ADDIS ABABA UNIVERSITY

OFFICE OF GRADUATE PROGRAMS

FACULTY OF SCIENCE

DEPARTMENT OF STATISTICS

Prevalence of ARV related adverse drug reactions among children taking HAART at Tikur Anbessa Specialized Hospital

BY

AKLILU YITBAREK

ADVISOR PROF. ESHETU WENCHEKO

A thesis submitted to the Department of Statistics of the Addis Ababa University in partial fulfillment of the requirements for the degree of Master of Science in Statistics

June, 2010

ADDIS ABABA UNIVERSITY

OFFICE OF GRADUATE PROGRAMS

FACULTY OF SCIENCE

DEPARTMENT OF STATISTICS

Prevalence of ARV related adverse drug reactions among children taking HAART at Tikur Anbessa Specialized Hospital

BY

AKLILU YITBAREK

Approved by the Board of Examiners:-

…….....	…….
Department head	Signature
……	……
Examiner	Signature
……...	……
Examiner	Signature

ACKNOWLEDGEMENT

It is my pleasure to express my appreciation to those who have influenced this work. My special gratitude goes to Professor Eshetu Wencheko for his encouragement, guidance and his kind correspondence up to the completion of this work.

I must thank the staff members of Tikur Anbessa Hospital ART Clinic. I also thank the Addis Ababa University for allowing me to join the postgraduate program and I am very grateful to the staff members of Department of Statistics for their cooperation especially Ato Mekonnen. Finally, I convey my thankful enjoyment to my family for the continuous encouragement in my studies.

ABSTRACT

Antiretroviral Treatment (ART), although not a cure, can help people from becoming ill for many years and this has improved the survival of HIV patients. In Ethiopia about 55,000 people and globally more than 1.3 million people have been taking ART until the end of 2006. Scaling up of ART treatment is planned by WHO and the Ministry of Health of the Ethiopian Government. Although ART treatment has decreased HIV associated mortality and morbidity, a number of patients still die after the start of ART. A total of 213 child patients have been considered from Tikur Anbessa Specialized Hospital ART clinic for the study. The analysis of the data using the binary logistic regression shows that AZT associated anemia, d4T associated peripheral neuropathy and NVP associated skin rash have influence on the survival of child patients. i.e. Child HIV patients under ART follow up has developed AZT associated anemia, D4T peripheral neuropathy and NVP associated skin rash. The study shows that adverse drug reaction has relation with Base Line Weight, Base Line CD4 Counts, WHO clinical stage, ART regimen and age.

TABLE OF CONTENT

LIST OF ABBREVIATIONS

ACTG	Aids clinical trial group
ABC	Abacavir
ADR	Adverse Drug Reaction
AIDS	Acquired Immune Deficiency Syndrome
ART	Antiretroviral Treatment
ARV	Antiretroviral
AZT	Azidothymidine
CD4	Cluster of differentiation 4
DACA	Drug Administration and Control Authority
D4T	Didehydro-deoxythymidine
EFV	Eferaphine
FHAPCO	Federal HIV/AIDS Prevention and Control Office
FMOH	Federal Ministry of Health
HAART	HIV/AIDS Anti Retroviral Treatment
Hb	Hemoglobin
HR	Hazard Ratio
MTCT	Mother to Child HIV Transmission
NVP	Nevraphine
PLWHA	People Living with HIV AIDS
PMTCT	Prevention of Mother to Child HIV Transmission
SJS	Stevens - Johnson syndrome
TDF	Tenofovir Disoproxil Fumarate
WHO	World Health Organization

MEDICAL WORDS DEFINITION

Cardiomyophaty	is a serious disease in which the heart muscle becomes inflamed and doesn't work as well as it should be.
Desqumative lesions	are clinical manifestations of several entities where histological alterations in the gingival basement membrane are frequent.
Erythematous	Abnormal redness of the skin due to local congestion
Hepatic steatosis	is a fatty liver collection of excessive amounts of triglycerides and other fats inside liver cells.
Maculopapular rash	a unique type of rash which is a flat, red area on the skin that is covered with small confluent bumps. It is a compound of the terms macule (spots) and papule (Bumps).
Mayophathy	is a disease or weakness of skeletal muscle which is not caused by nerve disorders.
Stevens - Johnson syndrome (SJS)	is a life threatening condition affecting the skin in which cell death causes the epidermis to separate from the dermis.

CHAPTER ONE

Introduction

1.1 Background

HIV/AIDS has created an enormous challenge to mankind since it became known in 1981. Close to 60 million people are infected out of which about 40 million are living with HIV/AIDS. There are more than 2.1 million children living with HIV/AIDS. Of these 90% live in sub-Saharan Africa. [1]

Ethiopia has an estimated population of 77 million people of whom 44% are children below 15 years. The adult prevalence of HIV is 10.5% in urban areas and 1.9% in rural areas with average prevalence 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 (HAART) by March 2008. This is less than 7% of the total eligible group [1]. More than 90% of children acquire the infection through mother-to-child HIV transmission (MTCT). Despite this, only 10% of HIV infected pregnant women are offered any form of prevention of mother-to-child HIV transmission (PMTCT) in Sub-Saharan countries. The Government of Ethiopia launched antiretroviral treatment in 2003 and free ART in 2005. By the end of March 2008 there were 97,000 adults and 4,800 children taking HAART.

The Federal HIV/AIDS prevention and Control Office (FHAPCO) working under the Federal Ministry of Health (FMOH) scaled up ART both in adults and children. In association with NGOs, the FHAPCO has implemented adult and child ART, PMTCT, counseling and testing, HIV surveillance and other preventive strategies. There are working guidelines developed for pediatric and adult ART, PMTCT and HIV counseling and testing.

The pediatric ART guidelines consist of specific ARV regimen for specific age groups who are eligible for treatment. The first line drugs used in children are presented below according to age group and history of PMTCT use for less than 1 year.

Children 1-3 years should take either of D4T + 3TC+NVP (FDC) or AZT+3TC+NVP.

Children three years and older should take D4T+3TC+NVP/EFV (FDC) or AZT+3TC+NVP/EFV.

Infants below one year with no PMTCT should take D4T+3TC+NVP (FDC) or AZT+3TC+NVP.

Infants below one year with PMTCT should take D4T+3TC+LPV/r or AZT+3TC+LPV/r.

Single drugs are substituted when severe toxicity is developed and the whole regimen will be switched when treatment failure is confirmed.

In resource rich settings HAART has changed the face of pediatric HIV. HIV infected children now survive to adolescence and adulthood. The experience in pediatric HIV/AIDS care treatment in Ethiopia is limited.

Developed countries and in some developing countries who have already implemented pediatric ART witnessed significant reduction of HIV-associated childhood morbidity and mortality. For a child it is extremely challenging to survive to adulthood. Poor drug adherence is one of the major reasons for treatment failure. Children depend on their parents and care-givers for appropriate drug administration which will be inconsistent due to care-taker fatigue. Moreover, there are no appropriate drug formulations which are supposed to be palatable and liquid for easy administration. At last but not least ARV related adverse drug reactions are frustrating and are reasons for drug discontinuation, drug changes, dropouts and treatment failure.

There are no data regarding the prevalence of ARV related adverse drug reactions among children taking HAART in Ethiopia. Data from developed countries are very limited.

Ample data are coming from adult HIV/AIDS patients but extrapolation into children is difficult as the two groups are different.

The aim of this study is to determine the prevalence of commonly encountered ARV related adverse drug reaction among children taking HAART. In 2005 there were about 1000 children enrolled in the Pediatric Infection Unit, Tikur Anbesa Specialized Hospital of the Faculty of Medicine, Addis Ababa University (FM-AAU). Out of these around 550 children already started ART. Free ART was launched in the Pediatric Department in January 2006 with manpower and infrastructural support from AAU, FMOH and NGOS.

Study design: It is a retrospective analysis conducted by collecting data from follow up charts of children taking HAART since January 2006.i.e. it is the analysis done solely based on the data.

Study Area: The study was being conducted in the Pediatrics and Child Health Department, Pediatrics Infection Sub unit, Tikur Anbesa Specialized Hospital, FM-AAU.

Study population: The study included all follow up charts and outpatient cards of Children taking HAART since Jan 2006.

The primary aim of the study is to analyze retrospectively the occurrence of anemia, skin rash and peripheral neuropathy in respect to each first line regimen by collecting data from charts of children taking HAART. The severity of the adverse effect will be determined by assessing whether drug change was made for severe toxicity. Moreover, reasons for drug change will be studied to see if drug change is because of adverse drug reaction, treatment failure, or other reasons. Besides, the association of ART regimen, age, gender, WHO clinical stage and CD4 with each specific adverse drug reaction will be studied.

The study shows secondary inputs like proportion of children in terms of age, gender, WHO clinical stage, average baseline CD4 count, average baseline weight and average increment of weight and CD4 count to evaluate the effectiveness of HAART.

Commonly encountered adverse drug reactions which are clinically detectable and could be supported with laboratory tests are chosen. Other adverse drug reactions which are difficult to document clinically or require sophisticated laboratory are left out.

1.2 STATEMENT OF THE PROBLEM

In spite of the fact that, ARV treatment has shown significant clinical importance by meeting the goal of the therapy, different types of antiretroviral adverse drug reactions occur commonly among patients taking ARV treatments. Some of the ARV adverse drug reactions occur early in the course of the therapy, others prevail late in the course of treatment. These antiretroviral adverse drugs reactions vary in their severity. A commonly cited cause of poor adherence to HAART is an adverse drug reaction. Short-term adverse effects are potential threats to successful introduction and maintenance of HAART. Although many factors may interfere with adherence to ARV therapy, adverse reactions to the medications are among the most important. In Ethiopia ARV treatment has been widely used over the last four years. Since then 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 Tikur Anbessa Specialized Hospital and children living with HIV/AIDS who have been transferred to Tikur Anbessa Specialized Hospital to continue ART treatment and regularly followed by ART physicians until June 2009.

1.3 Objectives

The general objective

The general objective of the study is to determine the prevalence of commonly encountered ARV related adverse drug reactions among children taking HAART from January 2006 to June 2009 in the Pediatrics Department, Tikur Anbessa Hospital, MF-AAU.

Specific Objectives

The specific objectives of the study are:

- to determine the prevalence of anemia, skin rash, 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, WHO clinical stage, and Cotrimoxazole use on the development of ARV related adverse drug reactions.

1.4 Possible application of the result

The outcome of the research may help health care workers to prescribe safe and effective regimen and also to anticipate and inform patients about the possible ARV adverse drug reaction they might encounter during ARV therapy. In addition, clinicians can decrease drug toxicity associated morbidity and mortality by early diagnosis and appropriate intervention.

Application of the result of the study may help to decrease hospital bed occupancy rate and treatment cost due to Adverse Drug Reaction (ADR). The result of the study may also enable healthcare providers and other concerned organizations especially DACA to enhance the awareness of the society about ARV adverse drug reactions and hence change the attitude of the public towards ARV drug use. It can also be used as a basis for revision of ART guidelines and as a source of information to other researchers in the future.

1.5 Definitions of some terms

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

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

Peripheral Neuropathy: the presence of documented persistent pain, numbness, tingling or burning sensation on the extremities or the presence of any documented peripheral neuropathy in the charts after started on ART.

Skin rash: the presence of documented generalized mildly itchy or non pruritic urticarial, erythematous or maculopapular rash, which may have vesicular lesion and desquamative lesions over the mucous membranes in severe cases, or the presence of documented skin rash after started on ART.

Prevalence of ADR: the proportions of patients experiencing the particular adverse drug reaction among those taking the incriminated ARV drug from the study group.

Age at the start of ART: the age of the patient in completed years documented on the patient follow up chart at the start of ART.

Baseline weight: weight in Kg documented on the date of initiation of ART.

Baseline CD4: the value of CD4 count done within one month before initiation of ART.

Baseline Hb: the value of Hb done within one month before initiation of ART.

Current Weight: the weight in Kg measured at the last visit of the patient prior to data collection.

Adult HIV/AIDS patients: HIV infected patient symptomatic or asymptomatic age 15 years and above.

Last CD4: the value of the last CD4 count done for the patient after started on ART prior to data collection.

Months on ART: The number of months the patient took ART from the time of initiation of ART till the end of June 2009.

AZT associated anemia: the presence of documented anemia on charts of patients after started AZT containing regimen.

D4T associated peripheral neuropathy: the presence of documented peripheral neuropathy on charts of patients after taking d4T containing regimen.

NVP associated skin rash: the presence of documented skin rash on charts of patients after taking NVP containing regimen.

Mild to moderate ADR: the presence of documented ADR on patient charts, which did not result in drug change.

Severe ADR: the presence of documented ADR on patient charts, which resulted in drug change.

CHAPTER TWO

LITRATURE REVIEW

2.1 Global overview of 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. [3] 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. [3] 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. [3]

Between 2001 and 2005, the number of people on antiretroviral therapy in low and middle-income countries increased more than fivefold from 240,000 to approximately 1.3 million. [3] As of June 2005 some 21 countries were providing antiretroviral to at least 50% of those in clinical need. [3] 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. [4, 1]

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 antiretrovirals by December 2005. [3] 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%. [3] Nearly 200 sites in Kenya were providing antiretrovirals by December 2005. [3] In South Africa the number of people receiving antiretrovirals grew from fewer than 5,000 at the beginning of 2004 to roughly 190,000 by the end of 2005. [3] Worldwide, it is estimated that between 250,000 and 350,000 deaths were averted in 2005 as a result of increased treatment access. [3]

2.2 National overview of PLWHA on ART

In 2005, it was estimated that 1.32 Million people live with HIV/AIDS in Ethiopia and 134,450 have already died of AIDS including 20,929 children. Currently, some 277,757 PLWHA including 213,306 adults are in need of Anti Retroviral Treatment (ART). [1]

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. [1]

Accordingly, the plan was to enroll 100,000 patients by the end of 2006[1]. Up to August 8, 2006, a total of 73,540 PLWHA were enrolled for HIV care out of which 45,595 had been started on ART at 132 facilities across the country. Of these, 35,460 are on treatment currently and the remaining 10,135 (22.2%) constitute lost to follow up, died and stopped treatment due to treatment failure or other problems. [1, 2] Of the people who ever started on ART, 47 % were adult males above 15 years of age, 48% were adult females above 15 years of age, and 5% were children.

2.3 Adverse drug reactions

The beneficial effects of drugs are coupled with the inescapable risk of untoward effects. The morbidity and mortality from these untoward effects often present diagnostic problems because they can involve every organ system of the body and are frequently mistaken for signs of underlying disease. Major advances in the investigation, development, and regulation of drugs ensure in most instances that drugs are uniform, effective and relatively safe and that their recognized hazards are publicized. However, prior to regulatory approval and marketing, new drugs are tested in relatively few patients who tend to be less sick and to have fewer concomitant diseases than those patients who subsequently receive the drug therapeutically. Because of the relatively small number of patients studied in clinical trials, and the selected nature of these patients, rare adverse effects may not be detected prior to the drugs approval and physicians need to be cautious in the prescription of new drugs and alert for the appearance of previously unrecognized adverse events.

Occasionally “adverse” effects may be exploited to develop an entirely new indication for a drug. Unwanted hair growth during minoxidil treatment of severely hypertensive patients lead to development of the drug for hair growth. Sildenafil was initially developed as an antianginal, but its effects to alleviate erectile dysfunction not only lead to a new drug indication but also to increased understanding of the role of type 5 phosphodiesterase in erectile tissue. This example further reinforces the concept that prescribers must remain vigilant to the possibility that unusual symptoms may reflect unappreciated drug effects.

Most adverse drug reactions are preventable, and recent studies using a system analysis approach suggest that the most common system failure associated with an adverse drug reaction is the failure to disseminate knowledge about drugs to individuals who prescribe and administer them. Most ADRs may be classified into groups. The most frequent ones result from exaggeration of an intended pharmacologic action of the drug, and the underlying mechanisms have been discussed above. Other adverse reactions ensue from toxic effects unrelated to the intended pharmacologic actions. The latter effects are often unpredictable and frequently severe, and result from recognized as well undiscovered mechanism.

The manifestations of drug-induced diseases frequently resemble those of other diseases. Recognition of the role of a drug or drugs in an illness depends on appreciation of the possible ADRs to drugs in any disease, on identification of the temporal relationship between drug administration and development of the illness, and on familiarity with the common manifestations of the drugs. Many associations between particular drugs and specific reactions have been described, but there is always a “first time” for a novel association, and any drug should be suspected of causing an adverse effect if the clinical setting is appropriated.

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 cardiac arrthymias 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. [5]

2.4 AZT associated anemia

Zudovudine (AZT; 3'-azido-2', 3'dideoxythymidine) was the first drug approved for the treatment of HIV infection and is the prototype nucleoside analogue. It inhibits the reverse transcriptase enzyme of the HIV virus. AZT also has a relatively high avidity for the DNA polymerase-γ of human mitochondria. This may contribute to the development of fatty liver and the myopathy sometimes observed in patients taking AZT. The clinical efficacy of AZT was clearly established in 1986 in phase II, randomized placebo-controlled trial. [5]

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. Some studies done abroad prevalence of AZT associated anemia is around 10%; the pathophysiologic mechanism being bone marrow toxicity. [6] There is one case report of AZT-induced pure red cell aplasia which occurred after 4 years of therapy with HAART from London's St Thomas' Hospital**.** [7]

2.5 D4T associated peripheral neuropathy

Stavudine (d4T; 2', 3'-didehydro-3'deoxythymidine) is the fourth drug licensed for the treatment of HIV infection. Peripheral neuropathy and hepatic steatosis are the main toxicities of stavudine. [11] Studies done in Africa have revealed that frequency of d4T associated peripheral neuropathy is around 5-15% the presumed cause is depletion of mitochondrial DNA. [8] [6] In one study 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%). In this study, the central role of d4T in the development of peripheral neuropathy is supported by the observed resolution on stopping this drug. [8]

2.6 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. [5]

In one study done in Africa NVP associated skin rash is about 17% and 7% of all patients required discontinuation of the drug.[6] 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. [6]

A study undertaken in Thailand 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. The risk factor assessment in the above mentioned study has revealed that being females with CD4 above 250, high BMI above 21.3 and a raise in CD4 above 53 cells/ml and an increase in alanine amino transferase at week four are risk factors for the development of NVP associated skin rash**.** [9]

In one case control and case cross over study on NVP and the risk of Stevens-Johnson syndrome or toxic epidermal necrolysis; from 18 HIV-1 infected patients who developed Stevens-Johnson syndrome or toxic epidermal necrolysis 15 had been exposed to nevirapine. The skin reaction began 10-240 days after the introduction of nevirapine (median, 12 days) and all patients had received escalating doses. In 10 patients, the reaction occurred with the initial dosage. In this study nevirapine was the only drug significantly associated with an increased risk of SJS or TEN in HIV-infected persons. Because of the severity of these reactions and the long elimination half-life of nevirapine, the researchers suggested discontinuation of the drug as soon as any eruption occurs. [10]

A study done in Western Australia about predisposition to nevirapine hypersensitivity suggest that HLA-DRB1*0101 and the CD4 status may determine susceptibility to

nevirapine hypersensitivity, consistent with a CD4 T-cell-dependent immune response to nevirapine-specific antigens.

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. [11]

2.7 Magnitude of ADRs of ARV drugs

Not surprisingly, adverse drug reactions are common. Most adverse drug reactions are relatively mild, and many disappear when the drug is stopped or the dose is changed. [12] Some gradually subside as the body adjusts to the drug. Other adverse drug reactions are more serious and last longer. Between 3% and 7% of hospital admissions in the United States are estimated to be for treatment of adverse drug reactions (12). Each time a person is hospitalized, the risk of having at least one adverse drug reaction is 10 to 20% [12].

A Meta-analysis of 39 prospective studies from US hospitals on the incidence of adverse drug reactions in hospitalized patients showed that the overall incidence of serious ADRs was 6.7% (95% confidence interval [CI], 5.2%-8.2%) and of fatal ADRs was 0.32% (95% CI, 0.23%-0.41%) of hospitalized patients [13]. Overall, 2216000 (1721000-2711000) hospitalized patients were estimated to have had serious ADRs and 106000 (76000-137000) to have had fatal ADRs in 1994, making these reactions between the fourth and sixth leading causes of death in the US [13].

Patients on HAART commonly suffer from side-effects [14, 15]. In Tororo, Uganda, among 1073 patients on d4T + 3TC + NVP, nearly 50% of the patients experienced some form of toxicity by 18 months. Toxicity requiring a change in therapy occurred in

21% of the cohort, most commonly a switch from d4T to AZT [11]. In Nairobi, Kenya, 284 patients received d4T + 3TC + NVP and the reported toxicity-free survival rate was 21% at 18 months. However, over 95% of patients remained on their original regimen despite these events [11]. In a report from Khayelitsha, South Africa on 1700 patients receiving ART, one agent was substituted in approximately 10% because of toxicity [16]. The rates were similar for d4T (8.5%), AZT (8.7%) and NVP (8.9%). Among the 1443 ART-naive patients who received regimens containing d4T or AZT in India, the most common toxicities were rash (66%), hepatotoxicity (27%) and anemia (23%) [17]. In Abidjan, Côte d'Ivoire, among 498 adults started on AZT + 3TC + EFV, 118 patients had grade 3/4 neutropenia and 23 had grade 3/4 anemia [18]. In a Swiss cohort of 1160 patients that received combination ARV therapy, 47% presented with clinical and 27% with laboratory adverse events attributed to anti retroviral drugs [19].

Side-effects are hard to avoid and can make life difficult. As a result, treatment of HIV infection has become a complicated balancing act between the benefits of durable HIV suppression and the risks of drug toxicity. In fact, side-effects are one of the main reasons why people living with HIV start missing doses of their medications or stop taking their drugs completely [20, 21, 19-21].

A study on adherence and interrelated factors of AIDS patients receiving antiretroviral treatment in Henan Province, China showed that the main reason (66.95%) for the patients' noncompliance is ART drug's side effects [22].All antiretroviral drugs can have both short-term and long-term adverse effects. The risk of specific side effects varies from drug to drug, from drug class to drug class, and from patient to patient [11,26]. A review on HIV and drug allergy showed that drug-related rashes have been estimated to be 100 times more common in HIV-positive patients than in the general population [23].

Analysis of 2,947 patients from US multi-centre HAART trials between 1996 and 2001 showed that severe or life-threatening side-effect (grade 4 adverse-event) was experienced by 675 individuals (11.4 cases per 100 person years) [24]. The cumulative percentage of patients with a severe or life-threatening side-effect at month twelve was

15.6%, at month 24, 23.7% and at month 36, 30.8%. Liver-related side-effects were the most frequently reported adverse events (148 patients, 2.6 per 100 person years) (24). The risk of severe or life-threatening side-effects, was found to be lower in younger patients (hazard ratio [HR] 0.83 for every decade in years, p=0.0001), and in patients who had never taken anti-HIV drugs before (HR=0.59, p=0.0001). The risks were increased for individuals with a history of injecting drug use (HR=1.41, p=0.0006), lower baseline CD4 cell count (for every 100 cells/mm3, HR=1.06, p=0.04), and with prior AIDS-defining illness (HR=1.22, p=0.03) (24). The investigators also found that women were at increased risk of experiencing severe or life-threatening neutropenia (HR= 1.76, p=0.03), whilst co-infection with hepatitis B (HR=5.97, p=0.0001) and hepatitis C (HR=2.74, p=0.009) were as well significantly associated with the risk of experiencing severe liver-related side-effects [24].

A review of data collected in the Italian post exposure prophylaxis (PEP) registry showed that the rates of side-effects were higher among females (67% vs 61%), among Protease Inhibitor (PI)-including post exposure prophylaxis (67.5% vs 57.3%), and among exposed as healthcare workers (70%) compared with 60% in exposed as safety/social workers, 53% sexual exposed route, 43% other [25].

Case study on the experience of the Khayelitsha programme in South Africa showed that most people tolerated the first-line regimen well [16]. Fourteen percent changed one of the ARV drugs because of either adverse events or a contraindication to treatment with that drug. The incidence of adverse events severe enough to require change in treatment was low, with 8% of patients needing to change an individual drug due to adverse events (usually attributed to either zidovudine or nevirapine) [16].

There is no study conducted to assess the magnitude of ADRs among AIDS patients on ART in Ethiopia. But few researches on areas of adherence have mentioned ADRs as a cause for non compliance. An assessment of adherence to antiretroviral therapy among 422 patients on ART in the hospital of the Ministry of National Defense Forces of Ethiopia showed that 221(54.0%) developed mild adverse drug reactions [28]. Another similar study showed that 22.6% had an adverse reaction to one or more of the ARVs

they were prescribed and 40% of those with adverse reaction to the ARVs had it in the first two weeks of the treatment, while the rest had it after two weeks with the treatment [26].

An evaluation of antiretroviral treatment conducted on thirty-three patients who were on triple ARV treatment at Hayat and Bethezatha hospitals also showed that, ten (30.3%) developed side effects of the drugs [27]. In that study, side effects of the drugs were the reason for change of the regimen in two patients and drug interruption in one patient.

The safety profile of ARV drugs and magnitude of ADRs among patients on ART in Ethiopia is virtually unknown. Nonetheless, patients on HAART suffer from ADRs. Several factors such as the sex of the patient, clinical condition, drug classes or agent used, pre-existing illness like liver dysfunction, are known to be associated with the occurrence, type and severity of ADRs among patients taking ART [29]. Thus, it is expected that these and other several unknown factors could also affect the prevalence of ADRs among patients taking ART.

CHAPTER THREE

3. Data and Methodology

3.1 The Data

This is a retrospective study which reviews the follow up charts of children taking HAART in Tikur Anbessa Hospital ART clinic. The clinic started its service in 2004. Currently three physicians, three nurses and three data clerks are attending HIV/AIDS patients regularly and filling the follow up charts.

The patient chart includes 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 use secondary data, which are collected from patient charts based on those variables to be considered in this study. The study include follow-up charts of all children living with HIV/AIDS who have been taking HAART regularly from January 2006 up to June 2009 in the Pediatric Department of Tikur Anbessa Specialized Hospital. This is the time frame when children initially enrolled and started HAART in the Pediatric Department up to the completion of data collection (June 2009).

3.2 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 between January 2006 and June 2009 in Pediatric Department –Tikur Anbessa 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

3.3 Methodology

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 from January 2006 to June 2009.

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 represents "failure". Just as we estimate the mean of a response variable when it is continuous, we would like to be able 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 [33].

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 [31].

3.3.3 The Logistic Function

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

$$p = \frac{e^{\alpha+\beta x}}{1+e^{\alpha+\beta x}}$$, where α=intercept and β=slope

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,

$$\ln[\frac{p}{1-p}] = \ln\left[e^{\alpha+\beta x}\right]$$

$$= \alpha + \beta x$$

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.

Instead of assuming that the relationship between p and x is linear, we assume that the relationship between $\ln[\frac{p}{1-p}]$ and x is linear. The technique of fitting a model of this form is known as logistic regression.

3.3.4 The Multiple Logistic Regression Model

Consider a collection of *k* explanatory variables which will be denoted by the vector

$\mathbf{X}' = (x_1, x_2, ..., x_n)$. 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(**X**)

$$p = \frac{e^{\alpha + \beta_1 x_1 + \ldots + \beta_k x_k}}{1 + e^{\alpha + \beta_1 x_1 + \ldots + \beta_k x_k}}$$

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

$$\ln\left[\frac{p}{1-p}\right] = \alpha + \beta_1 x_1 + \beta_2 x_2 + \ldots + \beta_k x_k$$

3.3.5 Fitting the Logistic Regression Model

Suppose we have a sample of *n* observations of the pairs (x_i, y_i) i = 1, 2,..., *n* where y_j denotes the value of dichotomous outcome variable and x_i is the value of the explanatory variable for the i^{th} subject. Fitting the model requires that we obtain estimates of the values of α and β_1 (represented by a vector **β′**).

In the linear regression the method used most often for estimating unknown parameters is the least squares. This method of estimation depends on the principle of obtaining those values of **β′** 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 the linear regression 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 [31].

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 the

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.

If Y is coded as zero or one then the expression for p(x) above provides (for an arbitrary value of $\boldsymbol{\beta}'$, the vector of parameters) the conditional probability that Y is equal to 1 given x (i.e., P(Y=1|x)). It follows that 1- p(x) gives the conditional probability that Y is equal to 0 given x, P(Y= 0|x). Thus, for those pairs (x_i, y_i), where y_i=1 the contribution to the likelihood function is p (x_i), and for those pairs where y_i=0 the contribution to likelihood function is 1-p (x_i), where the quantity p (x_i) denotes the value of p(x) computed at x_i. A convenient way to express the contribution to the likelihood function for the pair (x_i, y_i) is through the Bernoulli distribution,

$$\theta(x_i) = p(x_i)^{y_i}[1-p(x_i)]^{1-y_i} \text{ where } p(x_i) = \frac{e^{\alpha+\beta_1 x_i}}{1+e^{\alpha+\beta_1 x_i}}, \text{ i=1, 2,…, } n$$

Since the observations are assumed to be independent, the likelihood function is obtained as the product of the terms given in the above expression as follows:

$$L(\boldsymbol{\beta}) = \prod_{i=1}^{n} \theta(x_i) \text{ ----------(*)}$$

The principle of maximum likelihood states that we use as our estimate of β the value which maximizes the expression in equation (*). However, it is easier mathematically to work with the natural logarithm of equation (*),

$$L(\boldsymbol{\beta}) = \ln[l(\boldsymbol{\beta})] = \sum_{i=1}^{n} \{y_i \ln[p(x_i)] + (1-y_i)\ln[1-p(x_i)]\}.$$

To find the value of $\boldsymbol{\beta}$ that maximizes L ($\boldsymbol{\beta}$) we differentiate L ($\boldsymbol{\beta}$) with respect to α and $\boldsymbol{\beta}_1$ and set the resulting equation to zero.

These equations are as follows:

$$\sum_{i=1}^{n}[y_i - p(x_i)] = 0 \text{ ---------- (a) and}$$

$$\sum_{i=1}^{n} x_i[y_i - p(x_i)] = 0 \text{ ---------- (b)}$$

And these equations are called the likelihood equations. For logistic regression the expressions in (a) and (b) are non linear in α and β_1, and thus require special methods for their solution. These methods are iterative (like Newton-Raphson) in nature and have been programmed into available logistic regression packages like SPSS, STATA, SAS etc.

We can proceed to the multivariate case with the same steps followed in the univariate case above.

3.3.6 Model Building Strategies/Variable Selection

In modeling with many explanatory variables, one is usually concerned with the goal of selecting 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 in [31] 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 [31].

In general the following steps are recommended by [31] to aid in the selection of variables for a logistic regression. Firstly, the selection process should begin with univariate analysis of each variable. Secondly, selection of variables for the multivariate analysis will follow based on the results in the univariate analysis along with all variables of known biologic importance. Finally, the importance of each variable included in the multivariate 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 as they are available in different statistical software like SPSS and SAS.

3.3.7 Assessing the Fit of the Model

Once a model has been developed through the various steps indicated in the above section, we would like to know how effective the model is in describing the outcome variable. This is what is referred to as goodness-of-fit. We say our model fits well when summary measures of the distance between the observed response variable $Y' = (y_1, y_2, ..., y_n)$ and its fitted value $\hat{Y}' = (\hat{y}_1, \hat{y}_2, ..., \hat{y}_n)$ are small and the contribution of each pair $(y_i, \hat{y}_i)$, i= 1, 2, …, *n* to these summary measures is unsystematic and is small.

In testing the hypothesis that the model fits the data, the two common approaches are Pearson's X^2 statistic and the likelihood-ratio statistic(G^2) which are based on the comparison of the fitted and the observed counts. The large values of X^2 and G^2 indicate lack of fit of the model. When the fit is poor, residuals and other diagnostic measures describe the influence of individual observations on the model fit and highlight reasons for the inadequacy [32].

The likelihood-ratio statistic (G^2) is given by

$$G^2 = 2\sum\left[(Observed)\log\left(\frac{Observed}{Fitted}\right)\right] = -2\,LL_R - (-2LL_F) = -2\ln\left(\frac{likelhood_R}{likelhood_F}\right)$$

The likelihood ratio -2ln (likelihood R) for a restricted (smaller) model minus (-2 likelihood F) for a full (larger) model that is the same as the log of the ratio of the two likelihoods is distributed as chi-square. The full or larger model has all the parameters of interest in it. The restricted model is said to be nested in the larger model.

The restricted model has one or more of the parameters in the full model restricted to some value (usually zero). The parameters in the nested model must be a proper subset of the parameters in the full model. The chi-square is used to statistically test whether including a variable reduces the goodness- of-fit measure. This is analogous to producing an increment in R-square in hierarchical regression. If chi-square is significant, the variable is considered to be a significant predictor in the equation.

The Pearson's X^2 statistic is given by

$$X^2 = \sum\left[\frac{(Observed - Fitted)^2}{Fitted}\right] = \sum\left[\frac{(y_i - m_i\hat{p}_i)^2}{m_i\hat{p}_i(1-\hat{p}_i)}\right]$$

where m_i is number of subjects with $X=X_i$, $\hat{p}_i$ fitted probability and $\sum m_i = n$

The Hosmer-Lemeshow Test is another alternative to checking model fitness. This is based on the work of Hosmer and Lemeshow who proposed grouping based on the values of the estimated probabilities [31]. 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 2X'g table of observed and expected frequencies and is given as:

$$\hat{C} = \sum_{k=1}^{g} \frac{(o_k - \mathbf{n}'_k \overline{p}_k)^2}{\mathbf{n}'_k \overline{p}_k (1 - \overline{p}_k)}$$

where g is the number of groups, $\mathbf{n}'_k$ is the number of covariate patterns in the k^{th} group, $O_k = \sum_{j=1}^{n'_k} y_j$ the number of responses among the $\mathbf{n}'_k$ covariate patterns, and $\overline{p}_k = \sum_{j=1}^{n'_k} m_j \overline{p}_j / \mathbf{n}'_k$ the average estimated probability.

If the Hosmer-Lemeshow goodness-of-fit test statistic is greater than 0.5, 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. [31]

Finally, we conclude our discussion of model assessment by giving a diagnostic check for the significance of individual model estimates - 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 $\boldsymbol{\beta}_i = 0$ against $\boldsymbol{\beta}_i \neq 0$. For a dichotomous response variable the Wald statistic (W), is the squared ratio of the unstandardized logit coefficient to its standard error, that is,

$$W = Z^2 = \frac{\hat{\beta}_i^{\,2}}{\text{var}(\hat{\beta}_i)}$$

W has χ^2 distribution with one degree of freedom.

3.3.8 Interaction

In statistics, **interaction** is often used with a more restricted meaning than in general usage: specifically it means not only that effects of various changes operate simultaneously, but that their result is not additive.[35] An **interaction variable** is a variable constructed from an original set of variables to try to represent either all of the interaction present or some part of it. In exploratory statistical analyses it is common to use products of original variables as the basis of testing whether interaction is present with the possibility of substituting other more realistic interaction variables at a later stage. When there are more than two explanatory variables, several interaction variables are constructed, with pairwise-products representing pairwise-interactions and higher order products representing higher order interactions.

The notion of "interaction" is closely related to that of "moderation": the interaction between an explanatory variable and an environmental variable might lead to one saying that the effect of the explanatory variable has been moderated or modified by the environmental variable. [35]

The concept of homogeneity of regression coefficients is related to the concept of interaction between factors. Regression lines with equal slopes are parallel to one another, which means that there is no interaction between the factors involved. The two procedures that are commonly used for the specification of an appropriate functional form between a dependent variable and one or more independent variables are:-

a) The scatter diagram technique which is used primarily for the case of one independent variable (i.e. the simple regression).
b) The ANOVA technique is used primarily for the specification of interaction terms in multiple regressions. Let $y=\ln (p/1-p) = \alpha+\beta_1x_1 +\beta_2x_2+\beta_3x_3 +\beta_4x_1x_2 +\beta_5x_1x_3+\beta_6x_2x_3$. where, y is the variable of interest and $(x_1,x_2 ,x_3,)$ are the factors being tested. (35)

3.3.9 <u>Assumptions regarding the logistic regression model</u>

As indicated in the previous sections, one advantage of the logistic regression is 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 [30]:

1. 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, and to code its correlates also as +1 to assure positive correlation. For multinomial logistic regression, the class of greatest interest should be the last class. Logistic regression is predicting the log odds of being in the class of greatest interest.
2. 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.
3. 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.
4. 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.

CHAPTER FOUR

4. Data analysis, Result and Discussion

4.1. Introduction

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

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

The data analysis started by giving the summary statistics for the variables considered in the study, then proceed to the univariate analysis and complete the final model in the multivariate analysis.

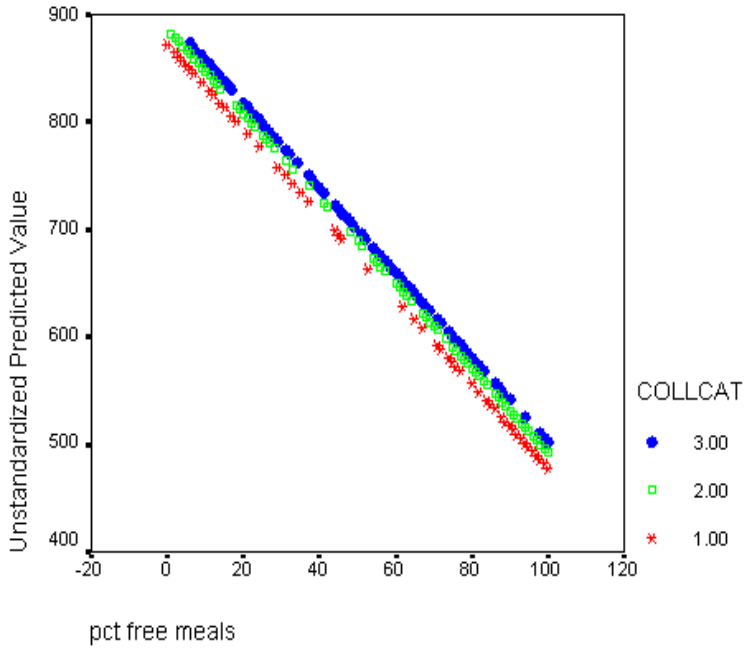
Interaction

In this study the interaction terms are assumed to be parallel or No interactions exists between variables because of three important reasons. Primarily, the natures of child patients hinder the interaction study as the children experience huge amount of physiological and psychological factors. Besides ART clinicians cannot trace back to the children's background before the child patients started the treatment. Secondly, the clinical trials involve relatively a small number of patients. Thirdly, adverse effect interactions are proven to be very difficult after the drugs are tried. According to the study, a lot of unrecognized effects are anticipated which are directly or indirectly related to the drug tasted. [5]

Coefficients

Covariates	Unstandardized Coefficients		t	Sig
	B	Std.Error		
(Constant)	8.33	4.01	0.745	0.50
WHO Clinical Stage	14.015	7.628	1.837	0.01
Age	17.233	6.581	2.618	0.001
Sex	-3.943	0.099	-39.892	0.00
WHO clinical stage X age	-.2.5	1.05	0.43	0.12
WHO clinical stage X Sex	16.000	5.001		0.215
Age X Sex	-0.243	0.376		0.518

Graphing the regression lines for each of the levels of **out put**



Regression lines are:

1= WHO Clinical Stage

2= Age

3= Sex

Pct free meals are the levels of output.

4.2. Summary statistics

4.2.1. Gender

There were 213 child patients on ARV treatment. From these 143 (67%) are females and 70 (33%) are males.

Table 1: Sex of patient

Sex	Frequency	Percent
Female	143	67
Male	70	33

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

4.2.2 Duration of ART therapy

The duration in which child patients are on ART ranges from 0 to 92 weeks. In the study group the majority of child patients, 172(81%) have been attending ART for less than two years; 30(14%) took ART medication for less than 6 weeks, 46 (22%) took ART from 7 to 12 weeks, 96 (45%) took from 13 to 24 weeks and others took for more than 24 weeks. The majority of child patients, 172(81%) have been on ART for less than two years due to late initiation of ART nationally. ART was launched in Ethiopia at the end 2003 but patient enrollment was very poor as the drug was not given freely for those who cannot bring testimonials from their 'Kebeles'. However, free ART program was launched in January, 2005 after which the majority of patients were enrolled in chronic HIV care. [29]

Table 2: Categorized duration of ART (in weeks)

Categorized months on ART	No of patients	Percent
Less than 6 weeks	30	14
7 to 12 weeks	46	22
13 to24 weeks	96	45
25 to 36 weeks	26	12
Above 36 weeks	15	7
Total	213	100

4.2.3. Weight

Baseline weight ranges from 3 Kg to 28 Kg. The mean baseline weight is 14.7Kg for the total study group. The average baseline weight for females is 11.3 Kg and 19.2kg for males. Most of patients 177 (83%) had baseline weight less than or equal to 20 kg.

Table 3: Categorized baseline weight

Wt	No of patients	Percent
wt <= 3 kg	26	12.2
3<Wt<=10 kg	78	36.6
10<Wt<=20 kg	73	34.3
Above 20 kg	36	16.9
Total	213	100

4.2.4. WHO Clinical Stage

Most of the cases 136 (63.7%) belong to WHO clinical stage III and 40 (18.6%) are in the WHO clinical stage IV during initiation of ART. This shows that larger number of patients started ART treatment late in the course of the disease, which is at WHO clinical stage III.

Table 4: WHO clinical stage

WHO clinical stage	No of patients	Percent
Stage (I)	6	2.8
Stage (II)	32	14.9
Stage (III)	136	63.7
Stage (IV)	40	18.6
Total	213	100

4.2.5. CD4

The count CD4 ranges from 01 to 596 cells /ml. The mean baseline CD4 is 131 cells/ml. Most of the cases (81.9%) started ART at baseline CD4 count below 200 out of which (41%) started ART at baseline CD4 count less than 100cells/ml and (40.9%) started at CD4 count between 101 to 200 cells/ml. Those who started ART treatment at CD4 count range between 201-350 cells/ml are (15.2%). This shows that most of child patients started ART late in the course of the disease.

Table 5: Categorized Baseline CD4

Baseline CD4	No of patients	Percent
CD4 <= 100	89	41.8
100<CD4 <= 200	88	41.3
200<CD4 <= 350	32	15
350<CD4 <= 500	3	1.4
CD4 above 500	1	0.5
Total	213	100

4.2.6. ART Regimen and Drug changes

The data show that 61 (28.6%) started with **1a30** regimen, 20 (9.4%) started with **1a40**, 42 (19.7%) started with **1b30,** 7 (3.3%) started with **1b40**, 41 (19.2%) with **1c** and 42 (19.7%) with

1d. 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, hepatotoxicity and interaction with anti Tb drugs. Moreover **EFV** is more potent than **NVP** and it is taken once daily thereby decreasing pill burden. The preference of d4T over **AZT** is still maintained as most of patients have low baseline Hb value. However, aggregate data have shown that **AZT** is more potent than **d4T**. In developed countries where there are more ARV drug options, **TDF** and **ABC** are preferred than **AZT** and **d4T** as the first two drugs are more potent, less toxic and have low pill burden. [34]

Table 6: Regimen at the start of ART

Regimen	No of patients	Percent
1a 30	61	28.6
1a 40	20	9.4
1b 30	42	19.7
1b 40	7	3.3
1c	41	19.2
1d	42	19.7
Total	213	100

4.3. AZT associated anemia

4.3.1 Prevalence In the study group the occurrence of anemia after having started ART is 88 (41.3%). Among those who have been taking AZT containing regimen 77(87.5%) and among those who have been taking d4T containing regimen 11(12.5%) developed anemia. Among patients who developed AZT associated anemia 51(66.2%) have Hb value less than or equal to 6.5gm/dl, 9(11.7%) have Hb value between 6.6 to 7.1gm/dl, 8(10.4%) have Hb between 7.2 to 8 gm/dl and 9 (11.7%) have Hb value above 8gm/dl at the time of detection of anemia. Among

patients who developed D4T associated anemia 1(9.1%) has Hb value less than or equal to 6.5gm/dl, 7 (63.6) have Hb value between 7.2 to 8 gm/dl and 3 (27.3) have Hb value above 8gm/dl. This shows that most of cases of AZT associated anemia are grade IV according to ACTG (AIDS clinical trial group) ADR grading.

Table 7: Hb value at the time of detection of anemia

Regimen	Hb (gm/dl)	No of patients	Percent
AZT	0<=Hb<=6.5	51	66.2
	6.6<=Hb<=7.1	9	11.7
	7.2<=Hb<=8	8	10.4
	8<Hb<=10	9	11.7
	Sub total	77	100
D4T	0<=Hb<=6.5	1	9.1
	6.6<=Hb<=7.1	0	0
	7.2<=Hb<=8	7	63.6
	8<Hb<=10	3	27.3
	Sub total	11	100
	Grand total	88	

4.3.2 Average time of detection

Most cases of AZT associated anemia 68 (88.4%) has occurred within six months of initiation of HAART, 23 (29.9%) cases of anemia occurred within two months, 29 (37.7%) cases occurred between two to four months and 16(20.8%) cases have occurred between four to six months.

Table 8: Time of detection of anemia after having started on ART

Time of detection	No of patients	Percent
Weeks < = 8	23	29.9
Weeks 9 to 16	29	37.7
Weeks 17 to 24	16	20.8
Longer than 24 weeks	9	11.7
Total	77	100.0

4.3.3 Drug change

The patients who changed drug due to anemia are those who were taking AZT regimens. Among 77 patients who developed AZT associated anemia, 68 (88.3%) cases required drug substitution to d4T or TDF. These is due to the development of sever anemia. From those who required drug substitution 45(66.3%) drug changes occurred in less than 5 months of ARV treatment. Among 11 patients who have developed anemia while taking d4T containing regimen, there is no documented drug substitution. From the 77 patients who developed AZT associated anemia 36 were females and 41 are males. This shows drug change occurs due to the development of sever AZT associated anemia, which is an adverse drug reaction. The average time of detection of AZT associated anemia is 18 weeks.

Table 9: Drug change secondary to Anemia

Drug change	**No of patients**	**Percent**
Yes	68	88.3
No	9	11.7
Total	77	100.0

4.3.4 Univariate Findings

In univariate analysis, using the Pearson chi-square test, the variable that is found to be significant is WHO Clinical Stage. The remaining variables appear to be non significant even at 25% level of significance.

Thus strong association (at α=0.05 level of significance) of AZT associated anemia is depicted (in univariate case) for WHO Clinical Stage. Table 10 summarizes the findings of the univarite analysis.

Table 10 Variables in the univariate analysis

Variable	Pearson chi-square	DF	P-value (Asymptotic)
Age	2.231	3	.526
Sex	0.369	1	.543
Baseline Weight	3.254	4	.516
Baseline CD4 Count	0.432	1	.514
WHO Clinical Stage	11.313	3	.010
Art regimen	1.342	3	.511

4.3.5 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 the multiple logistic regression analysis. Forward stepwise likelihood ratio method is used to select variables. To facilitate computation and interpretation, the coding scheme used in SPSS is given below in Table 11.

Table 11: Categorical Variables Coding

Variables selected		No of patients	Parameter coding (1)	(2)	(3)	(4)
categorized base WT	wt <= 4 kg	10	1	0	0	0
	4<wt <= 5 kg	58	0	1	0	0
	5<wt <= 6 kg	77	0	0	1	0
	6<wt <= 7 kg	42	0	0	0	1
	above 7 kg	25	0	0	0	0
categorized age	less than 3 years	69	1	0	0	
	3 to 4 years	91	0	1	0	
	4 to 5 years	38	0	0	1	
	above 5 years	15	0	0	0	
WHO clinical stage	Stage(I)	4	1	0	0	
	Stage(II)	37	0	1	0	
	Stage(III)	140	0	0	1	
	Stage(IV)	32	0	0	0	
Baseline CD4	CD4<=200	174	1			
	CD4 above 200	39	0			
Sex of patient	Female	106	1			
	Male	107	0			
Art regimen	1a30 and 1a40	81	1	0	0	
	1b30 and 1b40	49	0	1	0	
	1c	41	0	0	1	
	1d	42	0	0	0	

The variable that is found to be significant in the multiple logistic regression analysis is WHO Clinical Stage and this is in effect in line with the results obtained from the univariate analysis. The values of the Wald statistic for individual β coefficients support that the estimated values ($\hat{\beta}_i's$) are significantly different from zero at $\alpha=0.05$ 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 ($\hat{\beta}_i's$) for the covariates in the final model, their standard error and the odds ratio corresponding each estimated coefficient ($\hat{\beta}_i$) are given in Table 12.

Table 12: Variables in the final model with 95% confidence interval

							95% Confidence Interval	
Covariates	$\hat{\beta}$	**S.E.**	**Wald**	**DF**	**Sig.**	Exp($\hat{\beta}$)	**lower Bound**	**Upper Bound**
WHO stage	0.432	0.220	8.909	3	0.031			
WHO stage(1)	-19.447	10377.78	0	1	0.999	0.002	-11.897	54.46
WHO stage(2)	-1.415	0.485	8.507	1	0.004	0.243	-4.443	6.569
WHO stage(3)	-0.535	0.288	3.452	1	0.063	0.586	-2.675	4.765
Constant	-1.756	0.248	49.96	1	0	0.173	-3.731	2.928

The interpretation of the above result is that when we consider the WHO clinical stage, the chance of occurrence of AZT associated anemia increases with the severity of illness. That is, the higher the WHO clinical stage the more the chance of being at risk of AZT-associated anemia.

4.4. D4T associated peripheral neuropathy

4.4.1 Prevalence Those who developed peripheral neuropathy after starting ART are 17 (8%) of the total study group.

Table 13: Peripheral neuropathy after starting ART

Peripheral neuropathy	No of patients	Percent
YES	17	8
NO	196	92
Total	213	100.0

4.4.2 Univariate Findings

In the case of d4T associated peripheral neuropathy, the results from univariate analysis using Pearson chi-square test indicate that the only significant variable is Age. It has a very strong association with the occurrence of d4T-associated peripheral neuropathy as revealed by the small p-value of 0.001.The remaining five variables are not significantly associated with the occurrence of d4T associated peripheral neuropathy even at 25% level of significance. Table 14 summarizes the findings of the univarite analysis.

Table 14: Variables in the univarite analysis

Variable	Pearson chi-square	DF	P-value (Assymptotic)
Age	15.546	3	.001
Sex	1.009	1	.315
Baseline Weight	2.426	2	.297
Baseline CD4 Count	0.094	1	.760
WHO Clinical Stage	1.171	3	.279
Art regimen	0.082	3	.772

Again we used forward stepwise likelihood ratio method to select variables that affect d4T associated peripheral neuropathy in the multiple logistic regression analysis. The coding scheme used in SPSS for this analysis is given below in Table 15.

Table 15 Categorical Variables coding

Variables selected		No of patients	Parameter coding (1)	(2)	(3)	(4)
categorized base WT	wt <= 4 kg	17	1	0	0	0
	4<wt <= 5 kg	80	0	1	0	0
	5<wt <= 6 kg	71	0	0	1	0
	6<wt <= 7 kg	35	0	0	0	1
	above 7 kg	10	0	0	0	0
categorized age	less than 3 years	85	1	0	0	0
	3 to 4 years	87	0	1	0	0
	4 to 5 years	31	0	0	1	0
	above 5 years	10	0	0	0	0
WHO clinical stage	Stage(I)	4	1	0	0	0
	Stage(II)	32	0	1	0	0
	Stage(III)	147	0	0	1	0
	Stage(IV)	30	0	0	0	0
Baseline CD4	CD4<=200	174	1			
	CD4 above 200	39	0			
Sex of patient	Female	106	1			
	Male	107	0			
Art regimen	1a30 and 1a40	81	1	0	0	
	1b30 and 1b40	49	0	1	0	
	1c	41	0	0	1	
	1d	42	0	0	0	

In the case of d4T associated peripheral neuropathy, the variable that is found to be significant in the multiple logistic regression analysis is "categorized age". This is also in agreement with the results we obtained from the univariate analysis. The values of the Wald statistic for individual β coefficients support that the estimated values ($\hat{\beta}_i's$) are significantly different from zero at an α=0.05 level of significance for the variable "categorized age". The remaining variables which were used in the univariate analysis are found to be non significant. The estimated coefficients ($\hat{\beta}_i's$) for the covariates in the final model, their standard error and the odds ratio corresponding each estimated coefficient ($\hat{\beta}_i$) are given below in Table 16.

Table 16 Variables in the Final Model with 95%CI

							95% Confidence Interval	
Covariates	$\hat{\beta}$	**S.E.**	**Wald**	**DF**	**Sig.**	$Exp(\hat{\beta})$	**lower Bound**	**Upper Bound**
Categorized age	0.402	0.210	14.984	3	0.002			
Categorized age(1)	-1.066	0.36	8.746	1	0.003	0.345	-3.768	4.908
Categorized age(2)	-0.511	0.346	2.188	1	0.139	0.6	-1.5	5.87
Categorized age(3)	-0.243	0.376	0.419	1	0.518	0.784	-1	4.002
Constant	-1.485	0.32	21.588	1	0	0.226	-7.863	3.876

Interpretation When compared to the reference category (i.e. age> 5 years) the above table depicts the older the child the more the chance of being at risk of d4t associated peripheral neuropathy.

4.5 NVP associated skin rash

4.5.1 Prevalence

The magnitude of skin rash in the study group is 17 (8%). This shows patients taking NVP have comparable risk of developing skin rash.

Table 17: Skin rash after started on ART

Skin rash	No of patients	Percent
YES	17	8
NO	196	92
Total	213	100

4.5.2 Univariate Findings

Using Pearson chi-square test for the univariate analysis, the variables that are found to be significant are Sex and Baseline CD4. Sex (p-value=0.000) and Baseline CD4 (p-value=0.026) show very strong association with NVP-associated skin rash. Baseline weight and ART regimen appear to be significant if we use larger significant levels say 25%, the remaining two variables are not significant for the same significance level. Table 18 summarizes the findings of the univarite analysis.

Table 18. Variables in the univariate analysis

Variable	Pearson chi-square	DF	P-value (Assymptotic)
Age	2.406	3	.492
Sex	12.518	1	.000
Baseline Weight	6.543	4	.162
Baseline CD4 Count	7.265	2	.026
WHO Clinical Stage	0 .671	1	.413
Art regimen	5.234	3	.143

4.5.3 Findings from the multiple Logistic Regressions

In the multiple logistic regression analysis of NVP-Associated skin rash using forward stepwise likelihood ratio method, two of the six proposed variables are found to be significant. Table 19 below shows the coding scheme used in SPSS to facilitate computation and interpretation.

Table 19 Categorical variable Coding

Variables selected		No of patients	Parameter coding (1)	(2)	(3)	(4)
categorized base WT	wt <= 4 kg	15	1	0	0	0
	4<wt <= 5 kg	70	0	1	0	0
	5<wt <= 6 kg	74	0	0	1	0
	6<wt <= 7 kg	36	0	0	0	1
	above 7 kg	18	0	0	0	0
categorized age	less than 3 years	85	1	0	0	
	3 to 4 years	86	0	1	0	
	4 to 5 years	31	0	0	1	
	above 5 years	11	0	0	0	
WHO clinical stage	Stage(I)	6	1	0	0	
	Stage(II)	40	0	1	0	
	Stage(III)	140	0	0	1	
	Stage(IV)	27	0	0	0	
Baseline CD4	CD4<=200	174	1			
	CD4 above 200	39	0			
Sex of patient	Female	106	1			
	Male	107	0			
Art regimen	1a30 and 1a40	81	1	0	0	
	1b30 and 1b40	49	0	1	0	
	1c	41	0	0	1	
	1d	42	0	0	0	

The two variables that are found to be significant in the multiple logistic regression analysis of NVP-associated skin rash are sex and baseline CD4. Once again this is in agreement with our results obtained from the univariate analysis above. The values of the Wald statistic for individual β coefficients support that the estimated values ($\hat{\beta}_i's$) are significantly different from zero at α=0.05 level of significance for the two variables (sex and baseline CD4). On the other hand, the remaining four variables which were used in the univariate analysis are found to be non significant. The estimated coefficients ($\hat{\beta}_i's$) for the covariates in the final model, their standard error and the odds ratio corresponding each estimated coefficient ($\hat{\beta}_i$) are given in Table 20.

Table 20: Variables in the Final Model with 95%CI

							95% Confidence Interval	
Covariates	$\hat{\beta}$	**S.E.**	**Wald**	**DF**	**Sig.**	Exp($\hat{\beta}$)	**lower Bound**	**Upper Bound**
Sex(1)	0.797	0.228	12.281	1	0	2.22	-1.567	5.901
BaselineCD4			7.24	2	0.027			
BaselineCD4(1)	-0.187	0.267	0.493	1	0.482	0.829	-2.267	4.864
BaselineCD4(2)	-0.671	0.277	5.873	1	0.015	0.511	-1.769	5.78
Constant	-2.517	0.283	79.168	1	0	0.081	-5.431	7.773

4.6 Interpretation

The chance of being at risk of NVP-associated skin rash is high for females. It is about double for females compared to males (odds ratio=2.220). When we consider baseline CD4, the chance of being at risk of NVP-associated skin rash appears to decrease with increasing CD4 counts at baseline. Compared to the reference category (Baseline CD4 counts above 200), patients with CD4 counts 100 or less are about 17% less likely to be at risk of NVP-associated skin rash. In the same way, those patients with CD4 counts between 101 and 200 have about 49% lower risk of being at risk of NVP-associated skin rash.

4.7 Model diagnostic

The value of the Hosmer-Lemeshow Chi-Square goodness-of-fit statistic computed from the data is 11.6. And the corresponding p-value computed from the chi-square distribution is 0.82 at 5% level of significance. This indicates that there is no significant difference between observed and model predicted values, implying the model fits the data well.

CHAPTER FIVE

5. Conclusions and Recommendations

5.1 Conclusions

Severe adverse drug reactions are common resulting in an illness that affects the quality of life of patients and increasing the cost of healthcare system of the country; the commonest causes of ARV drug changes are severe ADRs.

ART has brought significant result in restoring the depleted immunity. The mean count for last CD4 i.e. (The number of CD4 after taking ARV) is 302 cells/ml but the mean baseline CD4 i.e. (The CD4 before taking ARV) was 131cells/ml.

The prevalence of AZT associated anemia is found to be 36.2%. This indicates AZT associated anemia is a significant problem in causing morbidity and increasing treatment cost. The risk of developing AZT associated anemia is found to be higher in child patients started ART at WHO clinical stage III.

The prevalence of d4T associated peripheral neuropathy is 8%. Generally, as age increases the probability of developing d4T associated peripheral neuropathy increases. Therefore, we can conclude that d4T causes significant problem in the quality of life of child patients.

The prevalence of NVP associated skin rash is 8%. The risk of developing skin rash is associated with female sex and low baseline CD4 count. From this we can conclude that NVP associated skin rash is causing a significant problem in child patients taking ART.

5.2 Recommendations

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

Early ART initiation has marked CD4 count increment when compared to those who started treatment late after their CD4 has dropped far below normal (2). Treatment

outcome highly depends on the base line CD4 count. More child patients die when treated with ARV after their CD4 has decreased below 50cells/ml compared with those patients whose CD4 is above 200 before ARV is initiated.

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 promote 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 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 lipodystrophy syndromes are significant problems. Therefore, it is better to substitute **AZT** and **d4T** by **ABC** and **TDF** as first line regimen.

NVP associated skin rash is also a significant problem. **NVP** should not be prescribed to females with baseline CD4 count below 250cells/ml and in males with baseline CD4 count below 400 cells/ml.

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

References

1. FMOH, Disease Prevention and Control Department, AIDS in Ethiopia, 6th Edition, Addis Ababa, 2006.
2. FMOH, HAPCO. ART update in Ethiopia, Hamle 1998.
3. Report on the global AIDS epidemic, treatment and care/ WHO/UNAIDS 2006.
4. Antiretroviral therapy for HIV infection in adults and adolescents in resource-limited settings: towards universal access. Recommendations for a public health approach, 2006 revision.
5. J.Harrison's Principles of internal medicine, 16th edition, Willy and Sons, New York.
6. John G. Bartlet, Medical management of HIV infection, 2007, Willy and Sons, New York.
7. AIDS: Volume 19(17)18 November 2005p 2046-2047 Zidovudine-induced pure red cell aplasia presenting after 4 years of therapy.
8. AIDS: Volume 14(5)31 March 2000p 615 Increased incidence of peripheral neuropathy with co-administration of stavudine and isoniazid in HIV-infected individuals.
9. Https://www.aidsonlne.org AIDS JOURNAL 2005 VOL.19 NO 2; Incidence and risk factors for rash in Thailand patients randomized to regimens with NVP, EFV or both.
10. AIDS: Volume 15(14)28 September 2001pp 1843-1848 Nevirapine and the risk of Stevens-Johnson syndrome or toxic epidermal necrolysis.
11. AIDS: Volume 19(1)3 January 2005p 97-99 Predisposition to nevirapine hypersensitivity associated with HLA-DRB1*0101 and abrogated by low CD4 T-cell counts.
12. Introduction to adverse drug reaction. Merck Manual, Home Edition, htm www.clinicaltrial.gov
13. Jason Lazarou. Incidence of Adverse Drug Reactions in Hospitalized Patients. A Meta-analysis of Prospective Studies, Journal of American Medical Association (JAMA). 1998;279:1200-1205
14. d'Arminio Monforte A, Lepri AC, Rezza G, et al. Insights into the reasons for

discontinuation of the first highly active antiretroviral therapy (HAART) regimen in a cohort of antiretroviral naïve patients.I.CO.N.A. Study Group. Italian Cohort of Antiretroviral-Naïve Patients. AIDS2000; 14:499-507. http://amedeo.com/lit.php?id=10780712

15. Eron JJ, Yetzer ES, Ruane PJ, et al. Efficacy, safety, and adherence with a twice-daily combination lamivudine/ zidovudine tablet formulation, plus a protease inhibitor, in HIV infection. AIDS 2000;14:671-81. http://amedeo.com/lit.php?id=10807190
16. Antiretroviral therapy in primary health care: Case study on experience of the Khayelitsha programme in South Africa, Perspectives and practice in antiretroviral treatment, World Health Organization 2003.
17. Kumarasamy N, Vallabhaneni SJ, et al. Reasons for modification of generic highly active antiretroviral therapeutic regimens among patients in southern India. Journal of AIDS (JAIDS).2006; 41(1):53-8.
18. Moh R, Danel C, Sorho S, et al. Haematological changes in adults receiving a zidovudinecontaining HAART regimen in combination with co-trimoxazole in Côte d'Ivoire. Antivir Ther 2005;10(5):615-24
19. Fellay J, Boubaker K. Ledergerber B et al. Prevalence of adverse drug events associated with potent antiretroviral treatment: Swiss HIV Cohort study. Lancet, 2001. 358(92):1322-7.
20. Ammassari A, Murri R, Pezzotti P, et al. Self-reported symptoms and medication side effects influence adherence to highly active antiretroviral therapy in persons with HIV infection. J Acquir Immune Defic Syndr 2001; 28:445-9. http://amedeo.com/lit.php?id=11744832
21. Lignani L Jr: Assessment of the compliance to antiretroviral drugs among HIV/AIDS patients. Rev Saude Publica. 2001 Dec;35(6):495-501.
22. Li H, Study on adherence and interrelated factors of acquired immunodeficiency syndrome patients receiving antiretroviral treatment, PMID: 16335002
23. Pirmohamed, Munir; Park, B. Kevin: HIV and drug allergy, Current Opinion in Allergy & Clinical Immunology. 1(4):311-316, August 2001.PubMed, PMID: 11964706
24. Reisler RB et al. Grade 4 events are as important as AIDS events in the era of HAART. Journal of AIDS (JAIDS). 34: 379 – 386, 2003.

25. V. Puro, G. De Carli, F. Soldani, Z. Lazarevic, F. Mattioli, G. Ippolito: Adverse Drug Reactions Associated with Post-exposure Prophylaxis; Italian Registry of Antiretroviral PEP, Rome, Italy.
26. Hoffmann, HIV Medicine: Management of Side Effects, 263-282, 2005 /www.HIVMedicine.com/
27. Habtegiorgis A, Gebreyesus S, Mulugeta E. Evaluation of antiretroviral treatment in two private medical center in Addis Ababa. Medical Journal Volume 41, Number 4, 2003.
28. Ayalew Mengesha. Assessment of adherence to antiretroviral therapy among 422 patients on ART at the Ministry of National Defense Force hospital. Unpublished Msc thesis. Addis Ababa University, April 2005.
29. Yonas Tadios. Antiretroviral treatment adherence and its correlates among people living with HIV/AIDS on Highly Active Antiretroviral Therapy in Addis Ababa, Ethiopia. Unpublished Msc thesis, Addis Ababa University DCH, AAU June, 2005.
30. Stat Notes (2006). Logistic Regression /PA765/ www2.chass.ncsu.edu/ga.
31. Hosmer D. and Lemeshow S. (1989). Applied Logistic Regression. John Wiley and Sons. Inc., New York.
32. Agresti, A. (1996). An Introduction to Categorical data Analysis. John Wiley and Sons. Inc., New York.
33. Pagano, M. and Gauvreau, K. (2000), Principles of Biostatistics. Thomson Learning, Boston.
34. Journal of American Medical Association (JAMA). Vol.296 No 7, Aug 16, 2006.
35. Overton, R. C. (2001), "Moderated multiple regression for interactions involving categorical variables: a statistical control for heterogeneous variance across two groups", *Psychol Methods* **6** (3): 218–33

Declaration

I, the undersigned, declare that the thesis is my original work, has not been presented for degrees in any other University and all sources of material used for the thesis have been duly acknowledged.

Name: Aklilu Yitbarek

Signature: .....

Place: Faculty of Science, Addis Ababa University

Date: June, 2010

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

……...

Professor Eshetu Wencheko