ADDIS ABABA UNIVERSITY

SCHOOL OF GRADUATE STUDIES

COLLEGE OF NATURAL SCIENCES

DEPARTMENT OF STATISTICS

Prevalence of ARV-related adverse drug reactions among children taking HAART at Hosanna Hospital

By

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ABSTRACT

In Ethiopia approximately 1.2 million people were living with HIV/AIDS in 2010. It is known that 134,586 children live with HIV/AIDS. Out of these, more than 67,000 are estimated to be eligible for Anti Retroviral Treatment (ART) but only 4863 were taking HIV/AIDS Anti Retroviral Treatment by March 2008. Although Antiretroviral Treatment (ART) has decreased HIV-associated mortality and morbidity, a number of patients still die after the start of ART. The objective of this study was to assess prevalence of some adverse drug reactions among HIV-infected children under ART. The patients were those on ART follow-up at Hosanna Hospital. A sample of 105 patients has been collected among patients on ART from May 2005 to April; 2013.The analysis of the data using the binary logistic regression showed that AZT-associated anemia, d4T-associated peripheral neuropathy and NVP-associated skin rash had influence on the survival of patients. i.e. Children HIV patients under ART follow up have developed AZT-associated anemia, d4T-associated peripheral neuropathy and NVP-associated skin rash. The results of the study indicated that adverse drug reaction has relation with age, baseline weight, baseline CD4 counts, WHO clinical stages and ART regimen. Health workers should take into account the relationship between clinical parameters and that of complete blood group count, chemistry tests and enzyme tests to decide the overall situation for all HIV-infected patients under ART. And the Drug Administration and Control Authority should strengthen the regular monitoring of ADRs especially those associated with ARVs.

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LIST OF ACRONYMS

ABC	Abacavir
ADR	Adverse Drug Reaction
AIDS	Acquired Immune Deficiency Syndrome
ART	Antiretroviral Treatment
ARV	Antiretroviral
AZT	Zidovidine
CD4	Cluster of differentiation 4
CD8	Cluster of differentiation 8
D4T	Didehydro-deoxythymidine
DACA	Drug Administration and Control Authority
EFV	Eferaphine
FMOH	Federal Ministry of Health
HAART	Highly Active AntiRetroviral Therapy
HAPCO	HIV/AIDS Prevention and Control Office
HIV	Human immune virus
NVP	Nevraphine
PMTCT	Prevention of mother to child HIV transmission
PLWHA	People Living with HIV AIDS
SNNPR	Southern Nations Nationalities and People's Region
TB	Tuberculosis
TDF	Tenofovir Disoproxil Fumanate

UNAIDS	Joint United Nations Programme on HIV/AIDS
VCT	Voluntary Counseling and Testing
WHO	World Health Organization

CHAPTER ONE

1. INTRODUCTION

1.1. Background

HIV/AIDS is an epidemic that affects every part of the globe. According to the latest figures, an estimated 33.4 million people were living with HIV. There were 2.7 million new infections in 2008 all over the world. Sub-Saharan Africa remains the region most heavily affected by HIV. In 2008, sub-Saharan Africa accounted for 67% of HIV infections worldwide, 68% of new HIV infections among adults and 91% of new HIV infections among children (UNAIDS/WHO, 2009).

Ethiopia has an estimated population of 91 million people of whom 44.6% are children below 15 years (EDP, 2013). The adult prevalence of HIV is 10.5% in urban areas and 1.9% in rural areas, and the average prevalence is around 4%. The exact level of prevalence of HIV among children in Ethiopia is not known. However, it is known that 134,586 children live with HIV/AIDS. Out of these, more than 67,000 are estimated to be eligible for Anti Retroviral Treatment (ART) but only 4863 were taking HIV/AIDS Anti Retroviral Treatment by March 2008 (FMOH, 2008).

The World Health Organization (WHO) had estimated that there were over 1.3 million people receiving anti retroviral therapy (ART) in low and middle income countries, representing 20% of 6.5 million estimated to need it, Great progress has been made in providing access to ART in sub-Saharan Africa; by April 2007, approximately 1.3 million people were receiving ART some 28% of the 4.8 million people estimated to be in need (AIDS, 2008).

In Ethiopia approximately 1.2 million people were living with HIV/AIDS in 2010 (EDHS, 2011). In 2003 the government of Ethiopia introduced ART program with the goal of reducing HIV related morbidity and mortality, improving quality of life of people living with HIV and mitigating some of the impact of epidemic.

In 2005 Ethiopia launched free ART and over 71, 000 were initiated by the end of November 2006 and 241 hospitals and health centers are now providing HIV care and treatment services in regions of the country (HIV care and ART, 2005).

The 2007 National HIV Prevalence Estimation report indicated that there will be 153,660 people living with HIV in the year 2009 in SNNPR. Among these, 44,064 will need ART. Moreover this problem has an impact on the annual numbers of TB cases, total population size, life expectancy and social development of the region as productivity reduces in the work place and loss of income at house hold levels.

According to HIV/AIDS Prevention and Control Office (HAPCO), ART has a potential impact on HIV/AIDS prevalence, decreasing HIV/AIDS orphans and HIV/AIDS deaths (Tesfaye, 2008).

Rapid progress in developing antiretroviral therapy (ART) led in 1996 to the introduction of highly active antiretroviral therapy (HAART). This revolutionized the treatment of HIV infection. HAART is a combination of at least three antiretroviral (ARV) drugs. As with anti-TB treatment, a combination of ARV drugs provides efficacy and decreases risk of drug resistance.

HAART is the global standard of care in the treatment of HIV infection. Although not a cure for HIV infection, HAART usually results in near complete suppression of HIV replication.

Treatment has to be lifelong. ART results in dramatic reductions in morbidity and mortality in HIV infected people. There are several requirements for successful use of ART. These include considerable efforts to maintain adherence to lifelong treatment and to monitor response to treatment, drug toxicities and drug interactions (WHO/HTM/TB/2004.329).

The success of anti retroviral treatment is highly dependent on willingness of HIV positive individuals to adhere to complex ARV regimens (FMOH, 2006). Unfortunately, up to 25% of patients discontinue their initial highly active anti retroviral therapy (HAART) regimen because of toxic effects, noncompliance or treatment failure within

the first 8 months of therapy (Adriana, et al., 2002). The occurrence of side effects can vary dramatically among different people (Montessori, 2004).

Some experience frequent and severe adverse reactions that require dose reductions or discontinuation of treatment, others have side effects that are uncomfortable or annoying and can interfere with their daily quality of line; others experience few or no adverse reactions.

Continuous evaluation of the benefit and harm of ART will help to achieve the ultimate goal of making safer and more effective treatment available to patients (Assegid, 2007). Therefore, many countries have adverse drug reactions (ADRs) monitoring centers, which are responsible for collecting, compiling and analyzing any ADRs information reported by health professionals. Based on this information, risk-benefit evaluations are made and safety measures are taken to protect the public from unnecessary harm. In Ethiopia, there has been an ADR Monitoring Division organized at the Drug Administration and Control Authority (DACA) since 2003 (Assegid, 2007). The Division has so far received 110 ADR reports out of which, 60 were ADRs on Anti Retroviral Drugs .Therefore, information on the type and severity of ADRs to ART is inadequate and the safety profile of ART drug regimens that are currently on use in Administration and Control Authority setup are unknown (DACA, 2006)..

Accordingly, ADR is one of the major problems associated with the treatment of HIV-1 patients in Ethiopia (FMOH, 2008). In spite of this, a lot work has not been done on ARV therapy in Ethiopia. Moreover, even though treating HIV patients in ARV is in progress since the late 1990's, a limited research work has been done in relation to ADR of the therapy.

In addition to successful treatment, it is also important to identify the overall adverse drug reaction effects of the treatment in order to reduce the morbidity and mortality rate.

In this study, we will try to investigate the effect of commonly encountered ARV related adverse drug reaction among children under ART at Hossana Hospital.

1.2 .Statement of the problem

In Ethiopia, there is a recent attempt to implement different ARV therapies that help to improve the life of HIV/AIDS patients. This therapy has declined the morbidity and mortality of HIV infected patients. Although many factors may interfere with adherence to ARV therapy, adverse reactions to the medications are among the most important. We observe ARV adverse drug reactions that occur early in the course of therapy. Therefore, by taking the significance of the problem into account this study attempts to investigate the common ARV adverse drug reactions occurring early in the course of treatment. The target population of the study is children having HIV/AIDS who started ARV therapy in Hosanna Hospital and children living with HIV/AIDS who have been transferred to Hosanna Hospital to continue ART treatment and regularly followed by ART physicians.

1.3. Objectives

The general objective of the study is to determine the prevalence of commonly encountered ARV related adverse drug reactions among children taking HAART.

Specific objectives:-

- to determine the prevalence of anemia, skin rash and peripheral neuropathy in relation to each ART regimen among children taking HAART.
- to assess the severity of adverse drug reactions by determining the rate of drug change due to HAART related severe toxicity.
- to evaluate the association of ART regimen, gender, age and WHO clinical stage on the development of ARV related adverse drug reactions.

1.4. Significance of the study

The outcome of the research will help healthcare workers to inform patients about the possible ARV related factors of adverse drug reactions they might encounter. Moreover, clinicians can decrease drug toxicity associated morbidity and mortality among HIV positive patients by early diagnosis and appropriate intervention.

In addition, the result of the study will help to improve the care provided to children, designing appropriate interventions adapted towards communities at high risk and enable clinicians and policy makers to enhance the awareness of the society about factors which increase the prevalence of ARV related adverse drug reaction of patients.

Furthermore, the result of this study could possibly be used as a source of information to other researchers for further study in the future.

CHAPTER TWO

2. LITERATURE REVIEW

2.1. Definitions of some terms

ART is a combination of three antiretroviral drugs given to HIV/AIDS patients eligible for treatment according to the national guideline.

Anemia is the presence of at least one documented hemoglobin value of <=10mg/dl after having started ART.

Peripheral Neuropathy is the presence of documented persistent pain, numbness, tingling or burning sensation on the extremities after having started ART.

Skin rash is the presence of documented generalized mildly itchy or nonpruritic urticarial, erythematous or maculopapular rash, which may have vesicular lesion and desquamate lesions over the mucous membranes in severe cases after having started on ART.

CD4 cells are a type of lymphocyte and are an important part of the immune system. CD4 cells are sometimes called T-cells or "helper" cells. They lead the attack against infections.

CD8 cells are "suppressor" cells that end the immune response. CD8 cells can also be "killer" cells that kill growth cells and cells infected with a virus.

2.2. Situation of People live with HIV/AIDS (PLWHA) on ART

There was a fear that antiretroviral treatment will remain beyond the reach of people living with HIV in low and middle-income countries. However, recognizing the universal right to treatment access, the world unanimously endorsed the Declaration of Commitment on HIV/AIDS by the United Nations General Assembly in 2001 that embraced equitable access to care and treatment as a fundamental component of a comprehensive and effective global HIV response.

In 2003, WHO launched the "3 by 5" initiative. At the same time, funding for treatment increased greatly as a result of initiatives such as the United States President's Emergency Plan for AIDS Relief and the Global Fund to Fight AIDS, Tuberculosis and Malaria (DACA, 2006).

Between 2001 and 2005, the number of people on antiretroviral therapy in low and middle-income countries increased more than five-fold from 240,000 to approximately 1.3 million (DACA, 2006). As of June 2005, 21 countries were providing antiretroviral treatment to at least 50% of those in clinical need (WHO, 2006).

The World Health Organization estimated that by the end of 2005, out of 6.5 million who need antiretroviral therapy in low and middle-income countries, over 1.3 million people were receiving it

The preliminary analysis conducted by MSF in Khayelitsh town ship in Cape Town for initiation of ARV treatment revealed that, after one year on the treatment, the frequency of opportunistic infection was reduced dramatically after the initiation of ARV treatment. The incidence rate of tuberculosis and oral candidiasis declined by two third for both diseases (WHO, 2003).

The number of people on antiretroviral therapy more than doubled in sub-Saharan Africa in 2005 alone, with roughly one in six people who needed treatment receiving antiretroviral by December 2005 (WHO, 2006). Coverage levels of 50% or greater have been achieved in countries such as Botswana and Uganda, while in others levels remained at less than 10% (WHO, 2006).

In 2009, the HIV/AIDS Prevention and Control Office (HAPCO) estimated that there were around 1,116,216 People Living With HIV/AIDS (PLWHA) and of these 336,160 needed ART. There were also a total of 855,720 AIDS orphans in the country (HAPCO, 2009). Recent Service Delivery Reports from HAPCO (February, 2010) indicate that the number of People Living With HIV/AIDS (PLWHA) ever enrolled in ART programme has increased to 443,964 while those ever started ART increased to 246,347 and the number of People Living With HIV/AIDS (PLWHA) on ART reached to 179,183.

In January 2005, the government launched the "Accelerating Access to HIV/AIDS Treatment in Ethiopia, Road map 2004-2006" that aimed at providing universal access to ART for all AIDS patients by the year 2008 (FMOH, 2006). Accordingly, the plan was to enroll 100,000 patients by the end of 2006 (FMOH, 2006). Up to August 2006, a total of 73,540 PLWHA were enrolled for HIV/care out of which 45,595 had started on ART at 132 facilities across the country. Of these, 35,460 were on treatment currently and the remaining 10,135 (22.2%) constitute lost for follow up, died or stopped treatment due to treatment failure or other problems (FMOH, 1998; FMOH, 2005). Of the people ever started on ART, 47 % were adult males greater than 14 years of age, 48% were adult females greater than 14 years of age, and 5% were children.

2.3 Adverse drug reactions

Adverse drug reactions are common ranging from mild to life threatening conditions. They usually occur within early week of treatment, but some like metabolic toxicities happen following prolonged use of ARVs. The mild toxicities required symptomatic therapy as they are self limiting but these toxicities may re-quire counseling so that patients need to continue treatments. Some adverse drug reaction is due to class specific effect while others are related to individual drugs (Edwards IR and Aronson JK).

There are few researches conducted on ADR of patients with ART. A research conducted by Monique, et al. (2000) showed that there were less ADR and toxicity in quadruple therapy. The researcher concludes that quadruple drug regimen is quite well tolerated. Diarrhea was frequently reported but could be relieve by the use of anti-diarrheal agents. With the exception of diarrhea, all gastrointestinal complaints observed were found to be associated with the level of exposure to Nelphinavir or Saquinavir.

The study undertaken in Hawassa University by Anteneh (2010) revealed that from all HIV/AIDS positive patients that follow ART treatment, 3.5% have changed the drug regimen. The study showed that most of regimen changes have occurred due to Nevraphine (NVP)-based combination of ART.

Binary logistic regression analysis was used to estimate change in the drug regimen because of toxicity. The researcher also reveals that the main risk factors associated with high tendency of drug change were base weight and early taking of TB treatment.

A study in Addis Ababa University by Assegid (2007) concluded that relatively very high rate of changing of drugs was noted with in first line regimen drugs, with high lost to follow up rate which may shorten the durability of the first line regimen.

The type of ADRs that the patient developed was very much associated with the duration of treatment and the regimen. Therefore, early diagnosis and appropriate management of ADRs is reckoned to decrease the rate of changing first line drugs which eventually maintain their efficacy and durability. The main reasons for changing ARV drugs were toxicity/side effects (81%) followed by illness (12 %), and pregnancy (3%).The most frequently diagnosed ADRs were Anemia (33.9%) followed by Peripheral Neuropathy (28.2%).

Another research done by Julio et al. (2007) utilizing the multivariable logistic model compared sex difference in clinical, immunological and virological parameters of HIV-1 infected patients. The researcher tried to compare the clinical,virological and immunological parameters of men and women at baseline and during antiretroviral treatment. The researcher concludes that women have more favorable clinical and immunological patterns than men both at baseline and during antiretroviral treatment. Sex has a significant influence on the clinical and laboratory outcomes of HIV infection.

Illness related to a drug's intended pharmacologic action is often more easily recognized than illness attributable to immune or other mechanisms. For example side effects such as cardiacarrthymias in patients receiving digitalis, hypoglycemia in patients given insulin, and bleeding in patients receiving anticoagulants are more readily related to a specific drug than are symptoms such as fever or rash, which may be caused by many drugs or by other factors (Harrison, 2000).

A study done in Addis Ababa University revealed that WHO clinical stage had strong association (at 0.05 level of significance) with AZT-associated anemia. Binary logistic regression analysis was used to estimate AZT-associated anemia.

In this study, the remaining variables such as; age, base weight, base CD4 count, ART regimen and sex had no significant effect on AZT-associated anemia (Aklilu, 2010).

2.4 D4T associated peripheral neuropathy

Stavudine is the fourth drug licensed for the treatment of HIV infection. Peripheral neuropathy and hepatic steatosis are the main toxicities of stavudine. In this study, the central role of d4T in the development of peripheral neuropathy is supported by the observed resolution on stopping this drug (Maria, et al., 2007). Studies done in Africa have revealed that frequency of d4T-associated peripheral neuropathy is around 5-15% and the presumed cause is depletion of mitochondrial DNA (Bartlet, 2007). In a study conducted by Michael et al., (2005), co-administration of INH with d4T led to a greatly increased incidence peripheral neuropathy: twelve out of 22 patients (55%) developed peripheral neuropathy with a median time to onset of 5 months (range 2-15 months) when compared with the use of d4T alone (11%).

A study done in Addis Ababa University had concluded that age has a very strong association with the occurrence of d4T-associated peripheral neuropathy as revealed by the small p-value of 0.001. Binary logistic regression analysis was used to estimate d4T-associated peripheral neuropathy (Aklilu, 2010).

2.5 AZT associated anemia

Among the side effects of AZT at the initiation of therapy are fatigue, malaise, nausea, and headache. The side effects often subside over time. Patients on AZT may develop a macrocitic anemia, mayophathy, cardiomyophathy, and lactic acidosis associated with fatty infiltration of the liver. Bartlet, (2007) indicated that the prevalence of AZT-associated anemia is around 10%; the pathophysiologic mechanism being bone marrow toxicity.

A study done in Addis Ababa University revealed that WHO clinical stage had strong association (at 0.05level of significance) with AZ- associated anemia. Binary logistic regression analysis was used to estimate AZT-associated anemia.

In this study, the remaining variables such as; age, base weight, base CD4 count, ART regimen and sex had no significant effect on AZT-associated anemia (Aklilu, 2010).

2.6 Adherence of PLWHA to ART

More than 95% treatment adherence levels are required to maintain virologic suppression in people on combination of ARV drugs (Daniele et al., 2007). However, actual adherence rates are lower. Most studies show that 40% to 60% of patients are less than 90% adherent (John A. and Bartlet, 2002). The most common reasons for non-adherence of patients include complexity of medication regimens, difficulty of integrating treatment schedules into their daily activities, side effects, worries about HIV disclosure, and forgetfulness in taking medication (Gifford, et al., 2000). Some people argue that a higher proportion of patients in Africa are likely to fall into the category of potential poor adherers unless resource intensive adherence programmes are available. However, recent findings from African countries showed that patients in African settings are also able to achieve excellent rates of adherence with access to routine medical care. Several studies on adherence to ARV therapy showed good adherence rate (Ayalew, 2005; Yonas, 2005)

2.7 NVP-associated skin rash

NVP is non nucleoside inhibitor of the HIV-1 reverse transcribtor. It is used in combination with nucleoside analogues for the treatment of HIV infected adults. It is associated with the development of maculopapular rash, generally seen with in the first few weeks of therapy (Harrison, 2000).

In one study done in Africa NVP-associated skin rash is about 17% and 7% of all patients required discontinuation of the drug (Bartlet, 2007). Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported and 3 deaths were ascribed to NVP skin rash. The prevalence of NVP-associated skin rash is found to be different in both males and females and baseline CD4 counts (Bartlet, 2007).

A study undertaken in Thailand by Avert (2005) has shown that out of the total 202 patients in the study group 21% of patients taking NVP 200mg twice a day and 38% of patients taking NVP 400mg once in a day developed skin rash within four weeks of therapy. Binary logistic regression analysis was used to estimate NVP-associated skin rash.

The risk factor assessment in the above mentioned study has revealed that being female with CD4 above 250, high BMI above 21.3 and a rise in CD4 above 53cells/ml and an increase in alanine amino transferase at week four are risk factors for the development of NVP-associated skin rash.

The study followed 235 patients on nevirapine for six weeks out of which 26 (11%) developed nevirapine hypersensitivity with median time of 14 to 21 days. Out of the total 26 cases, 12 had developed isolated skin rash mild to moderate degree and 14 cases had multisystem or hepatotoxic reactions. There was no skin rash report after six weeks of treatment. These indicates the hypothesis that the immunological recognition of nevirapine specific antigens plays an important role in conferring susceptibility to hepatic/systemic reactions associated with nevirapine, and furthermore that this may be abrogated by HIV associated CD4 T-cell depletion (AIDS, 2005).

A study was done by Aklilu (2010) utilizing binary logistic regression model to estimate NVP-associated skin rash. In this study sex and CD4 count had very strong association with NVP-associated skin rash.

CHAPTER THREE

3. DATA AND METHODOLOGY

3.1. Description of Study Area and Population

The study was carried out in Nigist Eleni Memorial Hospital in Hossana city. Hossana is the capital of Hadiya Zone. Hadiya zone is a zone in the Ethiopian, Southern, Nations, Nationalities and Peoples Region. The Zone was founded in 1985 E.C and bordered on the south by Kemabata-Tembaro, on the west by Omo River which separates it from Oromiya Region and the Yem special Woreda, on the north by Gurage ,and on the north east by Silte. The total population of the zone is 1,471,089 which is 8.7% of the SNNPR population with the population density of 415 people /sq.km. (Hadiya zone health department annual report 2004 E.C)

In Hadiya zone there are 366 governmental health facilities and 162 private health facilities. From the governmental health facilities, there are 60 health care centers, one hospital and 305 health post and from the private health facilities there are 121 clinics and 41 pharmacies with the health service coverage of 103% (Hadiya zone health department annual report 2004 E.C)

Hosaanna hospital (Nigist Eleni Memorial Hospital) is one of the health facilities in Hadiya zone which gives preventive ,curative and rehabilitative service for the catchment area population with the ratio of hospital to total population 1:1,471,089.(Hadiya zone health department annual report 2004 E.C)

3.2. Methods of Data collection

This is a retrospective study which is based on reviewed the follow up charts of children under HAART in Nigist Eleni Memorial Hospital in Hossana city in ART clinic from May 2005 to April 2013. The patient chart included the intake form, HIV care, ART follow up form and the regular patient card, which are prepared by FMOH to be uniformly used by clinicians to identify and document clinical and laboratory variables as early as possible. Thus, in this research we will use secondary data which are collected from patient charts based on those variables to be considered in this study.

The study includes follow-up charts of all children living with HIV/AIDS who have been under ART regularly in the Pediatric Department of Nigist Eleni Memorial Hospital in Hossana city.

Inclusion and Exclusion Criteria

The study will consider all HIV infected patients under ART whose age is less than 15 years regardless of their treatment category during the study in Nigist Eleni Memorial Hospital in Hossana city. However, the study was exclude those patients on ART were older than 15 years and those patients on ART who were transferred to other health institutions or those lost to follow up.

3.3. Methods of Data Analysis

The fact that we have variables of different nature in this research implies that different methodological approaches will be employed for analysis. We can generally group the target /response variables (and hence the methodological approaches used) in this study into two:

I. Determination of prevalence
II. Risk factor determination

3.3.1 Prevalence

In order to determine the prevalence of adverse drug reaction to a particular drug we calculate the prevalence by taking the proportions of patients experiencing the particular adverse effect among those taking the incriminated ARV drug.

3.3.2 Risk factor determination

There are many situations in which the response of interest is dichotomous rather than continuous. Examples of variables that assume only two possible values are disease status (the disease is either present or absent), presence of ARV drug adverse reaction (exist or does not exist) etc. In general the value 1 is used to represent "success" or the outcome we are interested in, and 0 represent "failure".

Just as we estimate the mean of a response variable when it is continuous, we would like to estimate the probability of the outcome of an event of a dichotomous response (which of course is also its mean) for various values of explanatory variables. Since the above explanation matches exactly with the case in this research regarding the factors influencing existence of ARV adverse effects we adopt the logistic regression as the analytic statistical methodology (Pagano and Gauvreau, 2000).

The logistic regression utilizes maximum likelihood estimation after transforming the response into a logit variable (the natural log of the odds of the response variable). After the transformation it is possible to estimate the probability of the occurrence of a certain event.

The logistic regression is also preferred to multiple regression and discriminant analysis as it results in a biologically meaningful interpretation, it is a mathematically flexible and easily used distribution and it requires fewer assumptions (Hosmer and Lemeshow ,2000).

3.3.3 Logistic Regression Model

Logistic regression can be binary or multinomial. The binary or binomial logistic regression is the type of regression which is used when the dependent variable is dichotomous and the independent variables are of any type while multinomial logistic regression is used when the dependent variable has more than two categories. When multiple classes of the dependent variable can be ranked, then ordinal logistic regression is preferred to multinomial logistic regression.

For a binary response variable Y and an explanatory variable X, let P=P(Y=1/X=x) and 1-P= (Y=0/X=x).One possible logistic regression model is given by

$$P=\frac{e^{\alpha+\beta X}}{1+e^{\alpha+\beta X}}, \text{ where } \alpha = \text{intercept and } \beta = \text{slope} \qquad (1)$$

Thus, if a success occurs with probability

$$P=\frac{e^{\alpha+\beta X}}{1+e^{\alpha+\beta X}},$$

the odds in favor of success are

$$\frac{P}{1-P}=\frac{e^{\alpha+\beta X}/1+e^{\alpha+\beta X}}{1/1+e^{\alpha+\beta X}}=e^{\alpha+\beta X}$$

Taking the natural logarithm of each side of this equation,

$$\ln[\frac{P}{1-P}]=\ln[e^{\alpha+\beta X}]=\alpha+\beta X$$

Thus, modeling the probability p with logistic function is equivalent to fitting a linear regression model in which the continuous response y has been replaced by the logarithm of the odds of success for a dichotomous random variable.

Logistic regression can be used to predict a dependent variable on the basis of continuous and/or categorical independent variables and to determine the percent of variance in the dependent variable explained by the independent variables; to rank the relative importance of independent variables; to assess interaction effects; and to understand the impact of covariate control variables. Logistic regression has many analogies to OLS regression: logit coefficients correspond to vector of **β** coefficients in the logistic regression equation, the standardized logit coefficients correspond to beta weights, and a pseudo R^2 statistic is available to summarize the strength of the relationship.

Unlike OLS regression, however, logistic regression does not assume linearity of relationship between the independent variables and the dependent variable, does not require normally distributed variables, does not assume homoscedasticity, and in general has less stringent requirements (Tabachnick, 2007).

3.3.4The Multiple Logistic Regression Model

Logistic regression model is used to investigate the effect of predictors on the probability of having adverse drug reaction among HIV-infected children under ART. The response variable is dichotomous and denoted by Y, which is a Bernoulli random variable with two

possible values, Y = 1 with probability of having adverse drug reaction P = P(Y = 1|**X**=**x**) and Y = 0 with probability of having no adverse drug reaction 1 – P = 1 – P(Y = 1|**X**=**x**).

Consider a collection of *k* explanatory variables which will be denoted by the vector $\mathbf{X}=(X_1, X_2, ..., X_k)'$ .Let the conditional probability that the outcome is present be denoted by P(Y=1| **X**) = p(**X**).

The multiple logistic regression model is given by P= P(**X**)

$$P=\frac{e^{\alpha+\beta_1 X_1+\beta_2 X_2+...+\beta_k X_k}}{1+e^{\alpha+\beta_1 X_1+\beta_2 X_2+...+\beta_k X_k}} \quad (2)$$

and the odds in favor of success for the multiple logistic regression will be

$$\ln[\frac{P}{1-P}] = \alpha+\beta_1 x_1+\beta_2 x_2+....\beta_k x_k$$

The coefficient of a continuous covariate is interpreted as the change in the log-odds of having adverse drug reaction per unit increment in corresponding covariate. In case of categorical predictor variable, it is interpreted as the log-odds of having adverse drug reaction among HIV/AIDS patients with a given category compared to the reference category.

3.4. Variables considered in the research

The variables of interest in this research are described below.

Prevalence is defined as the proportion of specific ARV adverse effects developed in children taking the incriminated ARV drug in Pediatric Department –Hosanna Hospital.

I-Prevalence

1. The prevalence of anemia
2. The prevalence of peripheral neuropathy

3. The prevalence of skin rash

II-Response/Dependent variables

1. The existence of anemia (exists=1,does not exist=0)
2. The existence of peripheral neuropathy (exists=1,does not exist=0)
3. The existence of skin rash (exists=1,does not exist=0)

III- Predictor/Independent variables

The variables that are proposed to influence the prediction of the response variables are:

1. Age
2. Gender
3. Baseline weight
4. Baseline CD4 count
5. WHO clinical stage
6. ART regimen

3.5Fitting the Logistic Regression Model

Suppose we have a sample of n independent observations of the pair (X_i, Y_i), i=1,2, …,n, where Y_i denotes the value of the dichotomous outcome variable and X_i is a vector of independent variables for the i^{th} subject. Fitting the model requires that we obtain estimates of the values of the vector $\boldsymbol{\beta}$.

In linear regression the method used most often for estimating unknown parameters is least squares. In that method we choose those values of vector $\boldsymbol{\beta}$ which minimize the sum of squared deviations of the observed values of Y from the predicted values based upon the model. Under the usual assumptions for linear regressions the method of least squares yields estimators with a number of desirable statistical properties. Unfortunately when the method of least squares is applied to a model with a dichotomous outcome the estimators no longer have these same properties (Hosmer and Lemeshow, 2000).

The general method of estimation that leads to the least squares function under the linear regression model (when the error terms are normally distributed) is called maximum likelihood. It is this method that provides the foundation for our approach to estimation with the logistic regression model.

In a very general sense the method of maximum likelihood yields values for the unknown parameters which maximize the probability of obtaining the observed set of data. In order to apply this, we must first construct a function called likelihood function. The maximum likelihood estimators of these parameters are chosen to be those values which maximize this function. Thus, the resulting estimators are those which agree most closely with the observed data.

Consider the logistic model $p_i=\frac{e^{X_i'\beta}}{1+e^{X_i'\beta}}$. Since the observed values of Y, Y_i,i=1,2,…, n, are independently distributed as Bernoulli random variables, the likelihood function of *Y* is the joint density function given by:

$$L(\beta/Y)=\prod_{i=1}^{n} p(y_i/x_{i1},x_{i2},...,x_{ik})=\prod_{i=1}^{n}\left[\frac{e^{X'_i\beta}}{1+e^{X'_i\beta}}\right]^{y_i}\left[\frac{1}{1+e^{X'_i\beta}}\right]^{1-y_i} \quad (3)$$

The maximum likelihood estimates of the parameters β are obtained by maximizing the log-likelihood function which is given by:

$$\log L(\beta/Y)=\sum_{i=1}^{n}\left\{y_i \log\left[\frac{e^{X'_i\beta}}{1+e^{X'_i\beta}}\right]+(1-y_i)\log\left[\frac{1}{1+e^{X'_i\beta}}\right]\right\} \quad (4)$$

The maximum likelihood estimate of the parameter vector β is found by differentiating the log-likelihood function with respect to each β and set each equation to zero.

Hence, through maximization of the above log-likelihood function, we can theoretically estimate the parameter vector β. But the equation is non-linear in β, and as a result the estimates do not have a closed form expression. Therefore, β was obtained by maximizing the likelihood function using a numerical iterative method (Agresti, 2002).

Odds Ratio

The odds ratio is the ratio of the odds of an event occurring in one group to the odds of occurring in another group.

The odds ratio (OR) is given by:

$$OR = \frac{p/1-p}{q/1-q}$$

where p is the probability of success for one group, and q is the probability of success for another group.

In binary logistic regression, odds ratio is the exponential of the estimated coefficient $\hat{\beta}$, that is (exp ($\hat{\beta}$)). An odds ratio of one corresponds to an explanatory variable that does not affect the outcome variable.

For continuous covariate, exp ($\hat{\beta}$) is the predicted change in the odds of having adverse drug reaction for a unit increase in a predictor variable.

In case of categorical predictor variable, exp ($\hat{\beta}$) is the predicted change in odds of having adverse drug reaction for a given category of the predictor variable with respect to the reference category.

3.5.1. Assumptions regarding the logistic regression model

As indicated in the previous sections, one advantage of the logistic regression is that it gives some relaxation with respect to the usual OLS assumptions. There are, however, other assumptions one should consider for the efficient use of logistic regression as detailed in (Tabachnick, 2007).

Meaningful coding: Logistic coefficients will be difficult to interpret if not coded meaningfully. The convention for binomial logistic regression is to code the response class of greatest interest as 1 and the other class as 0.

Logistic regression is predicting the log odds of being in the class of greatest interest.

- Inclusion of all relevant variables in the regression model: If relevant variables are omitted, the common variance they share with included variables may be wrongly attributed to those variables, or the error term may be inflated.
- Exclusion of all irrelevant variables: If causally irrelevant variables are included in the model, the common variance they share with included variables may be wrongly attributed to the irrelevant variables. The stronger the correlation of the irrelevant variable(s) with other explanatory variables, the greater the standard errors of the regression coefficients for these explanatory variable.
- Error terms are assumed to be independent (independent sampling). Violations of this assumption can have serious effects. Violations will occur, for instance, in correlated samples and repeated measures designs, such as before-after or matched-pairs studies, cluster sampling, or time-series data. That is, subjects cannot provide multiple observations at different time points.

3.5.2. Model Building Strategies/Variable Selection

In modeling with many independent variables, one is usually concerned with the aim of selection those variables that result in the "best" model within the scientific context of the problem.

Having a basic plan to follow in selecting the variables for the model and assessing the adequacy of the model both in terms of the individual variables and from the point of view of the overall fit of the model is required for achieving this "best" model. It is also highlighted (Hosmer and Lemeshow, 2000) that successful modeling of a complex data set is part science, part statistical methods, and part experience and common sense.

The traditional approach to statistical model building involves seeking the most parsimonious model that still explains the data. Recently researchers are shifting to

including all scientifically relevant variables in the model, irrespective of their contribution to the model. This is based on the fact that it is possible for individual variables not to exhibit strong association while they do show considerable association when taken collectively. Both approaches have their merits and demerits and details of this can be found in (Hosmer and Lemeshow, 2000).

In general the following steps are recommended (Hosmer and Lemeshow, 2000) to aid in the selection of variables for a logistic regression. Firstly, the selection process should begin with univariate analysis of each variable. Secondly, the selection of variables for the binary logistic regression analysis will follow along with all variables of the known importance based on the results in the univariate analysis. Finally, the importance of each variable included in the multiple logistic regression model should be verified by different model assessment techniques.

If we have a large number of possible explanatory variables then it may be worthwhile to employ stepwise selection procedures like forward stepwise or backward stepwise in fitting the models.

3.5.3. Assessing the Fit of the Model

Once a model has been developed through the various steps indicated in the above section, there are several techniques involved in assessing the appropriateness, adequacy and usefulness of the model. First, the overall goodness of fit of the model will be tested. Then the importance of each of the explanatory variables will be assessed by carrying out statistical tests of the significance of the coefficients.

In testing the hypothesis that the model fits the data, the Pearson's Chi-square test, the likelihood ratio test (LRT), 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, 2000).

3.5.3.1. Likelihood-Ratio Test

A widely used approach to testing the significance of a number of explanatory variables is the likelihood ratio test. This is appropriate for a variety of types of statistical models. Agresti (1990) argues that the likelihood ratio test is better, particularly if the sample size is small or the parameters are large. The test statistic is defined as two times the natural log of the ratio of likelihood functions of two models evaluated at their Maximum Likelihood Estimates (MLEs). The likelihood-ratio test uses the ratio of the maximized value of the likelihood function for the full model (LL_F) over the maximized value of the likelihood function for the reduced model (LL_R).

The likelihood-ratio test statistic is given by:

$$-2\log\left(\frac{LL_R}{LL_F}\right) = -2[\log(LL_R) - \log(LL_F)] = -2(LL_R - LL_F) \tag{5}$$

Where LL_R is the likelihood function of the restricted (smaller) model and LL_F is the likelihood function of the full model evaluated at the MLEs. This natural log transformation of the likelihood functions yields an asymptotically chi-squared statistic.

The likelihood-ratio test statistic is distributed with degree of freedom equal to the difference between the numbers of parameters estimated in the two models (Menard, 2002). It tests the null hypothesis that all population logistic regression coefficients are zero except the constant one. If chi-square is significant, the variable is considered to be a significant predictor in the equation.

The Pearson's χ^2 statistic is given by:

$$\chi^2 = \sum\left[\frac{(y_i - m_i\hat{p}_i)^2}{m_i\hat{p}_i(1-\hat{p}_i)}\right] \tag{6}$$

where $\hat{p}_i$ fitted probability and $\sum m_i = n$.

3.5.3.2. Hosmer -Lemeshow Test Statistic

The Hosmer-Lemeshow test is another alternative to checking model fit. This is based on the work of Hosmer and Lemeshow who proposed grouping based on the values of the estimated probabilities (Hosmer and Lemeshw, 2000). The grouping can be either based on the percentiles of the estimated probabilities or fixed values of the estimated probabilities. In either case, the Hosmer-Lemeshow goodness-of-fit statistic, $\hat{C}$, is obtained by calculating the Pearson chi-square statistic from the 2 by g contingency table of observed and expected frequencies and is given as:

$$\hat{C} = \sum_{k=1}^{g} \frac{\left(O_k - n'_k \overline{P}_k\right)^2}{n'_k \overline{P}_k \left(1 - \overline{P}_k\right)} \qquad (7)$$

where g is the number of groups, n'_k is the number of events in the kth group, $O_k = \sum_{j=1}^{n'_k} y_j$ is observed number of events in the kth group and $\overline{P_k} = \sum_{j=1}^{n'_k} m_j \overline{P_j} / n'_k$ is the average estimated probability.

If the Hosmer-Lemeshow goodness-of-fit test statistic is greater than 0.05, we will not reject the null hypothesis that there is no difference between observed and model predicted values, implying that the model estimates are adequate to fit the data at an acceptable level.

3.5.3.3. The Wald Test

The Wald statistic is another method which is commonly used to test the significance of individual logistic regression coefficients for each explanatory variable, which is Ho: $\beta_i = 0$ against H_1: $\beta_i \neq 0$. For a dichotomous response variable, the Wald statistic (W) is the squared ratio of the unstandardized logit coefficient to its standard error, that is,

$$W = \frac{\hat{\beta}_i^{\,2}}{Var(\hat{\beta}_i)}\ , \text{i=1,2, ..., k} \qquad (8)$$

Under H_0 W is distributed as chi-square with one degree of freedom.

Wald test statistics are easy to calculate but their reliability is questionable, particularly for small samples. For data that produce large estimates of the coefficient, the standard error is often inflated, resulting in a lower Wald test statistic, and therefore the explanatory variable may be incorrectly assumed to be unimportant in the model (Bewick, et al., 2005). The likelihood ratio test is more reliable for small sample sizes than the Wald test (Agresti, 2002).

3.6.4. Model Diagnostics

Regression model building is often an iterative and interactive process. The first model we try may prove to be inadequate. Regression diagnostics are used to detect problems with the model and suggest improvements.

There are three ways that an observation can be considered as unusual, namely outlier, influence and leverage. In logistic regression, observations whose values deviate from the expected range and produce extremely large residuals and may indicate a sample peculiarity are called **outliers**. These outliers can unduly influence the results of the analysis and lead to incorrect inferences. An observation is said to be **influential** if removing the observation substantially changes the estimate of coefficients.

Influence can be thought of as the product of leverage and outliers. An observation with an extreme value on a predictor variable is called a point with high leverage. **Leverage** is a measure of how far an independent variable deviates from its mean.

In fact, the leverage indicates the geometric extremeness of an observation in the multi-dimensional covariate space. These leverage points can have an unusually large effect on the estimate of logistic regression coefficients (Cook, 1998).

To identify an observation is outliers or influential, the following rules of thumbs were employed in this study.

- **Residuals:** Standardized, Studentized, deviance and Pearson residuals are obtained using SAS. Observations with values larger than 3 in absolute value are considered as outliers (Agresti, 2002).

- **Leverage Values (Hat Diag):** Measure of how far an observation is from the others in terms of the levels of the independent variables (not the dependent variable). Observations with values larger than 2(k+1)/n are considered to be potentially highly influential, where k is the number of predictors and n is the sample size (Belsley et al., 1980).

- **DFBETAS:** Measure of how much an observation has affected the estimate of a regression coefficient (there is one DFBETA for each regression coefficient, including the intercept). Values larger than $\frac{2}{\sqrt{n}}$ in absolute value are considered highly influential.

Cook's D: Measure of aggregate impact of each observation on the group of regression coefficients, as well as the group of fitted values. In logistic regression, a case is identified as influential if its Cook's distance is greater than 1 (Hosmer and Lemeshow, 2000).

CHAPTER FOUR

4. DATA ANALYSIS AND RESULTS

4.1 Introduction

The response variables are the existence of anemia (exist =1, does not exist =0), the existence of peripheral neuropathy (exist =1, does not exist =0) and the existence of skin rash (exist =1, does not exist =0). The logistic regression is used to describe the relationship between the independent variables and each of these responses.

The data are analyzed using the Statistical Package for Social Science (SPSS) Version 16 and SAS 9.2. The Pearson Chi-square test was conducted to assess the association between the independent variables and the response variables. The logistic regression analysis was conducted to assess the difference among the predictor categories and explanatory variables.

The data analysis started by giving the summary statistics for the variables considered in the study, then preceded to the univariate analysis and multiple logistic regression analysis.

4.2 Summary Statistics

4.2.1 Gender

There were 105 child patients on ARV treatment. From these 47 (44.8%) are females and 58 (55.2%) are males.

Table 4.1: Sex of the patient

Sex of the patient	Frequency	Percent
Female	47	44.8
male	58	55.2
Total	105	100.0

As the table depicts the number of male who take ART exceeds that of females.

4.2.2 Weight

Baseline weight ranges from 5 Kg to 41 Kg. The mean baseline weight is 17.5 Kg for the total group. The average baseline weight for the females is 17.68 Kg and 17.23 Kg for the males. A good number, 51 (48.6%) of the patients had baseline weight between 10 Kg and 20 Kg.

Table 4.2: Categorized baseline weight

Baseline weight	Frequency	Percent
Below 10 kg	18	17.1
10 kg<=weight<20 kg	51	48.6
20 kg<=weight<=30 kg	28	26.7
Above 30 kg	8	7.6
Total	105	100.0

4.2.3 WHO clinical Stage

While 42(40%) of the cases belong to WHO clinical stage III, 11(10.5%) are in the WHO clinical stage IV during initiation of ART. This shows that larger number of patients started ART treatment in the course of the disease, which is at WHO clinical stage III.

Table 4.3: WHO Clinical stage

WHO clinical stage	Frequency	Percent
Stage I	23	21.9
Stage II	29	27.6
Stage III	42	40.0
Stage IV	11	10.5
Total	105	100.0

4.2 4 Baseline CD4

The baseline CD4 count ranges from 10 to 1657 cells/ml. The mean baseline CD4 is 291.52cells/ml. Most of the cases 83(79%) started ART at baseline CD4 counts below 350 cells/ml out of which 44(41.9%) started ART below 200 cells/ml and 39(37.1%) started ART between at baseline CD4 200 cells/ml and 350 cells/ml.

Those who started ART treatment at baseline CD4 count above350 cells/ml are 22(21%). This shows that most of child patients started ART late in the course of the disease.

Table 4.4: Descriptive Statistics of baseline CD4 count

Variable	N	Minimum	Maximum	Mean
Baseline CD4 count	105	10	1657	291.52

Table 4.5: Baseline CD4 count category

Baseline CD4	Frequency	Percent
CD4 below 200	44	41.9
200<=CD4<=350	39	37.1
Above 350	22	21.0
Total	105	100.0

4.2.5 Drug Regimen

The data show that 63(or 60%) of the patients started with **4a** regimen, 14(13.3%) started with **4b** regimen, 24(22.9%) with **4c** regimen and 4(3.8%) with **4d** regimen. The numbers of patients who have been taking **NVP** based regimen are more than patients who have been taking **EFV** containing regimens. The reason is that during the time of initiation of ARV treatment program, there was shortage of **EFV**. However as there is no shortage of **EFV** currently, the trend is prescribing more of **EFV**-based regimen due to fear of **NVP** associated severe skin rash, hepatoxicity and interaction with anti TB drugs. Moreover **EFV** is more potent than **NVP** and it is taken once daily thereby decreasing pill burden. In developed countries where there are more ARV drug options, **TDF** and **ABC** are preferred to **AZT** and **d4T** as the first two drugs are more potent , less toxic and have low pill burden (Journal of American Medical Association (JAMA)).

Table 4. 6: Drug Regimen Category

Drug regimen	Frequency	Percent
4a=d4t-3TC-NVP	63	60.0
4b=d4t-3TC-EFV	14	13.3
4c=AZT-3TC-NVP	24	22.9
4c=AZT-3TC-EFV	4	3.8
Total	105	100.0

4.3 AZT-Associated Anemia

4.3.1 Prevalence

In the study group the occurrence of anemia after having started ART is 40(38.1%). Among those who have been taking AZT containing regimen 20(50%) and among those who have been taking d4T containing regimen 20(50%) developed anemia.

Table 4.7: Regimen associated anemia

Regimen	Number of patients	Percent
AZT	20	50.0
d4T	20	50.0
Total	40	100.0

4.3.2 Logistic Regression Analysis

4.3.2.1 Univariate Analysis for Existence of Anemia

The selection process will begin with a careful analysis of each variable. It is known that the likelihood ratio chi-square test with k-1 degrees of freedom is exactly equal to the value of the likelihood ratio test for the significance of the coefficients for the k-1 design variables in a univariate logistic regression model that contains the single independent variable. Since the Pearson chi-square test is asymptotically equivalent to the likelihood ratio chi-square test, it can also be used to test the significance of univariate relationships.

In univariate analysis, using the Pearson chi-square test, the variables that are found to be significant are age, baseline weight and ART regimen. The remaining variables except baseline CD4 count appear to be significant at 25% level of significance.

Thus, strong association (at α=0.05 level of significance) of AZT-associated anemia is depicted (in the univariate case) for age, baseline weight and ART regimen. Table 4.8 summarizes the findings of the univariate analysis.

Table 4.8: Variables in the univariate analysis

Variables	Pearson chi-square	DF	P-value(Asymptotic)
Age	29.546	2	.000
Sex	1.378	1	.240
Baseline weight	14.445	3	.003
Baseline CD4 count	.256	2	.880
WHO clinical stage	4.557	3	.207
ART regimen	20.083	3	.000

4.3.3 Findings from Multiple Logistic Regression

One problem with any univariate 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.

If this is thought to be a possibility, then we should choose a significance level large enough to allow the suspected variables to become candidates for inclusion in the multivariate model. It is for this reason that we have to include all the variables considered in the univariate analysis irrespective of their significance for multiple logistic regression analysis. Forward stepwise likelihood ratio method is used to select variables.

Multiple logistic regression analysis is carried out using the significant variables in the univariate analysis. Based on the results displayed in Table4.8, those predictor variables that are associated with existence of anemia at 25% level significance were considered

for multiple logistic regression analysis. Multiple logistic regression model was fitted using the forward selection (likelihood ratio) method.

The variables that are found to be significant in the multiple logistic regression analysis are age and ART regimen and this is in effect in line with the results obtained from the univariate analysis.

The values of Wald statistic for individual β coefficients support that the estimated values $\hat{\beta}_i$ are significantly different from zero at α=.05 level of significance for the above covariate. The remaining variables which were used in the univariate analysis are found to be non-significant. The estimated coefficients $\hat{\beta}_i$ for the final model, their standard error and odds ratios corresponding estimated coefficients $\hat{\beta}$ are given in table 4.9.

Table 4.9: Variables in the final model with 95% confidence interval

	B	S.E.	Wald	df	Sig.	Exp(B)	95.0% C.I.for EXP(B)	
							Lower	Upper
Age			*22.367*	*2*	*.000*			
Age(1)	-3.505	.856	16.755	1	.000	.030	.006	.161
Age(2)	-4.326	.995	18.904	1	.000	.013	.002	.093
ARTRe			19.090	3	.000			
ARTRe(1)	-4.392	1.489	8.706	1	.003	.012	.001	.229
ARTRe(2)	-3.405	1.618	4.427	1	.035	.033	.001	.792
ARTRe(3)	-.628	1.357	.214	1	.644	.534	.037	7.628
Constant	4.786	1.516	9.968	1	.002	119.771		

The interpretation of the above result is that when we consider the ART regimen, the chance of AZT-associated anemia increases with the increase of AZT-associated ART regimen.

That is, the higher the ART regimen with AZT the more the chance of being at risk of AZT-associated anemia. The result show that the odds of having AZT-associated anemia with 4a type is 98.8%lower than that of 4d type (reference category).

And also if we consider the patient age less than 5 years, the odds of having AZT-associated anemia is 97% lower than the above 7 years (reference category).

4.4 D4T Associated-Peripheral Neuropathy

4.4.1 Prevalence

Those who developed peripheral neuropathy after starting ART form 17(16.2%) of the total study group.

Table 4.10: Peripheral neuropathy after starting ART

Peripheral neuropathy	Number of patients	Percent
does not exist	88	83.8
Exist	17	16.2
Total	105	100.0

4.4.2 Univariate findings

In the case of d4T-associated peripheral neuropathy the result from univariate analysis using Pearson chi-square test indicates that the significant variables are age and sex. They have a very strong association with the occurrence of d4T-associated peripheral neuropathy as revealed by small P-values .013 and .014. The remaining variables except baseline CD4 count and WHO clinical stage are not significantly associated with the occurrence of d4T-associated peripheral neuropathy even at 25% level of significance. Table 4.11 summarizes the findings of the univariate analysis.

Table 4.11: Variables in the univariate analysis

Variables	Pearson chi-square	DF	P-value(Asymptotic)
Age	8.639	2	.013
Sex	6.031	1	.014
Baseline weight	3.595	3	.309
Baseline CD4 count	3.062	2	.216
WHO clinical stage	5.366	3	.147
ART regimen	2.819	3	.420

Again we used forward stepwise likelihood ratio method to select variables that affect d4T associated peripheral neuropathy in the multiple logistic regression analysis. From Table 4.11, the variables selected at 25% level for multiple logistic regression are age, sex, CD4 count and WHO clinical stage.

In the case of d4T-associated peripheral neuropathy, the variables that are found to be significant in the multiple logistic regression are sex, age and WHO clinical stage. This is also in agreement with the results we obtain from the univariate analysis. The values of the Wald statistic for the individual β coefficients support that they are significantly different from zero at α=.05 level of significance for variables sex, age and WHO clinical stage. The remaining variables which were used in univariate analysis are found to be non-significant. The estimated coefficients $\hat{\beta}_i$ for the covariates in the final model, their standard error and the odds ratio corresponding to each estimated coefficient $\hat{\beta}$ are given in table 4.12.

Table 4.12: Variables in the final model with 95% CI

	B	S.E.	Wald	df	Sig.	Exp(B)	95.0% C.I.for EXP(B)	
							Lower	Upper
Sex(1)	-1.671	.737	5.141	1	.023	.188	.044	.797
Age1			7.681	2	.021			
Age1(1)	-2.402	.867	7.673	1	.006	.091	.017	.495
Age1(2)	-.558	.722	.598	1	.440	.572	.139	2.357
WHocls			7.135	3	.006			
WHocls(1)	-1.431	1.094	1.710	1	.191	.239	.028	2.041
WHocls(2)	.137	1.092	.016	1	.900	1.147	.135	9.756
WHocls(3)	.744	1.026	.526	1	.468	2.105	.281	15.737
Constant	-.197	.918	.046	1	.830	.821		

The negative sign in column labeled' B' indicates inverse relationship of explanatory variable with the log odds of the dependent variable. In contrast the positive coefficient columns labeled 'B' indicate a direct relationship to the log odds of the dependent variable.

Interpretation: When we compare the sex of the patient, the odds of having d4T-associated peripheral neuropathy for the female is 81.2% lower than that of male patients. The risk of d4T-associated peripheral neuropathy is increasing with the increase of the age of the patient and the odds of having d4T-associated peripheral neuropathy for the age group below 5 years is 90.9% lower than that of age group above 7 years controlling for the variables in the model. Also when we consider WHO clinical stage, the odds of having d4T-associated peripheral neuropathy for WHO clinical stage I is 76.1% lower than the odds for WHO clinical stage IV (reference category).

4.5 NVP-associated skin rash

4.5.1 Prevalence

The magnitude of skin rash in the study is 19(18.1%). This shows patients taking NVP associated regimen have comparable risk of developing skin rash.

Table 4.13: Skin rash after started ART

Skin rash	Number of patients	Percent
does not exist	86	81.9
Exist	19	18.1
Total	105	100.0

4.5.2 Univariate Findings for Existence of Skin rash

Using Pearson chi-square test for the univariate analysis, the variables that are found to be significant are age (P-value=.000), baseline weight (P-value=0.014) and baseline CD4 count (P-value=.000). These variables show strong association with NVP-associated skin rash. Age, baseline weight and baseline CD4 count appear to be significant even if we use larger significance levels say 25%. The remaining three variables are not significant for the same significance level. Table 4.14 summarizes the findings of the uivariate analysis.

Table 4.14: Variables in the univariate analysis

Variables	Pearson chi-square	DF	P-value(Asymptotic)
Age	15.330	2	.000
Sex	.581	1	.446
Baseline weight	10.572	3	.014
Baseline CD4 count	19.121	2	.000
WHO clinical stage	2.909	3	.406
ART regimen	3.175	3	.365

4.5.3 Findings from the Multiple Logistic Regression

In the multiple logistic regression analysis of NVP-associated skin rash using forward stepwise likelihood ratio method, three of the six proposed variables age, baseline weight and baseline CD4 count are found to be significant.

The two variables that were found to be significant in the multiple logistic regression analysis of NVP-associated skin rash are age and baseline CD4 count. Once again this is in agreement with our results obtained from the univariate analysis above. The values of Wald statistic for individual β coefficients indicates that they are significantly different from zero at α=.05 level of significance for the two variables age, and baseline CD4 count. On the other hand, the remaining four variables are found to be non-significant. The estimated coefficient $\hat{\beta}_i$ for the covariates in the final model, their standard error and the odds ratio corresponding to each estimated coefficient $\hat{\beta}_i$ are given in the table 4.15.

Table 4.15: Variables in the Final model with 95% CI

	B	S.E.	Wald	df	Sig.	Exp(B)	95.0% C.I.for EXP(B)	
							Lower	Upper
Age1			11.337	2	.003			
Age1(1)	-2.142	.759	7.972	1	.005	.117	.027	.519
Age1(2)	-2.233	.879	6.452	1	.011	.107	.019	.600
BCD41			11.887	2	.003			
BCD41(1)	2.071	.870	5.672	1	.017	7.933	1.443	43.616
BCD41(2)	-1.046	1.288	.659	1	.417	.351	.028	4.388
Constant	-1.479	.781	3.584	1	.058	.228		

Children's age was significantly associated with the existence of skin rash. For patients whose age group is less than five years, the odds of having NVP-associated skin rash is 88.3% lower than the odds for children the age group of greater than seven years (reference category).

The ADR of skin rash was significantly associated with their baseline CD4 count at the start of ART. When we consider baseline CD4 count, the chance of being at risk of NVP-associated skin rash appears to decrease with increasing CD4 count at baseline. Patients whose CD4 count at the start of ART was less than 200ml/cells were 8 times more likely to have skin rash as compared to those with CD4 count greater than 350ml/cell controlling for the influence of other factors.

4.6 Assessment of Goodness of Fit of the Model

After fitting a logistic regression model, there are several techniques involved in assessing the appropriateness, adequacy and usefulness of the model. The Pearson's Chi-square, the likelihood ratio tests (LRT), Hosmer-Lemeshow goodness of fit test and the Wald tests are the most commonly used measures of goodness of fit for categorical data (Hosmer and Lemeshow, 2000).

4.6.1 Likelihood Ratio Test

The likelihood ratio test (G^2) is commonly used for assessing the overall fit of the logistic regression model. The likelihood-ratio test uses the ratio of the maximized value of the likelihood function for the full model (LL_F) over the maximized value of the likelihood function for the restricted (smaller) or intercept-only model (LL_R).

The natural log of the ratio of the likelihood functions is asymptotically distributed as chi-square with degree of freedom equal to the difference between the numbers of parameters estimated in the two models (Menard, 2002). It tests the null hypothesis that $\boldsymbol{\beta}=0$, where $\boldsymbol{\beta}= (\beta_1, \beta_2, ..., \beta_k)'$. The result presented in Table 4.16 shows that the likelihood ratio test statistic ($G^2=62.3199$) was significant for AZT-associated anemia at the 5% level. Thus, we reject the null hypothesis and we conclude that at least one of the predictors was significantly related with adverse drug reactions among HIV patients under ART.

Table 4.16: Overall Model Assessment Using Likelihood Ratio Test.

Model	-2 Log likelihood	Likelihood ratio	d.f	p-value
Intercept Only	139.551	62.3199	5	<.0001
Final	77.231			

4.6.2 Hosmer-Lemeshow Goodness of Fit Test

Hosmer and Lemeshow goodness-of-fit statistic measures the correspondence between the actual and predicted values of the dependent variable. Hosmer and Lemeshow Pearson chi-square statistic is used to test the overall model of goodness-of-fit test of the null hypothesis that the model adequately fit the data.

The result presented in Table 4.17 shows that the Hosmer-Lemeshow goodness-of-fit test statistic is not significant. Thus, we do not reject the null hypothesis, suggesting that the model fitted the data well.

The hypothesis to be tested is:

$\mathbf{H_O}$: Model fits the data versus $\mathbf{H_A}$: model does not fit the data.

Table 4.17: Hosmer-Lemeshow Goodness of fit Test

Chi-square	DF	Sig.
1.914	5	0.861

This shows that there is no sufficient evidence to reject the null hypothesis and it confirms that our model has a good fit.

4.6.3 Validations of predicted probabilities

Logistic regression predicts the logit of a limiting outcome from a set of predictors. Because the logit is the natural log of the odds, it can be transformed to the probability scale.

The resultant predicted probabilities can be revalidated with the actual outcome to determine if high probabilities are indeed associated with events and low probabilities with nonevents. An intuitively appealing way to summarize the results of a fitted logistic model is via a classification table. This table is the result of cross-classifying the outcome variable, Y, with a dichotomous variable whose values are derived from the estimated

logistic probabilities (Hosmer and Lemeshow, 2000). A classification table displays the tabulated cross-classifications of the observed category by the model-predicted category on the dependent variable and it is one way of assessing the goodness of fit of a model. A good model is the one that minimizes miss-classifications.

As shown in Table 4.18 the fitted model has an overall predictive accuracy of 80% with 76.9% of the Anemia does not exist group and 85% of the Anemia exist group being correctly classified and this may be considered sufficient.

Table 4.18: Classification Table of model with predictor variables

Observed		Predicted		
		Existence of Anemia		Percentage Correct
		does not exist	Exist	
Existence of Anemia	Does not exist	50	15	76.9
	Exist	6	34	85.0
Overall Percentage				80.0

By using the model chi-square goodness fit test, the Hosmer-Lemeshow test and the classification table, we can say the fitted model is statistically satisfactory.

4.7 Model Diagnostics for Existence of Anemia

In addition to global examination of a model, it is also useful to examine the characteristics of individual cases in our data set. We are concerned with cases that might unduly influence our parameter estimates. Cook's distance is one way of analyzing influence statistic in logistic regression, which a case has on the solution. This is the same statistic that is used as a measure of influence in multiple regression. However, the criteria for determining that a case is influential in logistic regression is differernt from the criteria in multiple regression. In logistic regression, a case is identified as influential if its Cook's distance is greater than one. This is based on a statement in Hosmer and Lemeshow(2000):" In our experience the influence diagnostic must be larger than 1.0 for individual covariate pattern to have an effected on the estimated coefficients." Since Cook's distances for each one of the observations in our data is less than one (see Table 4.19), we conclude that there are no influential observations.

Table 4.19: Cook's influence statistics

Mean	0
Mode	.001153
Minimum	.00016
Maximum	.95197

The residuals like, deviance and standardized residuals are all less than 3 in absolute value. The residuals less than 3 in absolute value show the absence of an outlier observation. The DFBETAs for model parameters (including the constant term) and Leverage Values (Hat Diag) were less 0.195 and 1 respectively. DFBETAs less than 0.195 imply an observation has no effect on the estimate of a regression coefficient while the leverage statistic less than one showed that no observation is far apart from the others in terms of the levels of the independent variables (not the dependent variable) (see Table 4. 20).

Table 4.20: Descriptive Statistics for Model diagnostics

Variables	N	Minimum	Maximum
Leverage value	105	.01109	.04494
Standard residual	105	-1.90430	2.54456
Deviance value	105	-1.79157	2.51222
DFBETA for constant	105	-.17785	.15589
DFBETA for Age1(1)	105	-.08882	.15724
DFBETA for Age1(2)	105	-.14563	.19840
DFBETA for ARTRe1(1)	105	-.18936	.14691
DFBETA for ARTRe1(2)	105	-.19099	.14406
DFBETA for ARTRe1(3)	105	-.18754	.14521

Thus, from the above goodness of fit tests and diagnostic checking, we can say that our model is adequate.

Using the same criteria of goodness of fit and model adequacy above, the other two models are also well fitted and adequate (see appendix B and C).

CHAPTER FIVE

5. DISCUSSION, CONCLUSION AND RECOMMENDATION

5.1 Discussion of Results

The results of the analysis presented in the study identified factors that are significantly associated with adverse drug reactions (i.e. existence of AZT-associated anemia, d4T-associated peripheral neuropathy and NVP-associated skin rash).

Most of the results obtained from the summary (descriptive statistics) match with the findings of multiple logistic regression analysis. For example, it showed that patients of the age group above 5 years who have taken ART were at higher risk of peripheral neuropathy.

In multiple logistic regression analysis, the variables age and ART regimen were found to significant factors affecting AZT-associated anemia. Patients of the age group below 5 years who have taken ART were at lower risk (odds ratio=.03) of anemia as compared to the age group of above 7 years of HIV/AIDS patients. The risk of developing peripheral neuropathy increases with the increase of the age of the patients. In other words the patients whose age was between 5 years and 7 years have about 42.8% higher risk of developing peripheral neuropathy as compared to patients whose age was below 5 years. This result is in agreement with the study done in Hawassa University (Erabo, 2012)

The variables age and baseline CD4 count were found to be significant for skin rash at 5% level of significance. When we consider baseline CD4 count, the chance of being at risk of skin rash appears to decrease when the baseline CD4 counts increases. In other words, patients who have CD4 counts below 200 ml/cells have about 8 times higher risk of skin rash as compared to patients whose baseline CD4 counts are between 200 ml/cells and 350 ml/cells. This result is in agreement with the study done in Addis Ababa University (Aklilu, 2010).

5.2 Conclusion

Severe adverse drug reactions are common resulting in an illness that affects the quality of life of patients and increasing the cost of health care system of the country; the commonest causes of ARV drug changes are severe ADRs. ART has brought significant result in restoring the depleted immunity, since the aim of ART is to improve the health of HIV-positive individuals.

The prevalence of AZT-associated anemia was found to be 41%. This indicates AZT-associated anemia was a significant problem in causing morbidity and increasing treatment cost. The risk of developing AZT-associated anemia was found to be higher among child patients that have started ART when they were under five years of age.

The prevalence of d4T-associated peripheral neuropathy was 15.2%. Generally, as the age increases the probability of developing d4T associated peripheral neuropathy increased and also the risk of developing d4T-associated peripheral neuropathy was found to be higher among the child patients that have started ART at WHO clinical stage III and the male patients have higher risk of developing d4T-associated neuropathy. Therefore, we can conclude that d4T-associated peripheral neuropathy causes significant problem in the quality of life of child patients.

The prevalence of NVP-associated skin rash was 18.1%. The risk of developing skin rash is associated with low age and low baseline CD4 count. From this we conclude that NVP-associated skin rash is causing a significant problem in child patients taking ART.

5.3 Recommendation

Most of the patients started taking ART late in the course of the disease. The current recommendation is that patients should start ART before the CD4 count goes below 200cells/ml. Early initiation of ART has long term clinical and economical benefits.

FMOH has to strengthen healthcare facilities in terms of infrastructure, human power and allocate adequate budget so that the affected people can have access to quality comprehensive HIV care, treatment and support services. FMOH and stakeholders should also have strict implementations of VCT, ART, PITC and PMTCT protocols to enhance early HIV screening and link of PLWHA with ART clinics.

This could be done by giving trainings to healthcare workers, designing appropriate work set up, performing routine monitoring and periodic evaluation of the program activity, boosting the moral of healthcare workers and giving recognition to all levels of front line healthcare workers who are working to their best in fight against HIV.

Severe adverse drug reactions are common in the study group. Methods should be devised to reduce the occurrence of ADR in HIV/AIDS in child patients. ARV treatment guidelines need to be revised regularly to include new, potent and less toxic drugs. DACA should strengthen the regular monitoring of ADRs especially those associated with ARVs.

AZT-associated anemia, d4T-associated peripheral neuropathy and lipodstrophy syndromes are significant problems. Therefore, it is better to substitute AZT and d4T by ABC and TDF as first line regimen.

FMOH in collaboration with DACA and other stakeholders need to support further studies on ADRs. In addition to this, healthcare provides should be trained and updates on appropriate selection of ARVs, early identification of ARV side effects timely substitution of offending drugs and management ADRs.

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APPENDIX

A. Existence of Anemia

Logistic regression analysis out put

Case Processing Summary

Unweighted Cases[a]		N	Percent
Selected Cases	Included in Analysis	105	100.0
	Missing Cases	0	.0
	Total	105	100.0
Unselected Cases		0	.0
Total		105	100.0

a. If weight is in effect, see classification table for the total number of cases.

Dependent Variable Encoding

Original Value	Internal Value
does not exist	0
Exist	1

Block 1: Method = Forward Stepwise (Likelihood Ratio)

Model Summary

Step	-2 Log likelihood	Cox & Snell R Square	Nagelkerke R Square
1	109.423[a]	.249	.339
2	77.231[b]	.448	.609

a. Estimation terminated at iteration number 4 because parameter estimates changed by less than .001.

b. Estimation terminated at iteration number 6 because parameter estimates changed by less than .001.

Categorical Variables Codings

		Frequency	Parameter coding		
			(1)	(2)	(3)
ART drug regimen 1	d4t-3TC-NVP	63	1.000	.000	.000
	d4t-3TC-EFV	14	.000	1.000	.000
	AZT-3TC-NVP	24	.000	.000	1.000
	AZT-3TC-EFV	4	.000	.000	.000
Weight category	Below 10 kg	18	1.000	.000	.000
	10 kg<=weight<20 kg	51	.000	1.000	.000
	20 kg<=weight<=30 kg	28	.000	.000	1.000
	Above 30 kg	8	.000	.000	.000
WHO clinical stage	I	23	1.000	.000	.000
	II	29	.000	1.000	.000
	III	42	.000	.000	1.000
	IV	11	.000	.000	.000
Age category	Below 5 years	39	1.000	.000	
	5<=years<=7	29	.000	1.000	
	Above 7 years	37	.000	.000	
Sex of the patient	Female	47	1.000		
	male	58	.000		

Hosmer and Lemeshow Test

Step	Chi-square	df	Sig.
1	.000	1	1.000
2	1.914	5	.861

Contingency Table for Hosmer and Lemeshow Test

		Existence of Anemia = does not exist		Existence of Anemia = Exist		Total
		Observed	Expected	Observed	Expected	
Step 1	1	24	24.000	5	5.000	29
	2	31	31.000	8	8.000	39
	3	10	10.000	27	27.000	37
Step 2	1	14	13.731	0	.269	14
	2	26	26.807	2	1.193	28
	3	10	10.388	4	3.612	14
	4	9	8.462	12	12.538	21
	5	5	3.857	6	7.143	11
	6	1	1.624	7	6.376	8
	7	0	.132	9	8.868	9

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95.0% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	Age1			25.580	2	.000			
	Age1(1)	-2.348	.542	18.730	1	.000	.096	.033	.277
	Age1(2)	-2.562	.615	17.331	1	.000	.077	.023	.258
	Constant	.993	.370	7.199	1	.007	2.700		
Step 2[b]	Age1			22.367	2	.000			
	Age1(1)	-3.505	.856	16.755	1	.000	.030	.006	.161
	Age1(2)	-4.326	.995	18.904	1	.000	.013	.002	.093
	ARTRe1			19.090	3	.000			
	ARTRe1(1)	-4.392	1.489	8.706	1	.003	.012	.001	.229
	ARTRe1(2)	-3.405	1.618	4.427	1	.035	.033	.001	.792
	ARTRe1(3)	-.628	1.357	.214	1	.644	.534	.037	7.628
	Constant	4.786	1.516	9.968	1	.002	119.771		

a. Variable(s) entered on step 1: Age1.

b. Variable(s) entered on step 2: ARTRe1.

Variables not in the Equation

			Score	df	Sig.
Step 1	Variables	Sex(1)	.220	1	.639
		Basew1	2.395	3	.495
		Basew1(1)	.751	1	.386
		Basew1(2)	.135	1	.713
		Basew1(3)	.208	1	.648
		WHocls	5.199	3	.158
		WHocls(1)	.904	1	.342
		WHocls(2)	1.851	1	.174
		WHocls(3)	5.061	1	.024
		ARTRe1	29.568	3	.000
		ARTRe1(1)	21.864	1	.000
		ARTRe1(2)	.062	1	.804
		ARTRe1(3)	21.055	1	.000
	Overall Statistics		32.381	10	.000
Step 2	Variables	Sex(1)	1.927	1	.165
		Basew1	.669	3	.880
		Basew1(1)	.142	1	.706
		Basew1(2)	.522	1	.470
		Basew1(3)	.071	1	.789
		WHocls	2.358	3	.501
		WHocls(1)	.281	1	.596
		WHocls(2)	1.222	1	.269
		WHocls(3)	1.143	1	.285
	Overall Statistics		6.183	7	.519

B. Existence of peripheral neuropathy

Dependent Variable Encoding

Original Value	Internal Value
does not exist	0
Exist	1

Categorical Variables Codings

		Frequency	Parameter coding		
			(1)	(2)	(3)
WHO clinical stage	I	23	1.000	.000	.000
	II	29	.000	1.000	.000
	III	42	.000	.000	1.000
	IV	11	.000	.000	.000
CD4 category	CD4 below 200	44	1.000	.000	
	200<=CD4<=350	39	.000	1.000	
	Above 350	22	.000	.000	
Age category	Below 5 years	39	1.000	.000	
	5<=years<=7	29	.000	1.000	
	Above 7 years	37	.000	.000	
Sex of the patient	Female	47	1.000		
	male	58	.000		

Model Summary

Step	-2 Log likelihood	Cox & Snell R Square	Nagelkerke R Square
1	84.080[a]	.081	.138
2	78.776[a]	.127	.216
3	70.196[a]	.195	.332

a. Estimation terminated at iteration number 6 because parameter estimates changed by less than .001.

Hosmer and Lemeshow Test

Step	Chi-square	df	Sig.
1	.000	1	1.000
2	3.321	4	.506
3	1.561	7	.980

Contingency Table for Hosmer and Lemeshow Test

		Existence of prepheral neuropathy = does not exist		Existence of prepheral neuropathy = Exist		
		Observed	Expected	Observed	Expected	Total
Step 1	1	37	37.000	2	2.000	39
	2	25	25.000	4	4.000	29
	3	26	26.000	11	11.000	37
Step 2	1	19	18.616	0	.384	19
	2	15	14.071	0	.929	15
	3	18	18.384	2	1.616	20
	4	10	11.314	3	1.686	13
	5	10	10.929	4	3.071	14
	6	16	14.686	8	9.314	24
Step 3	1	10	9.925	0	.075	10
	2	14	13.738	0	.262	14
	3	12	11.615	0	.385	12
	4	8	8.311	1	.689	9
	5	13	12.630	1	1.370	14
	6	8	8.618	2	1.382	10
	7	11	10.888	2	2.112	13
	8	6	6.645	4	3.355	10
	9	6	5.630	7	7.370	13

Observed			Predicted		
			Existence of prepheral neuropathy		
			does not exist	Exist	Percentage Correct
Step 1	Existence of prepheral neuropathy	does not exist	88	0	100.0
		Exist	17	0	
	Overall Percentage				83.8
Step 2	Existence of prepheral neuropathy	does not exist	88	0	100.0
		Exist	17	0	
	Overall Percentage				83.8
Step 3	Existence of prepheral neuropathy	does not exist	85	3	96.6
		Exist	13	4	23.5
	Overall Percentage				84.8

a. The cut value is .500

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95.0% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	Age1			7.266	2	.026			
	Age1(1)	-2.058	.810	6.450	1	.011	.128	.026	.625
	Age1(2)	-.972	.648	2.255	1	.133	.378	.106	1.346
	Constant	-.860	.360	5.720	1	.017	.423		
Step 2[b]	Age1			6.168	2	.046			
	Age1(1)	-1.976	.823	5.773	1	.016	.139	.028	.695
	Age1(2)	-.814	.669	1.482	1	.224	.443	.119	1.643
	Sex(1)	-1.448	.689	4.417	1	.036	.235	.061	.907
	Constant	-.455	.399	1.301	1	.254	.634		
Step 3[c]	Age1			7.681	2	.021			
	Age1(1)	-2.402	.867	7.673	1	.006	.091	.017	.495
	Age1(2)	-.558	.722	.598	1	.440	.572	.139	2.357
	Sex(1)	-1.671	.737	5.141	1	.023	.188	.044	.797

WHocls			7.135	3	.006			
WHocls(1)	-1.431	1.094	1.710	1	.191	.239	.028	2.041
WHocls(2)	.137	1.092	.016	1	.900	1.147	.135	9.756
WHocls(3)	.744	1.026	.526	1	.468	2.105	.281	15.737
Constant	-.197	.918	.046	1	.830	.821		

Variables not in the Equation

			Score	df	Sig.
Step 1	Variables	BCD41	4.909	2	.086
		BCD41(1)	4.146	1	.042
		BCD41(2)	3.904	1	.048
		Sex(1)	4.932	1	.026
		WHocls	7.286	3	.063
		WHocls(1)	.266	1	.606
		WHocls(2)	4.501	1	.034
		WHocls(3)	6.440	1	.011
	Overall Statistics		16.268	6	.012
Step 2	Variables	BCD41	5.294	2	.071
		BCD41(1)	3.523	1	.061
		BCD41(2)	4.826	1	.028
		WHocls	8.151	3	.043
		WHocls(1)	.350	1	.554
		WHocls(2)	5.087	1	.024
		WHocls(3)	7.110	1	.008
	Overall Statistics		12.575	5	.028
Step 3	Variables	BCD41	5.313	2	.070
		BCD41(1)	3.115	1	.078
		BCD41(2)	5.100	1	.024
	Overall Statistics		5.313	2	.070

Analog of Cook' influence statistics

N	Valid	105
	Missing	0
Mean		.1065067
Mode		.00229
Minimum		.00000
Maximum		.91724

Overall model assessment using likelihood ratio test for the existence of peripheral neuropathy.

	-2 Log likelihood	Likelihood ratio	d. f	p-value
Intercept Only	92.991	22.7952	6	.0009
Final	70.196			

Descriptive Statistics for Model diagnostics for Existence of peripheral neuropathy

Variables	N	Minimum	Maximum
Leverage value	105	.00524	.25130
Standard residual	105	-1.48115	2.32600
Deviance value	105	-1.41690	2.25537
DFBETA for constant	105	-.14801	.17808
DFBETA for Sex(1)	105	-.15240	.14777
DFBETA for Age1(1)	105	-.14199	.15550
DFBETA for Age1(2)	105	-.16783	.13791
DFBETA for WHocls(1)	105	-.18362	.14330
DFBETA for WHocls(2)	105	-.19230	.19176
DFBETA for WHocls(3)	105	-.17927	.14500

C .Existence of Skin rash

Case Processing Summary

Unweighted Cases[a]		N	Percent
Selected Cases	Included in Analysis	105	100.0
	Missing Cases	0	.0
	Total	105	100.0
Unselected Cases		0	.0
Total		105	100.0

a. If weight is in effect, see classification table for the total number of cases.

Dependent Variable Encoding

Original Value	Internal Value
does not exist	0
Exist	1

Categorical Variables Codings

			Parameter coding		
		Frequency	(1)	(2)	(3)
Weight category	Below 10 kg	18	1.000	.000	.000
	10 kg<=weight<20 kg	51	.000	1.000	.000
	20 kg<=weight<=30 kg	28	.000	.000	1.000
	Above 30 kg	8	.000	.000	.000
CD4 category	CD4 below 200	44	1.000	.000	
	200<=CD4<=350	39	.000	1.000	
	Above 350	22	.000	.000	
Age category	Below 5 years	39	1.000	.000	
	5<=years<=7	29	.000	1.000	
	Above 7 years	37	.000	.000	

Model Summary

Step	-2 Log likelihood	Cox & Snell R Square	Nagelkerke R Square
1	80.388[a]	.165	.269
2	67.065[a]	.264	.432

a. Estimation terminated at iteration number 6 because parameter estimates changed by less than .001.

Hosmer and Lemeshow Test

Step	Chi-square	df	Sig.
1	.000	1	1.000
2	8.448	6	.207

Contingency Table for Hosmer and Lemeshow Test

		Existence of skin rash = does not exist		Existence of skin rash = Exist		
		Observed	Expected	Observed	Expected	Total
Step 1	1	38	38.000	1	1.000	39
	2	20	20.000	2	2.000	22
	3	28	28.000	16	16.000	44
Step 2	1	13	13.881	1	.119	14
	2	15	14.860	0	.140	15
	3	13	12.670	0	.330	13
	4	10	9.259	0	.741	10
	5	10	9.215	1	1.785	11
	6	12	12.374	3	2.626	15
	7	7	7.330	2	1.670	9
	8	6	6.411	12	11.589	18

Classification Table[a]

Observed			Predicted		
			Existence of skin rash		Percentage Correct
			does not exist	Exist	
Step 1	Existence of skin rash	does not exist	86	0	100.0
		Exist	19	0	.0
	Overall Percentage				81.9
Step 2	Existence of skin rash	does not exist	80	6	93.0
		Exist	7	12	63.2
	Overall Percentage				87.6

a. The cut value is .500

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95.0% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	BCD41			11.822	2	.003			
	BCD41(1)	1.743	.805	4.687	1	.030	5.714	1.179	27.687
	BCD41(2)	-1.335	1.256	1.131	1	.288	.263	.022	3.083
	Constant	-2.303	.742	9.640	1	.002	.100		
Step 2[b]	Age1			11.337	2	.003			
	Age1(1)	-2.142	.759	7.972	1	.005	.117	.027	.519
	Age1(2)	-2.233	.879	6.452	1	.011	.107	.019	.600
	BCD41			11.887	2	.003			
	BCD41(1)	2.071	.870	5.672	1	.017	7.933	1.443	43.616
	BCD41(2)	-1.046	1.288	.659	1	.417	.351	.028	4.388
	Constant	-1.479	.781	3.584	1	.058	.228		

a. Variable(s) entered on step 1: BCD41.

b. Variable(s) entered on step 2: Age1.

DECLARIATION

I declare that this thesis is my original work and that all sources of materials used for this thesis has been duly acknowledged. This thesis has been submitted in partial fulfillments of the requirements for M.Sc. degree at Addis Ababa University.

Name: Eshetu Yoseph

Signature: _____

Date: 25/06/2013

This thesis has been submitted for examination with my approval as a university advisor

_____

Mekonnen Tadesse (Assistant professor)