the blood.

Creatinine is a chemical waste product in the blood that passes through the kidneys to be filtered and eliminated in urine, and is the most commonly used indicator of renal function. Some antiretrovirals may increase the risk of chronic kidney disease due to their nephrotoxicity. An increased level of creatinine may be a sign of poor kidney function.

Aspartate aminotransferase (AST) is an enzyme found in the liver, heart, skeletal muscle, kidneys, brain and red blood cells, and is commonly measured clinically as a maker for liver health. It is raised (elevated) in acute liver damage.

This paper is organized as follows: Section one discusses the background and rationale of the study. The second section deals with description of the research methodology employed including description of the study area, sampling techniques and methods of data analysis/model specification. The results of the study are presented and discussed in Section three. The last section presents conclusions and recommendations.

2. Materials and Methods

2.1 Description of study area and sample

The study was carried out in Hawassa city which is the capital of SNNP Regional State. The city is located 270 km South of Addis Ababa with an altitude of 1708m above sea level. According to the population projection of Central Statistics Agency (CSA), Hawassa city administration had an estimated population of 351,567 in 2017 from which 170,510 were females and 181,057 were males.

The data used for the study is secondary data which is taken from the follow-up charts of children taking ART at Hawassa University Referral Hospital (HURH) from 2007 to 2011. The study considered all HIV infected patients under ART whose age is less than 15 years regardless of their treatment category during the study period. The study excluded those patients on ART whose age is greater than 15 years, who are transferred to other health institutions or lost to follow up, and those with incomplete records. After excluding those children who didn't meet these inclusion criteria, data on a total of 250 HIV infected children under ART were utilized in the final analysis.

2.2 Methods of data analysis

Both multiple logistic regression and multivariate multiple linear regression have been used to identify and analyze correlates of commonly encountered ADRs among children under ART follow-up.

2.3 Variables considered in the study

One of the adverse effects of antiretroviral medication is PN. Thus, the dependent variables in the logistic regression analysis was the existence of PN (1 = exists, 0 = does not exist). The independent variables that are assumed to be associated with adverse drug reactions of HIV-infected children under ART are gender, age, baseline WHO clinical stage, drug regimen during the start of ART, baseline CD4 count, weight, ever taken treatment of TB and amount of haemoglobin.

In the multivariate regression analysis, a vector consisting of baseline CD4 count and baseline CD8 count of patients was used as a vector of dependent variables. The independent variables that are assumed to be associated with these clinical parameters are complete blood count (red blood cells, white blood cells and platelets), Hematocrit, Creatinine and Aspartate aminotransferase (AST).

2.4 Multiple logistic regression model

Logistic regression is the model of choice when the dependent variable is categorical (or nominal). Binary logistic regression is the statistical technique used to predict the relationship between predictor variables and the response variable when the dependent variable is dichotomous (often coded as 1 and 0). The independent variables may be continuous, categorical or a mix of these two. The two main uses of logistic regression are predicting group membership (since logistic regression calculates the probability of success over the probability of failure), and providing knowledge of the relationships and strengths among response and explanatory variables.

The standard binary logistic regression model is defined as (Agresti, 2002):

$$\eta_i = \ln\left(\frac{\pi_i}{1-\pi_i}\right) = X_i'\beta \ , \quad i = 1, 2, \ldots, n \quad \ldots\ldots\ldots\ldots\ldots\ldots (1)$$

where $\pi_i = E(y_i \mid X_i) = Pr(y_i = 1 \mid X_i)$ is the response probability or the probability of i^{th} child under ART follow-up having ADR given his/her individual characteristics, $X_i = (x_{1i}, x_{2i}, \ldots, x_{pi})'$ is the (p×1) covariate vector and $\beta = (\beta_1, \beta_2, \ldots, \beta_p)'$ is the (p×1) vector of unknown regression coefficients that measure the impact of changes in the predictor variables on the probability of ADR. Often β_1 is the intercept term.

The response probability and the covariate vector are related through $\pi_i = F(\eta_i)$, where $F(\cdot)$ is the logit link function defined as (Agresti, 2002):

$$F(\eta_i) = \frac{\exp(\eta_i)}{1+\exp(\eta_i)} = \frac{\exp(X_i'\beta)}{1+\exp(X_i'\beta)} \quad \ldots\ldots\ldots\ldots\ldots\ldots (2)$$

The estimation of parameters in binary choice models is usually based on the method of maximum likelihood. Unlike linear models, the likelihood function is nonlinear and the solution ($\hat{\beta}$) is obtained through an iterative process. The coefficient of a continuous covariate is interpreted as the change in the log-odds of having ADR per unit increment in the corresponding covariate. In case of categorical predictor variable, it is interpreted as the log-odds of having ADR among HIV/AIDS patients in a given category compared to the reference category.

It is crucial to test the goodness of fit of a model before proceeding to make statistical inferences. The Pearson's Chi-square test, the likelihood ratio test, Hosmer and Lemeshow goodness-of-fit test and the Wald test are the most commonly used measures of goodness of fit for categorical data (Hosmer and Lemeshow, 1989).

2.5 Multivariate multiple linear regression model

The multivariate extension of multiple linear regression is used to modeling the relationship between **m** responses $Y_1, Y_2, \ldots, Y_m$ and a single set of **r** predictor variables $Z_1, Z_2, \ldots, Z_r$. Each of the **m** responses is assumed to follow its own regression model so that:

$$Y_i = \beta_{0i} + \beta_{1i}Z_1 + \beta_{2i}Z_2, \ldots, \beta_{ri}Z_r + \varepsilon_i \ , \quad i = 1, 2, \ldots, m \quad \ldots\ldots\ldots\ldots (3)$$

The error term $\varepsilon = (\varepsilon_1, \varepsilon_2, \ldots, \varepsilon_m)'$ is such that $E(\varepsilon) = 0$ and $var(\varepsilon) = \Sigma$. Thus, the error terms associated with different responses may be correlated.

Let $Z_{nx(r+1)}$ be the design matrix. Define $Y_{(i)} = (y_{1i}, y_{2i}, \ldots, y_{ni})'$, $\beta_{(i)} = (\beta_{0i}, \beta_{1i}, \ldots, \beta_{ri})'$ and $\varepsilon_{(i)} = (\varepsilon_{1i}, \varepsilon_{2i}, \ldots, \varepsilon_{ni})'$, $i = 1, 2, \ldots, m$. The multiple linear regression model for the i^{th} response is given by:

$$Y_{(i)} = Z\beta_{(i)} + \varepsilon_{(i)}, \quad i = 1, 2, \ldots, m \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (4)$$

with $E[\varepsilon_{(i)}] = 0$ and $cov[\varepsilon_{(i)}, \varepsilon_{(k)}] = \sigma_{ik} I_n$, $i, k = 1, 2, \ldots, m$. The **m** observed responses on the same subject (trial) may have a non-zero covariance matrix, but observations from different subjects are uncorrelated (Johnson, 2007)

The ordinary least-squares (OLS) estimator of $\beta = [\beta_{(1)} | \beta_{(2)} | --- | \beta_{(m)}]$ is obtained in analogous fashion to the univariate case. We begin by taking a single response solution as:

$$\hat{\beta}_{(i)} = (Z'Z)^{-1} Z'Y_{(i)}, \quad i = 1, 2, \ldots, m \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (5)$$

Collecting the univariate least-squares estimators, we obtain:

$$\hat{\beta} = (Z'Z)^{-1} Z'[Y_{(1)} | Y_{(2)} | --- | Y_{(m)}] = (Z'Z)^{-1} Z'Y \quad \ldots\ldots\ldots\ldots (6)$$

Let $vec(\hat{\beta})$ denote the $(nm \times 1)$ vector that stacks the columns of $\hat{\beta}$. Then the variance-covariance matrix of $vec(\hat{\beta})$ is given by:

$$\Psi = \Sigma \otimes (Z'Z)^{-1} \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (7)$$

Since Σ is unknown, we replace it by the unbiased estimator of the variance-covariance matrix of the errors:

$$\hat{\Sigma} = \frac{\hat{\varepsilon}'\hat{\varepsilon}}{n - r - 1} \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (8)$$

where $\hat{\varepsilon} = [I - Z(Z'Z)^{-1} Z']Y$.

Note that, even though we can get the OLS estimators by running separate models for each of the response variables, there is a possibility of non-zero between-equation covariances. Consequently, if separate tests of significance are performed for each response variable models, the probability of obtaining a false significant test statistic would increase in direct proportion to the number of response

variables being tested. Thus, the variance-covariance matrix of the model coefficients (as in equation (7)) needs to be taken into account when testing the null hypothesis that all regression coefficients are equal to zero across all response models (Johnson, 2007).

It is essential to examine the adequacy of the model before the estimated function becomes a permanent part of the decision making apparatus. All the sample information on lack of fit is contained in the residuals. Normality of residuals may indicate more generally that the model is a good representation of the data. Therefore, testing this distributional assumption is desirable. Jarque & Bera (1987) established a test of normality of residuals.

3. Results and Discussion

As stated earlier, the data for this study was obtained from 250 children taking ART at Hawassa University Referral Hospital (HURH). Our objective is to identify and analyze correlates of commonly encountered ADRs among children under ART follow-up using binary logistic regression and multivariate multiple linear regression.

3.1 Results and discussion of logistic regression analysis

Here the dependent variable is whether children under ART follow-up developed adverse drug reaction (peripheral neuropathy) or not. We need to assess the goodness-of-fit and adequacy of the fitted model before moving to statistical inference. Hosmer and Lemeshow Pearson Chi-square test was used to test the null hypothesis that the model adequately fits the data. The Hosmer-Lemeshow test statistic was found to be statistically insignificant, suggesting that the model fitted the data well. The likelihood ratio test (G^2) is commonly used for assessing the overall fit of the logistic regression model. The result indicated that the likelihood ratio test statistic (G^2=54.652) is significant at the 1% level. Thus, we reject the null hypothesis and conclude that at least one of the predictors was significantly related with adverse drug reactions among HIV patients under ART.

After an assessment of the overall model goodness-of-fit, statistical tests of individual predictors were conducted to identify the risk factors for the ADR of PN among HIV-infected children under ART. The statistical significance of individual regression coefficients was tested using the Wald Chi-square statistic and significantly associated predictors were selected using stepwise regression (Likelihood ratio) method. The results are displayed in Table 1.

The results revealed that age, baseline CD4 count, ART-regimen, amount of haemoglobin and ever taken treatment of TB were significantly associated with PN among HIV patients under ART. On the other hand, baseline weight, baseline WHO clinical stage and sex of children were not significantly associated with PN. The study by Mehta et al. (2011) also found no significant association between incidence of PN and weight, height, BMI, and WHO clinical stage. Unlike our finding regarding sex, however, the study reported that women were more likely to develop PN than men.

Children's age was significantly associated with the ADR of PN. The likelihood of developing PN is about 4.5 times higher for child patients whose age group is less than five years as compared to those children with age over seven years (and less than 15), controlling for the influence of other factors. The findings in the literature are mixed. While Mehta et al. (2011) found no significant associations between incidences of PN and age; Evans et al. (2011) reported that older age is associated with higher odds of PN. However, our result may not be comparable since these studies involve adult HIV patients under ART follow-up.

The ADR of PN was significantly associated with the baseline CD4 count of children under ART. The odds of having PN are about 4.6 and 5.4 times higher for those children whose CD4 count at the start of ART was less than 100 cells/ml and 100-250 cells/ml as compared to those with baseline CD4 count of greater than 250 cells/ml, respectively. This is a reflection that advanced disease is a risk for PN. This result is inconsistent with that of Mehta et al. (2011) who found no significant association between incidence of PN and baseline CD4 count.

Moreover, children who did not take treatment of TB are 2.6 times more likely to develop PN as compared to those who took treatment of TB, controlling for the influence of other factors. According to Blain et al. (1998), in addition to the medications used to treat TB, there are a number of other factors that can lead to damage of the peripheral nerves and the development of neuropathy, including TB in and of itself and other co-morbid conditions (the most common of which is HIV).

The other significant covariate was the type of drugs used (ART regimen). Child patients who used Stavudine (didehydro-deoxythymidine or D4T) drug combination (ART regimen 4a) are 4.7 times more likely to be exposed to adverse drug reaction as compared to those patients who used Zidovudine (AZT) - Efavirenz (EFV) drug combination (ART regimen 4d). This result is consistent with the findings of Riddler et al. (1995) and Browne et al. (1993). The study by Mehta et al. (2011), however, did not find a significant association between development of PN and a D4T-based regimen. Furthermore, the

likelihood of developing PN is about 2.7 times higher for children under ART whose haemoglobin level is less than 7 mg/dl as compared to those children with haemoglobin levels over 10 mg/dl. A study by Mehta et al. (2011) also revealed that higher levels of haemoglobin correspond to a lower risk of PN.

Table 1: Logistic regression results of the ADR of peripheral neuropathy among children under ART

Covariate	B	S.E.	Wald	Df	Sig.	Exp(B)
Age			6.230	2	0. 044*	
Below five years	1.513	0.756	4.011	1	0.045*	4.542
5-7 years	1.117	0.573	3.799	1	0.051	3.054
Over 7 years [ref]						
CD4 count			13.505	2	0.001**	
Below 100 cells/ml	1.534	0.570	7.248	1	0.007**	4.636
100-250 cells/ml	1.686	0.466	13.065	1	0.000**	5.398
Over 250 cells/ml [ref]						
Weight			0.738	3	0.864	
Below 10 kgs	18.836	1.969E4	0.000	1	0.999	1.515E8
10-20 kgs	0.460	0.673	0.466	1	0.495	1.583
20-30 kgs	0.333	0.420	0.628	1	0.428	1.395
Over 30 kgs [ref]						
ART regimen			14.480	3	0.002**	
4a	1.552	0.673	5.326	1	0.021*	4.722
4b	-0.553	0.581	0.905	1	0.341	0.575
4c	0.150	0.611	0.060	1	0.806	1.162
4d [ref]						
Treatment of TB						
No	0.966	0.394	6.018	1	0.014*	2.628
Yes [ref]						
Haemoglobin level			6.446	2	0.040*	
Below 7 mg/dl	0.996	0.484	4.239	1	0.040*	2.708
7-10 mg/dl	-0.267	0.408	0.427	1	0.513	0.766
Over 10 mg/dl [ref]						
Constant	-1.437	0.749	3.685	1	0.055	0.238

***Significant at 1%, *significant at 5%, ref-reference category*

3.2 Results and discussion of multivariate multiple regression analysis

The multivariate multiple regression analysis of was performed using two response variables, namely, CD4 count and CD8 count, and a single set of six predictor variables: red blood cells (RBC), white blood cells (WBC), platelet, hematocrit (HCT), creatinine and asprartate aminotransferase (AST). The results are presented in Table 2.

First, the adequacy of the fitted model was assessed using several methods. Some observations were found to be outliers with high values of leverages and DFBETA's. These observations were deleted from the data set and subsequent analysis performed has shown a significant improvement in model fit statistics. The plots of the observed values of each of the dependent variables against predicted values exhibited clear pattern approaching linearity. Moreover, the plots involving standardized residuals showed a cloud-like random pattern of points. The results of the Jarque-Bera test also indicated that the null hypothesis of normality of residuals cannot be rejected. Since our model passes all diagnostic tests, we conclude that its results may be trusted.

Creatinine (which is elevated when kidneys are affected possibly due to adverse drug reactions) is significantly and negatively associated with baseline CD4 count at the one percent significance level. A study conducted on adult HIV patients in Nigeria by Adedeji et al. (2015) also found that creatinine was inversely correlated with CD4 (r = -0.228, P = .025). Thus, despite improved outcomes among persons living with HIV who are treated with antiretroviral therapy, they remain at increased risk of adverse drug reaction prompting acute and chronic kidney diseases.

Table 2: Results of the fitted multivariate multiple linear regression model

Response variable	Covariate	Coef.	S.E	t statistic	p-value	η^2
CD4 count	Intercept	298.559	6.402	46.633	.000	.904
	WBC	-.060	1.806	-.033	.974	.021
	RBC	-1.012	3.898	-.260	.795	.013
	Platelet	.880	3.823	.230	.818	.003
	HCT	5.413	3.854	1.405	.162	.008
	Creatinine	-51.682	3.947	-13.094	.000*	.426
	AST	5.862	3.911	1.499	.135	.010
CD8 count	Intercept	299.652	6.788	44.144	.000	.894
	WBC	-.744	1.915	-.389	.698	.011
	RBC	1.040	4.133	.252	.802	.002
	Platelet	.221	4.053	.054	.957	.001
	HCT	7.827	4.086	1.916	.057**	.085
	Creatinine	55.459	4.185	13.253	.000*	.432
	AST	6.691	4.147	1.614	.108	.012

** Significant at 1% level, ** Significant at 10% level*

Creatinine is significantly and positively associated with baseline CD8 count at the 99% confidence level. According to Routy and Mehraj (2017), an elevation of CD8-T cells persists in absence of ART and only partially decreases even after a decade of treatment. Such persistence of elevated CD8-T cell counts (independent of CD4-T cell reconstitution) has been linked with an increased risk of non-AIDS-related

clinical events, including renal diseases (signaled by an increased level of creatinine). Furthermore, hematocrit (which is elevated due to some disorders) is positively and significantly associated with CD8 count at the 10% level of significance.

4. Conclusion and Recommendations

4.1 Conclusion

Among the strategies deployed to combat the HIV epidemic, the introduction of ART is one of the most significant interventions that changed the landscape of HIV-related morbidity and mortality. However, adverse drug reactions associated with ART can rapidly reverse the gains of ART resulting in poor health outcomes. The objective of this study was to identify and analyze correlates of peripheral neuropathy (PN) among children under ART and to assess the relationship between clinical parameters and complete blood group count, renal function and liver enzyme tests.

The logistic regression analysis based on data from the ART Pediatric Clinic of Hawassa University Referral Hospital showed that the likelihood of developing PN was higher for child patients whose age group was less than five years (as compared to those children with age over seven years); whose CD4 count at the start of ART was less than 100 cells/ml and 100-250 cells/ml (as compared to those with baseline CD4 count of greater than 250 cells/ml); and whose haemoglobin level was less than 7 mg/dl (as compared to those children with haemoglobin levels over 10 mg/dl). As to ART regimen, children under ART follow-up who used Stavudine (D4T) drug combination were more likely to be exposed to adverse drug reaction as compared to those patients who used Zidovudine (AZT) - Efavirenz (EFV) drug combination.

Multivariate multiple regression analysis revealed that creatinine (which is elevated when kidney is affected possibly due to adverse drug reactions) was significantly and negatively associated with baseline CD4 count, while it was significantly and positively associated with baseline CD8 count of patients under ART.

4.2 Recommendations

Based on the results of this study, we make the following recommendations for policy makers and clinicians:

- ✓ Special monitoring for possible ADRs should be implemented for children under ART who are under-5, who used Stavudine (D4T) ART regimen, with low baseline CD4 counts and lower amount of haemoglobin.
- ✓ Health workers should take into account the relationship between clinical parameters and that of complete blood group count, renal function and liver enzyme tests to tackle the problem of side effects in HIV-infected children under ART.

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