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SCHOOL OF GRADUATE STUDIES

ASSESSMENT OF THE PREVALENCE OF ADVERSE DRUG REACTION AMONG HIV-INFECTED ADULTS ON ANTI RETROVIRAL THERAPY AND FACTORS ASSOCIATED WITH IT AT ZEWDITU MEMORIAL HOSPITAL

BY

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Profile of Adverse Drug Reaction among HIV-infected adults on Anti-retroviral therapy and factors associated with it at Zewditu Memorial Hospital

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Acronyms

ACTG – AIDS Clinical Trial Group

ADRs – Adverse Drug Reactions

AIDS – Acquired Immune deficiency syndrome

ART – Anti Retroviral Therapy

ART-Clinic-A unit in hospitals responsible for counseling, investigating, and treating HIV infected persons with antiretroviral drugs

ARV – Antiretroviral drugs used for the treatment of HIV infection

AST/ALT – Aspartate aminotransferase / Alanine aminotransferase

CDC Ethiopia – Centers for Disease Control and Prevention (Ethiopia)

CI – Confidence Interval

d4T- stavudine

DACA– Drug Administration and Control Authority

HAART –highly active antiretroviral therapy

HCV– Hepatitis C virus

HIV – Human Immune deficiency virus

ITECH – International Training and Education Center on HIV

MOH – Ministry of Health

MSH-RPM^{+} – Management Science for Health-Rational Pharmaceutical Management $^{+}$

NFV- nelfinavir

NRTI – Nucleoside reverse transcriptase inhibitor

NNRTI – Non-nucleoside reverse transcriptase inhibitor

PEP– Post exposure prophylaxis

PI – Protease Inhibitor

PLWHA– People living with HIV and manifestations of AIDS

OR - Odds Ratio

VCT – Voluntary Counseling and Testing

WHO – World Health Organization

ZDV- zidovudine

ZMH – Zewditu Memorial Hospital

3TC - lamivudine

Abstract

Background: The success of Anti Retroviral Treatment (ART) is highly dependent on adherence to complex ARV regimens. Unfortunately, up to 25% of patients discontinue their initial HAART regimen mainly because of toxic effects.

Objectives: To assess the magnitude of adverse drug reactions (ADRs) and associated factors among patients on Anti Retroviral Treatment

Methods: Out of the source population that consisted of 3240 adult AIDS patients started on ART at Zewditu Memorial Hospital from January 2004 to December 2005, 554 study subjects' clinical records were selected using systematic random sampling technique. The study was an institution based cross sectional study conducted using review of clinical records of adult patients on ART to examine the status of ADRs and factors associated with it among patients on ART. Independent predictors of the development of ADRs, types and severity were assessed with binary logistic regression.

Results: Out of the total of 554 clinical records, 526 (94.9%) were reviewed. At least one of the drugs was changed in 120(22.8%) of the patients. There were 73 (13.7%) lost for follow up. The main reasons for changing ARV drugs were toxicity/side effects 97(81%) followed by illness in 14(12 %), and pregnancy in 4(3%). The frequency of ADRs was 124(24%). The most frequently diagnosed ADRs were Anemia 42(33.9%) followed by Peripheral Neuropathy 35 (28.2%) and Elevated ALT 31(25%). Majority 94(75.8%) of the ADRs were classified as grade III. Variables associated with ADRs were regimen containing NEV (OR=1.60; CI=1.04-2.47), treatment durations 6-10, 11-15 and >15 months OR 3.50 (1.47, 8.33), 3.36 (1.34, 8.40) and 5.08 (2.20, 11.75) respectively and taking other drugs (OR=1.80; CI=1.06- 3.03).

Conclusions: 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 most frequent ADR was anemia followed by Peripheral Neuropathy and Elevated ALT. 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.

1. Introduction

1.32 Million people live with HIV/AIDS in Ethiopia and 134,450 have already died of AIDS. Currently, some 277,757 PLWHA are in need of Anti Retroviral Treatment (ART) (1). Fee based ART program begun in Ethiopia in July 2003. By March 2005, Global Fund funded free ART service has been started at least at one site in all regions. Currently, 132 sites are providing ART services (2). 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. Currently 35,460 are on ART. Some 10,135 (22.2%) constitute lost for follow up, died, and stopped treatment due to treatment failure or other problems (2).

The success of the anti retroviral treatment is highly dependent on willingness of HIV-positive individuals to adhere to complex ARV regimens (3,4). Unfortunately, up to 25% of patients discontinue their initial HAART regimen because of toxic effects, noncompliance or treatment failure within the first 8 months of therapy (5).

The occurrence of side effects can vary dramatically among different people (6). Some experience frequent and severe adverse reactions that necessitate dose reductions or discontinuation of treatment; others have side effects that are uncomfortable or annoying and can interfere with their daily quality of life; still 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 (7, 8). Therefore, many countries have ADRs monitoring centers, which are responsible for collecting, compiling and analyzing any ADRs information reported by health

professionals. Based on these information, risk-benefit evaluation 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 (7). The Division has so far received 110 ADR reports out of which, 60 were ADRs on Anti Retroviral Drugs (9). 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 our setup are unknown.

Therefore, the aim of this study was to gain knowledge on the profile of ADR associated with ARV drugs, the burden of adverse drug reactions of ART in our setup and factors associated with it, with the ultimate goal of improving the tolerability and effectiveness of HIV treatment.

2. Literature 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 (10). 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 (10). 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 (10).

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 (10). As of June 2005, 21 countries were providing antiretrovirals to at least 50% of those in clinical need (10). 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 (11, 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 (10). 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% (10). Nearly 200 sites in Kenya were providing antiretrovirals by

December 2005(10). In South Africa the number of people receiving antiretrovirals grew from fewer than 5000 at the beginning of 2004 to roughly 190,000 by the end of 2005 (10).

Worldwide, it is estimated that between 250,000 and 350,000 deaths were averted in 2005 as a result of increased treatment access (10).

2.2 National overview of PLWHA on ART

In 2005, it is 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 for follow up, died and stopped treatment due to treatment failure or other problems (1, 2). Of the people ever started on ART, 47 % were adult males >14 years of age, 48% were adult females >14 years of age, and 4% were children.

2.3 Adherence of PLWHA to ART

More than 95% treatment adherence levels are required to maintain virologic suppression in people on combination of ARV drugs. However, actual adherence rates are lower. Most studies show that 40% to 60% of patients are less than 90% adherent (12).

The most common reasons for non-adherence of patients included complexity of medication regimens, difficulty of integrating treatment schedules into their daily activities, side effects, worries about HIV disclosure, and forgetfulness in taking medication (13).

Some people supposed 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. (14). 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 (15-17).

Several studies on adherence to ARV therapy in our setup showed good adherence rate (18, 19). In an assessment of adherence to antiretroviral therapy among patients at the national defense force hospitals, the average adherence rate to antiretroviral medication was found to be 82.8% (18). In another similar study, 81.2% of patients were >95% adherent by self report in the week before the assessment and 78.9% claimed never to have missed a single dose over the past week (19). Higher rate of adverse reaction (16.8%) was also found in the non-adherent patients than in the

adherent patients 5.8% (19).

2.4 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 (20). 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 (20). Each time a person is hospitalized, the risk of having at least one adverse drug reaction is 10 to 20% (20).

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 (21). Overall, 2216000 (1721000-2711000) hospitalized patients 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 (21).

Patients on HAART commonly suffer from side effects (22, 23). 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 (24). 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 anaemia (23%) (25). 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 (26). 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 (27).

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 (5,22,27-29).

A study on adherence and interrelated factors of Acquired Immune-Deficiency Syndrome 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 (30).

All antiretroviral drugs can have both short-term and long-term adverse events. The risk of specific side effects varies from drug to drug, from drug class to drug class, and from patient to patient (31,32). 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 (33).

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)(34). 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) (34). 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) (34). 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 (34).

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 (35).

Case study on the experience of the Khayelitsha programme in South Africa showed that most people tolerated the first-line regimen well (24). 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) (24).

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 at the Ministry of National Defense Force hospitals showed that 221(54.0%) developed mild adverse drug reactions (18). 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 (19).

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 (36). 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 (32). Thus, it is expected that these and other several unknown factors could also affect the prevalence of ADRs among patients taking ART in our setup. Therefore, this study tried to assess the prevalence of ADRs and identify factors associated in patients taking ARV drugs at ZMH.

3. Objectives

3.1 General Objective

To assess the magnitude of adverse drug reactions (ADRs) and associated factors among patients on Anti Retroviral Treatment

3.2 Specific Objectives

1. To assess the magnitude of adverse drug reactions (ADRs) in patients on ART
2. To describe the profile of ADR associated with ARV drugs
3. To find out factors associated with occurrence of ADRs

4. Methods

4.1 Study area

Zewditu Memorial Hospital (ZMH) ART Clinic is one of the earliest ART sites in the Country which was started as HIV Clinic in 1991, before the introduction of HAART in the Country. On July 2003, the Hospital started providing ART treatment for paying AIDS patients according to the national treatment guideline and subsequently also for those free patients who can produce a free paper from their place of residence "Kebele".

ZMH ART clinic is staffed with five physicians, one pharmacist, two pharmacy technicians, five counselor nurses and six laboratory technicians working full time. All are trained on ART treatment and adherence counseling which is mandatory to work as ART Team.

The Hospital is under the Addis Ababa Administration Health Bureau and often gets technical and financial assistance from CDC Ethiopia, ITECH, John Hopkins University, WHO and Management Science for Health-Rational Pharmaceutical Management Plus (MSH-RPM+). In addition to adherence counseling and ART for AIDS patients from Addis Ababa, it also provides screening, follow up and referral services for TB patients.

Thus, ZMH was taken as the research area since it has sufficient number of patients on ART, is well staffed and organized, and has relatively good recording of the clinical events using patient flow chart provided by the MOH.

4.2 Source Population

The source population consisted of 3240 adult AIDS patients started on Anti retroviral treatment at ZMH from January 2004 to December 2005.

4.3 Study Subjects

Any selected adult patients on ART who fulfilled the inclusion criteria of study subject.

4.4 Study Design

Institution based cross sectional study conducted using review of clinical records of adult patients started on ART from January 2004 to December 2005 at Zewditu Memorial Hospital ART Clinic.

4.5 Sample Size

The sample size for the study was determined based on the assumption that 54% of patients taking ART develop ADRs (24). Taking critical value at 95 % confidence level, degree of precision 0.04, missing or incomplete record 10% and the source population of 3240, the total sample size was 554.

Single population proportion formula was used to calculate the sample size.

$$\frac{Z\,\alpha/2 \; * P * (1- P)}{D^2} = \frac{(1.96)2 * 0.54*(1-0.54)}{(0.04)^2} = 504$$

$$504 + (10\% * 504) = 554.4 = 554$$

P=54% (From a thesis Submitted to the School of Graduate Studies, Addis Ababa University by Ayalew Mengesha (BSc), April 2005 on Assessment of adherence to antiretroviral therapy among 422 patients on ART at the Ministry of National Defense

Force Hospitals (24)

D=0.04 Missing or incomplete clinical record =10%

4.6 Sampling Technique

From the sampling frame of list of all adult patients on ART at ZMH from January 2004 to December 2005, 554 study subjects' clinical records were selected using systematic random sampling technique.

K (sampling interval) = N (source population)/ n (sample size)

= 3240/554 ≈ 5.8 = 6

The first number was decided by simple random sampling. Every 6^{th} patient's clinical record was included in the sample. Those patient's clinical records which did not fulfill the inclusion criteria or missing were substituted with the next patient on the list.

4.7 Inclusion and exclusion criteria

4.7.1 Inclusion criteria

All adult AIDS patients aged greater than or equal to 16 years who were registered for Anti Retroviral Treatment at ZMH from January 2004 to December 2005.

4.7.2. Exclusion criteria

Any patient with deliberate or unintended overdose, missing clinical record, incomplete data or those transferred in after they have been on ART for more than one month were excluded from the study.

4.8 Study variables

Independent

1. Socio-demographic variables
2. Clinical and laboratory state at the beginning of ART
3. Anti Retroviral Treatment
4. Drug used other than ARV drugs

Dependent

1. Frequency of ADRs
2. Types of ADRs
3. Severity of ADRs

4.9 Data Collection Procedure

The clinical records of study the subjects were reviewed retrospectively for ADRs. Information on patient's details, the WHO clinical staging of the disease at the start of ART, duration of treatment, drug details, nature of the adverse drug reactions, severity, outcome, and result of investigations performed were collected using a data collection format (Annex III).

Data were collected from May15 to July 15, 2006.

4.10 Data Quality Control

Two physicians who were working at ZMH ART Clinic were recruited & provided with one day training on the study protocol as well as the recording formats. A pretest was carried out on randomly selected patients' clinical records at ZMH ART Clinic. Based on the results, the instrument was modified. The principal investigator closely supervised the data collector on a daily basis.

4.11 Operational definitions

1. An adverse drug reaction (ADR) is 'a response to a medicine which is noxious and unintended, and which occurs at doses normally used in human'.

2. A side effect is 'any unintended effect of a pharmaceutical product occurring at doses normally used by a patient which, is related to the pharmacological properties of the drug'.

3. ADRS to ART and Severity grading (See Annex I)

4.12 Data Processing and Management

Data entry and cleaning were done using EPI6 and analysis was done using SPSS statistical software. Tables and graphs were used to present frequencies of severe adverse drug reactions (ADRs) in patients on ART. Associations between the independent and dependent variables were tested using OR and 95 % CI was used to measure the strength of the association between the independent and dependent variables.

4.13 Ethical Considerations

Ethical clearance was obtained from the Addis Ababa University Faculty of Medicine Ethical Clearance Committee and official letter was written to Zewditu Memorial Hospital to secure permission. Since data collection was conducted by physicians who were working at ZMH ART Clinic by review of medical records of patients on ART drug treatment and as the study did not directly involve patients in anyway, there was no direct risk to study subjects from participating in the study. Therefore, informed consent

was not sought from the study subjects. But the investigator made sure that confidentiality of the information was assured in such a way that no disclosure of any name of the patient, the health care provider or drug product in relation to the finding was made.

5. Results

Out of a total of 554 clinical records, 526 (94.9%) were reviewed. The remaining 5.1% were omitted since the cards were missing or were short of relevant information and the next patient on the list could not fulfill the inclusion criteria.

Socio-demographic distribution of the study population

The median age of patients was 35 years, ranging from 20–75 years. Majority 411(78.1%) were between the ages of 26-45 years. Females accounted for only 192 (36.5%) (Table 1). Data on the marital status, educational status and religion were missing for more than 50% of the cases. Fifty one point five percent of those, whose marital status was known, were married followed by single 62(26.4%), widowed 31(13.2%) and divorced 21(8.9%). Majority 155(74.9%) of the patients didn't complete high school. Orthodox Christianity 166(79.4%) was the commonest religion found in patients who are on ART followed by Protestant 20(9.6%) and Muslim 16(7.7%).

Table-1: Socio-demographic distribution of the study population on ART at Zewditu Memorial Hospital ART Clinic, Addis Ababa, 2004-2005.

Variables	N (%)
Age group	
16-25	46(8.8%)
26-35	232(44.4%)
36-45	179(34.3%)
46-55	51(9.8%)
56-65	12(2.3%)
66-75	2(0.4%)
Sex	
Male	334(63.5%)
Female	192(36.5%)
Marital status	
Single	62(26.4%)
Married	121(51.5%)
Divorced	21(8.9%)
Widowed	31(13.2%)
Education	
Illiterate	11(5.3%)
Grade 1-8	54(26.1%)
Grade 9-12	90(43.5%)
High school certificate	21(10.1%)
Diploma and above	31(15.0%)
Religion	
Orthodox	166(79.4%)
Muslim	16(7.7%)
Catholic	4(1.9%)
Protestant	20(9.6%)
Others	3(1.4%)

Clinical and laboratory findings of patients at the time of initiation of ARV drugs

Two hundred seventy three (52%) of patients at the initiation of treatment were at clinical stage III, while 149(28.3%) at stage IV, 100(19.0%) at stage II and 4(0.8%) at stage I respectively (Table 2). Functionally, 219(41.6%) were ambulatory, 166(37.3%) were bed ridden and 111(21.1%) were working. Patients weighing bellow 55kg at the initiation of treatment were 301(59%) and 121(23.7%) weighed less than 45 kg. Majority 301(57.3%) were having CD4 count less than 101 cell/mm3. Nearly 146(28%) were bellow 50 cells/ mm3 and 83(15.8%) were 151-200 cell/mm3. Initial TL count was > 1200 cells/ mm3 in 258(65.3%) (Table 2). Nearly 346(89%) of the patients were having absolute Neutrophil count greater than 1500 cells/ mm3 and Hgb < 12.6 g/dl at the time of initiation were found in 236(54%) of the patients.

Table-2: Clinical and laboratory conditions of patients at the time of initiation of ARV drugs at ZMH ART Clinic, Addis Ababa, 2004-2005.

Variables	N (%)
Stage	
Stage I	4(.8%)
Stage II	100(19.0%)
Stage III	273(51.9%)
Stage IV	149(28.3%)
Functional stage	
Working	111(21.1%)
Ambulatory	219(41.6%)
Bed ridden	196(37.3%)
Weight	
<=35	14(2.7%)
36-45	107(21.0%)
46-55	180(35.3%)
56-65	132(25.9%)
66-75	55(10.8%)
>76	22(4.3%)
CD4	
1-50	146(27.8%)
51-100	155(29.5%)
101-150	117(22.3%)
151-200	83(15.8%)
>200	24(4.6%)
TLC	
<=1200	137(34.7%)
>1200	258(65.3%)
Absolute Nutrophil Count	
>1500	346(88.7%)
1000-1500	24(6.2%)
750-999	6(1.5%)
500-750	8(2.1%)
<500	6(1.5%)
Initial Hemoglobin	
<7.0	3(.7%)
7.0-9.9	41(9.4%)
10.0-12.5	192(43.9%)
12.6-17.5	193(44.2%)
>17.5	8(1.8%)

Initial regimen and current regimen patients on

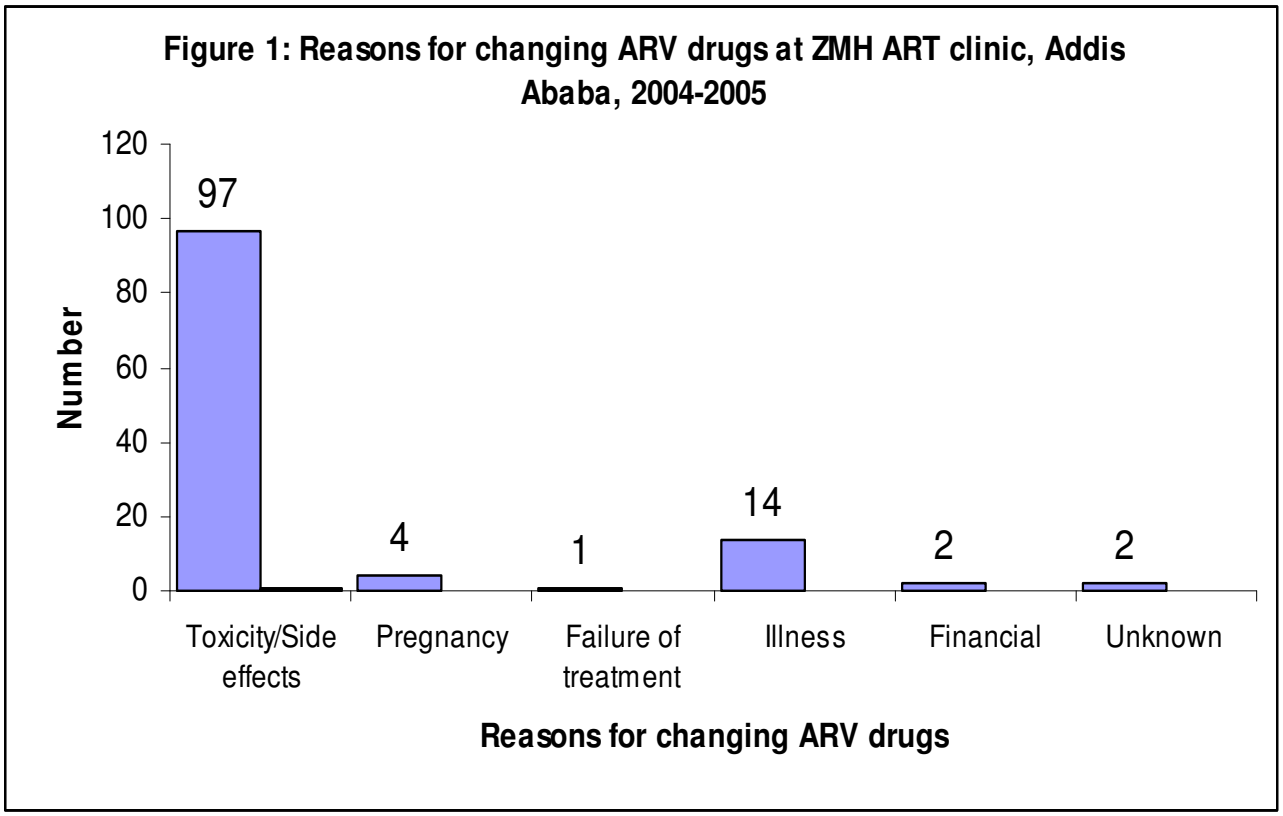
Very few 18(3.4%) were antiretroviral drug experienced. The most commonly prescribed initial regimen was ZDV/3TC/NVP in 179(34%) of cases, followed by D4T/3TC/NVP 147(27.9%), ZDV/3TC/EFV 114(21.7%) and D4T/3TC/EFV 86(16.3%) (Table 3). Majority 406(77.2%) were still on initial regimen whereas one or two drugs changed during their follow up in 117(22.2%). Most drug changes were made with in the first line regimens. Only 2 (0.4%) were shifted to second line regimen. Nearly 315 (60%) were still on follow up at the Clinic while 114 (22%) were transferred out to other ART site, 73 (14%) were lost for follow up and the remaining 24 (5%) were expired.

Table 3: Treatment and follow up state of patients on ATR at Zewditu Memorial Hospital ART Clinic, Addis Ababa, 2004-2005

Variables	N (%)
Treatment experienced	
No(Naïve)	506(96.2%)
Yes(Non naïve)	18(3.4%)
Unknown	2(0.4)
Initial Regimen	
ZDV/3TC/NEV	179/ 34.0%
D4T/3TC/NEV	147/ 27.9%
ZDV/3TC/EFV	114/ 21.7%
D4T/3TC/EFV	86/ 16.3%
Current treatment status	
On initial regimen	406(77.2%)
One or two drug changed	117(22.2%)
Regimen changed 2L	2(0.4%)
All drugs stopped	1(0.2%)
Current Regimen	
First line regimen	524(99.6%)
Second line regimen	2(.4%)
Follow up status	
Still on follow up	315(60%%)
Transfer out	114(22%%)
Lost for follow up	73(14%%)
Expired	24(5%%)

Reasons for changing ARV drugs

The main reasons for changing ARV drugs were toxicity/side effects in 97(81%) of cases followed by illness in 14(12%), and pregnancy in 4(3%) (Figure 1).



Initial treatment and follow up status of patients started on ART

Of those patients who were still on follow up, 80(25.4%) had at least one drug changed during their follow up. Similarly, 20(17.5%) of transferred out patients, 10(13.7%) of lost patients and 7(29.2%) expired had at least one drug changed during their follow up (Table 4).

Table 4: Treatment and follow up status of patients on ART at Zewditu Memorial Hospital ART Clinic, Addis Ababa, 2004-2005.

	Treatment status				
Follow up status	On initial regimen	One or two drug changed	Regimen changed 2L	All drugs stopped	Total
Still on follow up	234	80	1		315
	74.3%	25.4%	.3%		100.0%
Transfer out	93	20	1		114
	81.6%	17.5%	.9%		100.0%
Lost for follow up	62	10		1	73
	84.9%	13.7%		1.4%	100.0%
Expired	17	7			24
	70.8%	29.2%			100.0%
Total	406	117	2	1	526
	77.2%	22.2%	.4%	.2%	100.0%

Total duration of treatment with current follow up status

Forty six (40%) of the transfer outs were before 6 months (Table 5). Majority of the lost cases 45(61.1%) were lost within the first 1-2 months after initiation of treatment, while 62(84.7%) were lost with in the first 5 months. It was observed that as the duration of treatment increased the rate of lost for follow up decreased. In those known to have died after starting ART, 20(82.7%) expired with in the first 5 months out of which 13(56.5%) died within 1-2 months.

Table 5: Total duration of treatment with current follow up status at Zewditu Memorial Hospital ART Clinic, Addis Ababa, 2004-2005

	Total duration on follow up interval					
Follow up status	1-2	3-5	6-10	11-15	>15	Total
Still on follow up		1	87	68	159	315
Transfer out	24	22	39	18	11	114
Lost for follow up	45	17	10	1		73
Expired	13	7	2	1	1	24
Total	82	47	138	88	171	526

Total duration of treatment by current follow up status with the level of initial functional stage

The number of patients lost in the early (1-2 months) follow up period was found to be higher in those bed-ridden ones (31) than started treatment while they were ambulatory (8) and working (6) (Table 6). Similarly, the number of patients expired in the first 1-2 months were 12 in bed-ridden patients were as only one and none were expired in ambulatory and working patients respectively.

Table 6: Total duration of treatment by current follow up status with the level of initial functional stage at Zewditu Memorial Hospital ART Clinic, Addis Ababa, 2004-2005

Functional stage working						
Follow up status	Total duration on follow up					Total
	1-2	3-5	6-10	11-15	>15	
			Working			
Still on follow up		1	30	13	38	82
Transfer out	3	3	5	2	5	18
Lost for follow up	6	1	3	1		11
Total	9	5	38	16	43	111
	8.1%	4.5%	34.2%	14.4%	38.7%	100.0%
			Ambulatory			
Still on follow up			33	28	81	142
Transfer out	7	9	20	13	3	52
Lost for follow up	8	11	4			23
Expired	1	1				2
Total	16	21	57	41	84	219
	7.3%	9.6%	26.0%	18.7%	38.4%	100.0%
			Bed ridden			
Still on follow up			24	27	40	91
Transfer out	14	10	14	3	3	44
Lost for follow up	31	5	3			39
Expired	12	6	2	1	1	22
Total	57	21	43	31	44	196
	29.1%	10.7%	21.9%	15.8%	22.4%	100.0%

Frequency of ADRs and severity

The frequency of ADRs among patients who were on ARV drugs was about 124 (24%) (Table 7). The most frequently diagnosed ADRs were Anemia 42(33.9%) followed by Peripheral Neuropathy 35(28.2%) and Elevated ALT 31(25%). Out of the 124 patients who developed ADRs, majority 94 (75.8%) patients were grade III which required substitution of the drug suspected as a cause of the reaction where as grade I and II ADRs occurred in 16(12.9%) and 10(8.1%) of the patients respectively. Grade IV was reported only in 4 (3.2%) of the patients.

Table 7: Distribution and severity of ADRs to antiretroviral drugs at Zewditu Memorial Hospital ART Clinic, Addis Ababa, 2004-2005

Variables	N (%)
ADR	
Yes	124(24%)
No	402(76%)
Types of ADR	
Nausea	2(1.6%)
Vomiting	2 (1.6 %)
Fatigue	1(.8 %)
Peripheral Neuropathy	35(28.2%)
Rash	5(4.0%)
Lipodystrophy	6(4.8%)
Anemia	42(33.9%)
Elevated ALT	31(25.0%)
Severity	
Grade I	16 (12.9%)
Grade II	10(8.1%)
Grade III	94(75.8%)
Grade IV	4(3.2%)

Frequency of ADRs by follow up status

Out of the 124 patients diagnosed to have ADRs, majorities 86(69.4%) were still on follow up (Table 8). Some, 21(16.9%) were transferred out, 10(8.1%) were lost for follow up and only 7(5.6%) were found to have expired. Majority 96(77.4%) of patients who had developed ADRs got one or two of their drugs changed where as 26(21%) of them remained on the same drugs. Very few required their regimen stopped or changed to second line drugs.

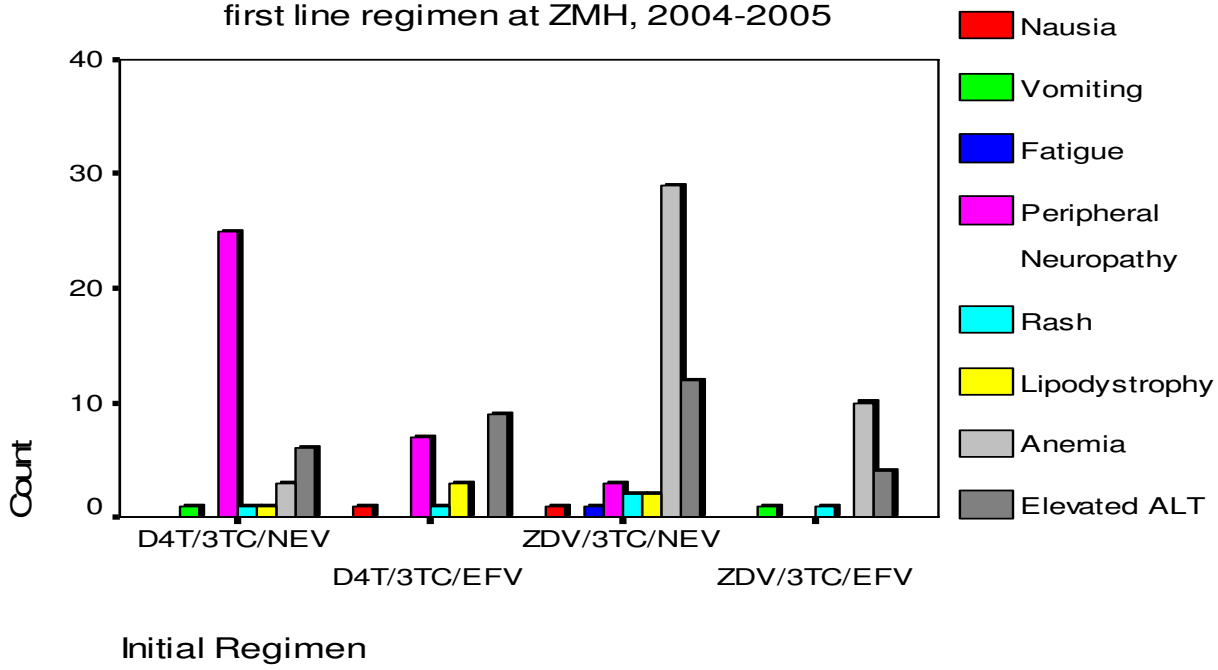
Table 8: Follow up and treatment status of patients who developed ADRs at Zewditu Memorial Hospital ART Clinic, Addis Ababa, 2004-2005.

	Patient developed ADRs		
	Yes	No	
Follow up status	No.(%)	No.(%)	Frequency
Still on follow up	86(69.4%)	229(57 %)	315(60%)
Transfer out	21(16.9%)	93(23 %)	114(22%)
Lost for follow up	10(8.1%)	63(16 %)	73(14%)
Expired	7(5.6%)	17(4 %)	24(5%)
Current treatment status			
On initial regimen	26(21.0%)	380(94.3%)	406(77.2%)
One or two drug changed	96(77.4%)	21(5.2%)	117(22.2%)
Regimen changed 2L	1(0.8%)	1(0.3%)	2(0.4%)
All drugs stopped	1(0.8%)	-	1(0.2%)

Common ADRs among patients on first line regimen

Peripheral Neuropathy was common among patients on D4T/3TC/NEV and Anemia among patients on ZDV/3TC/NEV (Figure 2). Elevated ALT was reported in all treatment regimens.

Figure 2: Frequency of ADRs by first line regimen at ZMH, 2004-2005



Types of clinical and Lab ADRs by duration of treatment

Anemia and Elevated ALT were reported throughout treatment duration where as most Peripheral Neuropathies were diagnosed beyond 6 months duration (Table 9). Peripheral Neuropathy was common among patients on treatment for more than 15 months whereas all the lipodystrophy cases were found in those who were on treatment for more than 15 months.

Table 9: Types of clinical and Lab ADRs by the duration at Zewditu Memorial Hospital ART Clinic, Addis Ababa, 2004-2005.

Name of the ADR	Total duration on follow up interval					Total
	1-2	3-5	6-10	11-15	>15	
Nausea				1	1	2(1.6%)
Vomiting			1	1		2(1.6%)
Fatigue				1		1(.8%)
Peripheral Neuropathy		1	10	7	17	35(28.2%)
Rash		1	3		1	5(4.0%)
Lipodystrophy					6	6(4.8%)
Anemia	5	4	9	7	17	42(33.9%)
Elevated ALT	2	1	11	4	13	31(25%)
Total	7(5.6%)	7(5.6%)	34(27.4%)	21(16.9%)	55(44.4%)	124(100.0%

Variables associated with development of ADRs

Both age and sex showed no statistically significant association with the development, severity and/or types of ADRs in this study (Table 10). Marital status, educational status, religion, Clinical stage, functional stage, CD4 count, TL count, hemoglobin, ALT and the other lab results before the initiation of ARV drugs also showed no significant association with the development of ADR.

Initial ARV regimen with NEV, duration of treatment and concomitant use of other drugs were significantly associated with the development of ADRs. Similarly, variables such as lost for follow up and one or two drug changed were associated with the development of ADR.

Table 10: Relation of socio-demographic, clinical and laboratory and Antiretroviral Treatment state with ADR development among patients on ART at Zewditu Memorial Hospital ART Clinic, Addis Ababa, 2004-2005

Variables	Yes	No	OR	95% CI
Age				
16-25	15	31	1	
26-35	52	180	.597	(0.300, 1.190)
36-45	36	143	.520	(0.254, 1.065)
46-55	16	35	.945	(0.402, 2.220)
56-65	4	8	1.033	(0.268,3.983)
66-75		2	.011	(0.000, 1544202.349)
Sex				
Female	39	153	1	
Male	85	249	1.34	(0.87, 2.06)
Marital status				
Single	12	50	1	
Married	32	89	1.498	(0.709, 3.167)
Divorced	2	19	.439	(0.090, 2.145)
Widowed	6	25	1.000	(0.336, 2.978)
Education				
Illiterate	1	10		
Grade 1-8	11	43	2.558	(0.295, 22.174)
Grade 9-12	25	65	3.846	(0.468, 31.620)
High school certificate	2	19	1.053	(0.085, 13.077)
Diploma and above	8	23	3.478	(0.383, 31.625)
Religion				
Orthodox	35	131	1	
Muslim	6	10	2.246	(0.764, 6.604)
Catholic	1	3	1.248	(0.126, 12.366)
Protestant	5	15	1.248	(0.424, 3.669)
Others	1	2	1.871	(0.165, 21.241)
Clinical stage				
Stage I		4	1	
Stage II	20	80	123.149	(0.000, 3.6E+11)
Stage III	64	209	150.842	(0.000, 4.4E+11)
Stage IV	40	109	180.769	(0.000, 5.2E+11)
Functional stage				
Working	19	92	1	
Ambulatory	57	162	1.703	(0.955, 3.039)
Bed ridden	48	148	1.570	(0.869, 2.837)
Weight				
<=35	4	10	1	
36-45	28	79	.886	(0.257, 3.053)
46-55	34	146	.582	(0.172, 1.968)
56-65	40	92	1.087	(0.322, 3.673)
66-75	13	42	.774	(0.208, 2.885)

Variables	Yes	No	OR	95% CI
>76	3	19	.395	(0.074, 2.122)
CD4				
1-50	35	111	1	
51-100	36	119	.959	(0.563, 1.634)
101-150	26	91	.906	(0.508, 1.615)
151-200	22	61	1.144	(0.617, 2.122)
>200	5	19	.835	(0.290, 2.399)
TLC				
<=1200	35	102	1	
>1200	61	197	.902	(0.559, 1.458)
Absolute Nutrophil Count				
>1500	82	264	1	
1000-1500	7	17	1.326	(0.531, 3.308)
750-999		6	.007	(0.000, 350202.381)
500-750	2	6	1.073	(0.213, 5.419)
<500	3	3	3.220	(0.638, 16.258)
Initial Hemoglobin				
<7.0		3	1	
7.0-9.9	12	29	203.832	(0.000, 1.74E+13)
10.0-12.5	50	142	173.449	(0.000, 1.47E+13)
12.6-17.5	40	153	128.783	(0.000, 1.09E+13)
>17.5	2	6	164.198	(0.000, 1.47E+13)
Follow up status	Yes	No		
Still on follow up	86	229	1	
Transfer out	21	93	.601	(0.352, 1.026)
Lost for follow up	10	63	.423	(0.208, 0.862)*
Expired	7	17	1.096	(0.439, 2.736)
Current treatment status				
On initial regimen	26	380	1	
One or two drug changed	96	21	66.813	(36.047, 123.840)*
Regimen changed 2L	1	1	14.615	(0.889, 240.378)
All drugs stopped	1		7199.456	(0.000, 6.14E+22)
Regimens				
ZDV	66	227	1	
D4T	58	175	1.14	(0.76, 1.71)
EFV	37	163	1	
NEV	87	239	1.60	(1.04, 2.47)*
Other drugs				
No	21	101	1	
Yes	100	268	1.794	(1.063, 3.028)*
Treatment Duration				
1-2	7	75	1	
3-5	7	40	1.875	(0.614, 5.722)
6-10	34	104	3.503	(1.473, 8.327)*
11-15	21	67	3.358	(1.343, 8.398)*

Variables	Yes	No	OR	95% CI
>15	55	116	5.080	(2.197, 11.748)*

Relation of selected variables and development of ADRs

Variables significantly associated with the development of ADRs were also reevaluated again separately with development of ADRs as dependent variable and controlling for the effect of duration, follow up status and socio demographic variables. The odds of developing ADRs in those on regimen containing D4T was not significantly higher than ZDV containing regimen (Table 11). The odds of developing ADRs in those on regimen containing NEV was 1.60 (1.04, 2.47) times higher than those EFV containing regimen. But the association becomes insignificant when variables such as duration of treatment and presence of other drugs are controlled. Compared with those on treatment for 1-2 months, the odds of developing ADRs was significantly higher among patients on treatment for 6-10, 11-15 and >15 months OR 3.50 (1.47, 8.33), 3.36 (1.34, 8.40) and 5.08 (2.20, 11.75) respectively which remained significant when the types of regimen that the patient is on, functional stage and follow up status are controlled. Compared with those who were not taking additional drugs other than ARV drugs, those taking other drugs had 1.80 (1.06, 3.03) times higher ADRs which remained significant when variables such as regimen and duration of treatment are controlled.

Table-11, Relation of selected variables and development of ADRs among patients on ART at Zewditu Memorial Hospital ART Clinic, Addis Ababa, 2004-2005

	Variables	ADR		Crude OR. / 95% CI	†Adjusted OR/95% CI
		Yes	No		
Regimens	ZDV	66	227	1	1
	D4T	57	175	1.14 (0.76, 1.71)	1.23(0.80,1.90)
	EFV	37	163	1	1
	NEV	87	239	1.60 (1.04, 2.47)*	1.449(0.92,2.29)
† Adjusted for duration of treatment, other drugs					
Total duration of treatment	1-2	7	75	1	1
	3-5	7	40	1.88 (0.61, 5.72)	1.59(0.492,5.11)
	6-10	34	104	3.50 (1.47, 8.33)*	3.28(1.36,7.90)*
	11-15	21	67	3.36 (1.34, 8.40)*	3.06(1.21,7.76) *
	>15	55	116	5.08 (2.20, 11.75)*	4.99(2.12,11.73) *
† Adjusted for functional stage, regimens and follow up status					
Other drugs	No	21	101	1	1
	Yes	100	268	1.80 (1.06,3.03)*	1.90(1.11,3.26)*
† Adjusted for regimen, duration of treatment at the time of ADR development					

Relation of selected variables and types of ADRs

The odds of exposure to D4T was 25.85 (7.27, 91.90) higher than ZDV in those patients who developed peripheral neuropathy which remain significant when adjusted for duration of treatment and presence of other drugs (Table 12). Similarly, the odds of exposure to D4T was 0.04 (0.01, 0.13) lesser among patients who developed anemia than those exposed to ZDV which remained significant when variables such as duration of treatment and presence of other drugs are controlled.

Table-12 Relation of selected variables and types of ADRs among patients on ART at Zewditu Memorial Hospital ART Clinic, Addis Ababa, 2004-2005

Variables	No	Yes	Crude OR. / 95% CI	† Adjusted OR/95% CI
Nausea				
ZDV	65	1	1	1
D4T	57	1	1.14(0.07, 18.65)	1.75(0.10, 30.59)
EFV	36	1	1	1
NEV	86	1	0.42(0.03, 6.88)	0.28 (0.02, 4.90)
Vomiting				
ZDV	65	1	1	1
D4T	56	2	2.32(0.21, 26.29)	2.41 (0.20 , 29.25)
EFV	35	2	1	1
NEV	86	1	0.20(0.02, 2.32)	0.20 (0.02, 2.48)
Peripheral Neuropathy				
ZDV	63	3	1	1
D4T	26	32	25.85 (7.27, 91.90)*	33.74 (8.52, 133.56)*
EFV	30	7	1	1
NEV	59	28	2.03 (0.80, 5.19)	2.09 (0.78, 5.65)
Rash				
ZDV	63	3	1	1
D4T	56	2	0.75 (0.12 , 4.65)	1.19 (0.13, 10.81)
EFV	35	2	1	1
NEV	84	3	0.63(0.10 , 3.91)	0.46 (0.05, 4.14)
Lipodystrophy				
ZDV	64	2	1	1
D4T	54	4	2.37(0.42, 13.44)	2.19 (0.36, 13.39)
EFV	34	3	1	1
NEV	84	3	0.41(0.08 , 2.11)	0.15(0.02, 1.03)
Anemia				
ZDV	27	39		1
D4T	55	3	0.04(0.01 , 0.13)*	0.03 (0.01, 0.13)*
EFV	27	10		1
NEV	55	32	1.57(0.67, 3.66)	1.63 (0.65, 4.09)
ALT				
ZDV	50	16	1	1
D4T	43	15	1.09(0.48 , 2.46)	0.91 (0.38, 2.17)
EFV	24	13	1	1
NEV	69	18	0.48 (0.21 , 1.13)	0.59 (0.24, 1.49)

† Adjusted for Duration, Other drugs

Relation of selected variables and severity of ADRs

The odds of exposure among those patients who developed grade I ADRs to NEV

containing regimen was 0.20 (0.07, 0.60) lower compared with those patients taking regimen containing EFV which remained significant when the effects of variable such as duration of treatment at the time of ADR development, types of ADRs and presence of other drugs are controlled. The odds of exposure to NEV among patients who developed grade III ADRs was 4.84 (2.02, 11.61) times higher compared with those patients taking regimen containing EFV which became insignificant when the effects of variable such as duration of treatment at the time of ADR development, types of ADRs and presence of other drugs controlled. (Table-13).

Table-13, Relation of selected variables and severity of ADRs among patients on ART at Zewditu Memorial Hospital ART Clinic, Addis Ababa, 2004-2005

Variables	No	Yes	Crude OR. / 95% CI	† Adjusted OR/95% CI
	GRADEI			
ZDV	59	7	1	1
D4T	49	9	1.55 (0.54, 4.46)	1.84 (0.19, 17.40)
EFV	27	10	1	1
NEV	81	6	0.20 (0.07, 0.60)*	0.07 (0.01, 0.60)*
	GRADEII			
ZDV	61	5	1	1
D4T	53	5	1.15 (0.32, 4.19)	0.92 (0.16, 5.35)
EFV	33	4	1	1
NEV	81	6	0.61 (0.16, 2.31)	0.95 (0.20, 4.65)
	GRADEIII			
ZDV	15	51	1	1
D4T	15	43	0.84 (0.37, 1.92)	6.24 (1.77, 21.97)*
EFV	17	20	1	1
NEV	13	74	4.84 (2.02, 11.61)*	1.01 (0.24, 4.21)
	GRADEIV			
ZDV	63	3	1	1
D4T	57	1	0.37 (0.04, 3.64)	0.00 (0.00, 4.87+100)
EFV	34	3	1	1
NEV	86	1	0.13 (0.013, 1.31)	0.000 (0.000, 1.20+155)

† Adjusted for Duration of treatment at the time of ADR development, Types of ADRS and Other drugs

6. Discussion

The selection of the existing first-line and second-line drug regimens were based on the availability of fixed-dose combinations (ARVs with once-daily or twice-daily dosing), affordability, toxicity profile, need for laboratory monitoring, coexistent conditions (TB and hepatitis B), potential for maintenance of future treatment options and special considerations for women of childbearing potential (3). These standardized simplified first-line and second-line regimens have been essential in expanding access to ART in resource limited countries (11). If these drugs are not used appropriately, the current first-line regimen will lose its efficacy sooner than it had to. To maximize durability of first-line regimen one has to deal with factors that affect the adherence of patients to ART. One of the major reasons for non- adherence and dropout is adverse drug reactions/ side effects (13,30,37). The risk of specific side effects varies from drug to drug, from drug class to drug class, and from patient to patient (31,32)

In this study, most of the patients were antiretroviral naive. The first line initial regimen prescribed was ZDV/3TC/NVP in 34% of the cases, followed by D4T/3TC/NVP (27.9%), ZDV/3TC/EFV (21.7%) and D4T/3TC/EFV (16.3%). At least one of the drugs was changed in 117 (22.2%) of the patients which is very high compared to other countries where nearly similar first line initial regimen used. Experience of the Khayelitsha programme in South Africa showed that most people tolerated the first-line regimen well with only 14% changing one of the ARV drugs because of either adverse events or a contraindication to treatment with that drug (24). Similarly, the percentage of patients shifted to second line regimen was found to be higher (0.4%) compared with 0.13% of the national figure (2).

Nearly a quarter of those patients who were still on follow up had at least one drug changed during their follow up. Similarly, 17.5% of transferred out patients, 13.9% of lost to follow up patients and 30.4% expired had at least one drug changed during their follow up. The main reasons for changing ARV drugs were found to be toxicity/side effects in 82.20%.

As there is difficulty to differentiate most ADRs from other clinical illnesses, the diagnosis of ADRs was taken as it is on the clinical records and cases were not graded according to the ACTG classification or the national ART guidelines, which may result with higher frequency than the real figure.

Regarding follow up of patients, nearly 315 (60%) were still on follow up at the Clinic regardless of their adherence to their treatment, where as 73 (13.7%) were lost for follow up, 24 (4.6%) expired and the remaining were transferred out which is nearly similar with 15 % lost to follow-up and 6 percent expired in northern Thailand hospitals (35). Majority of the lost cases (61.1%) were lost within the first 1-2 months after initiation of treatment and the rate of lost for follow up decreases with increase in total duration of treatment. In those known to have died after starting ART, 82.7% expired with in the first 5 months out of which 56.5% died within 1-2months. In the northern Thailand (35) also dropout rate was highest during the first two months of HAART therapy; after the fourth month the dropout rate declined steadily and the proportion of clients remaining in the program was 64 percent after 56 weeks.

Though the reasons for those who were lost were not traced in this study, it may be due to a number of reasons such as poor adherence counseling, poor management of

emergency opportunistic infections and poor diagnosis and management of side effects of ARV drugs. The high percentage of lost in the first two months when drug intolerance are likely to occur, may indicate that the main cause of lost for follow up could be due to early ADRs as it was the case in northern Thailand (35). Urgency to treat patients with ARV drugs and urge to be on ARV by patients before proper preparation will eventually lead to increased lost for follow up and poorly adherent cases and emergence of resistant strain.

In this study, the frequency of ADRs among patients who were on ARV drugs was found out to be about 24% (124) which is close to the 22.6% finding in a study on Antiretroviral treatment adherence and its correlates in Addis Ababa(19). But another study on adherence to antiretroviral therapy at the Ministry of National Defense Force hospitals showed higher (54.0%) frequency of mild adverse drug reactions (18). 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%, most commonly a switch from d4T to AZT (11). Swiss cohort of 1160 patients also showed that 47% presented with clinical and 27% with laboratory adverse events attributed to anti retroviral drugs (27). This variation in the prevalence of ADRs among different studies can be due to the different methodology used or the variation in the definitions of side effects and ADRs.

Nearly 19 % of patients taking ART developed Grade III and IV ADRs which is higher than 15.6% severe or life threatening side-effects at month twelve at US multi-centre HAART trials (34) and 14% that of Khayelitsha programme in South Africa, where one

of the ARV drugs was changed because of either adverse events or a contraindication (24).

The most frequently recorded ADRs in this study were anemia in 33.9% of the cases followed by Peripheral Neuropathy (28.2%) and Elevated ALT (25%). In a study in India between 1996 and 2004, 1443 ART-naive patients who received regimens containing d4T or AZT, the most common toxicities were rash (66%), hepatotoxicity (27%) and anemia (23%) (25). In Abidjan, Côte d'Ivoire, out of 498 adults with median baseline hemoglobin of 113 g/l who were started on AZT + 3TC + EFV, 23 had grade 3/4 anemia (26). Adverse effects which are common in those patients at earlier clinical stage like skin rash were found to be low which may be because most of the patients accepted for the HIV care and treatment came at the later stage and minor side effects are often undermined by both patients and doctors.

There was no significant association between the initial hemoglobin level of the patient at the initiation of treatment and severity of anemia $P>0.05$. This may be due to the fact that those with low initial hemoglobin were started on regimen that doesn't have ZDV.

Duration of treatment at diagnosis of ADRs was also significantly associated with the type of ADRs. Anemia and Elevated ALT were reported throughout treatment duration; where as most Peripheral Neuropathies were diagnosed beyond 6 months duration. Peripheral Neuropathy was common among patients on treatment for more than 15 months and the lipodystrophy cases were found in those who were on treatment for more than 15 months.

Initial ARV drugs regimen that the patients were on were significantly associated with the development of ADRs and severity. Peripheral Neuropathy was common among patients on D4T/3TC/NEV; Anemia among patients on ZDV/3TC/NEV. A prospective study conducted from 2001 to 2003 in Brazil also showed that adverse reactions were independently associated with regimens with nevirapine (RH = 1.78; 95 percent CI = 1.07-2.96), indinavir or indinavir/ ritonavir combinations (RH = 2.05; 95 percent CI = 1.15-3.64) (38). Elevated ALT was reported in all treatment regimens. Elevated liver function tests, which could as well be due to drugs concurrently used, are common with HAART, and severe hepatotoxicity occurs in up to 6 % of patients (32). It is also known that some of the antiretroviral drugs (especially zidovudine) are myelosuppressive, which leads to anemia usually during the first 3 months of therapy, but sometimes even after years on treatment (32). Peripheral polyneuropathy is mainly caused by the NRTI such as stavudine and rash may occur in patients on NNRTIs such as Nevirapine (32). This implies that most ADRs are known and common reactions of the drugs included in the regimen and can be diagnosed and managed accordingly with proper clinical and laboratory follow up.

In this study, socio-demographic and initial clinical state of patients were found to have no significant association with the development of ADRs which is consistent with similar study in Brazil where all socio-demographic and initial clinical state of patients except for gender were found to have no significant association with the development of ADRs (38). However, in another study, the risks of severe or life-threatening side-effects were found to be lower in younger patients (33). Lower baseline CD4 cell count and prior AIDS-defining illness are said to increase the risks of ADRs. Similarly, women

were at increased risk of experiencing severe or life-threatening neutropenia, whilst co-infection with hepatitis B and hepatitis C were as well significantly associated with the risk of experiencing severe liver-related side-effects (33).

Even though, functional stage at initiation of treatment didn't show significant association with the development and severity of ADRs, it was significantly associated with follow up status and average total duration of follow up. Working and ambulatory patients tend to follow their treatment as bed ridden ones tend to get lost from follow up.

7. Strength and Limitations

Strength

Clinical record reviewed using pre-tested structured data collection format which minimize information bias.

Data quality was assured by recruiting ART trained physician data collectors and close supervision.

This study is the first of its kind in the country. With all the limitations, it has tried to assess the profile and magnitude of ADRs. It has also tried to identify factors associated with the occurrence of ADRs in our set up. It can be used as a preliminary study to do further prospective studies.

Limitations

This study used a cross sectional survey from secondary data in a single hospital. The result may not be representative of the national picture as it is done in one hospital with relatively well organized ART Clinic.

The diagnosis and severity were taken as recorded on the clinical records. The clinical records were very often incomplete lacking important socio-demographic and clinical variables. It was also difficult to find follow up report from the clinical records of patients who developed ADRs. There is a tendency to record ADRs/ side effects which are severe enough to change the drug or discontinue treatment.

There was no mechanism in place to trace patients lost for follow up. Therefore, the reason for those patients lost for follow up was not known which could bias the finding.

8. Conclusion and Recommendation

There is relatively very high rate of (22.8%) changing with in first line regimen drugs with high lost for follow up rate (13.7%) which may shorten the durability of the first line drugs. Majority of the lost (61.1%) and expired (56.5%) were within the first 1-2 months after initiation of treatment. Functional stage was strongly associated with follow up status and average total duration of follow up. Those who were functionally good at the time of initiation tend to follow longer.

Although, ADRs among patients who were on ARV drugs was lower than expected (24%) which may be due to the very much lower than expected (5%) mild to moderate ADRs that resulted from failure to record mild- moderate ADRs, severe (Grade III and IV) ADRs which account for 19 % was higher compared with other countries.

The most frequent ADR was anemia which accounted for 33.9% followed by Peripheral Neuropathy (28.2%) and Elevated ALT (25%). Rash which is the commonest in other countries was found to be lower, which may also be due to lack of documentation of mild to moderate cases.

No significant association between initial hemoglobin level of the patient with the development and severity of anemia and similarly initial ALT level has no significant association with the development and severity of increased ALT later with treatment.

None of the socio-demographic variables, the initial clinical and laboratory state were significantly associated with the development of ADRs which needs to be confirmed with further prospective study.

The type of ADRs that the patient developed was very much associated with the duration of treatment and the regimen that the patient was on. Similarly, the severity of ADRs was also associated with type of ADRs and the duration of treatment. Therefore, one can safely conclude that most of the ADRs can be expected from the regimen that the patient was taking and the duration of treatment.

Consequently, the following recommendations have been made based on the findings in this study:

Recommendations

- Even if majority of patients tolerate HAART well, the monitoring of treatment according to the national guideline is recommended. Patients should be routinely investigated with full blood count, liver, pancreas and renal function tests, as well as fasting cholesterol, triglycerides and glucose levels.
- As much as possible, clinicians should stick to the national antiretroviral drug use guideline for the management and follow up of patients receiving HAART.
- Lost patients should be traced to ensure regular follow up.
- Patients should be evaluated and managed for opportunistic infections and adequately prepared for ART treatment with adherence counseling before embarking on ARV treatment which will reduce the high rate of lost for follow up and improve adherence.
- Improve the clinical recording of patients on ART by keeping complete clinical record including initial and follow up laboratory investigation results. The patient follow up chart have to be improved in such a way that it is easy to monitor

adherence and ADRs.

- Patients should be educated on the possible ADRs of ARV drugs
- ADR monitoring should be strengthened
- Finally, further prospective study is recommended to over come the limitations of retrospective cross sectional study and use of secondary data from clinical records with the existing clinical record keeping condition.

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Annex I: Severity grading of clinical and laboratory toxicities

Source: ANTIRETROVIRAL THERAPY FOR HIV INFECTION IN ADULTS AND ADOLESCENTS IN RESOURCE-LIMITED SETTINGS: TOWARDS UNIVERSAL ACCESS Recommendations for a public health approach 2006 revision

GRADE 1	Mild. Transient or mild discomfort; no limitation in activity; no medical intervention/therapy required.
GRADE2	Moderate. Limitation in activity - some assistance may be needed; no or minimal medical intervention/therapy required.
GRADE 3	Severe. Marked limitation in activity, some assistance usually required; medical intervention/therapy required, hospitalization possible.
GRADE 4	Severe life-threatening. Extreme limitation in activity, significant assistance required; significant medical intervention/therapy required, hospitalization or hospice care.

	Grade 1	Grade 2	Grade 3	Grade 4
Haemoglobin	8.0 - 9.4 g/dl OR 80 – 94 g/l OR 4.93 - 5.83 mmol/l	7.0 - 7.9 g/dl OR 70 – 79 g/l OR 4.31 - 4.92 mmol/l	6.5 - 6.9 g/dl OR 65 – 69 g/l OR 4.03 - 4.30 mmol/l	<6.5 g/dl OR <65 g/l OR <4.03 mmol/l
Absolute neutrophil count	1000 -1500/ mm3 OR 1.0 - 1.5/G/l*	750 - 999/ mm3 OR 0.75 - 0.99/G/l*	500 - 749/ mm3 OR 0.5 - 0.749/G/l*	<500/mm3 OR <0.5/G/l*
Hyperbilirubinaemia	>1.0 - 1.5 x ULN	>1.5 - 2.5 x ULN	>2.5 - 5 x ULN	>5 x ULN
Hypoglycaemia	55 - 64 mg/dl OR 3.01 - 3.55 mmol/l	40 - 54 mg/dl OR 2.19 - 3.00 mmol/l	30 - 39 mg/dl OR 1.67 - 2.18 mmol/l	<30 mg/dl OR <1.67 mmol/l
Hyperglycaemia (non fasting and no prior diabetes)	116 – 160 mg/dl OR 6.44 - 8.90 mmol/l	161 - 250 mg/ dl OR 8.91-13.88 mmol/l	251 - 500 mg/ dl OR 13.89 - 27.76 mmol/l	>500 mg/dl OR >27.76 mmol/l
Triglycerides	200 – 399 mg/dl OR 2.25 - 4.51 mmol/l	400 – 750 mg/dl OR 4.52 - 8.47 mmol/l	751 – 1200 mg/dl OR 8.48 - 13.55 mmol/l	>1200 mg/dl OR >13.55 mmol/l
Creatinine	>1.0 - 1.5 x ULN	>1.5 - 3.0 x ULN	>3.0 - 6.0 xULN	>6.0 x ULN
AST (SGOT)	1.25 - 2.5 x ULN	>2.5 - 5.0 x ULN	>5.0 - 10.0 x ULN	>10.0 x ULN
ALT (SGPT)	1.25 - 2.5 x ULN	>2.5 - 5.0 x ULN	>5.0 - 10.0 x ULN	>10.0 x ULN
amylase	>1.0 - 1.5 x ULN	>1.5 - 2.0 x ULN	>2.0 - 5.0 x ULN	>5.0 x ULN
Lipase	>1.0 - 1.5 x ULN	>1.5 - 2.0 x ULN	>2.0 - 5.0 x ULN	>5.0 x ULN
Lactate	<2.0 x ULN without acidosis	>2.0 x ULN without acidosis	Increased lactate with pH <7.3 without life-threatening consequences	Increased lactate with pH <7.3 with life- threatening consequences
Nausea	Mild OR transient; reasonable intake maintained	Moderate Discomfort OR intake decreased for <3 days	Severe discomfort OR minimal intake for >3 days	Hospitalization required
Vomiting	Mild OR transient; 2-3 episodes per day OR mild vomiting lasting <1 week	Moderate OR persistent; 4-5 episodes per day OR vomiting lasting >1 week	Severe vomiting of all foods/fluids in 24 hours OR Orthostatic hypotension OR intravenous Rx required	Hypotensive shock OR hospitalization for intravenous Rx required
Diarrhoea	Mild OR transient; 3-4 loose stools per day OR mild diarrhea lasting <1 week	Moderate OR persistent; 5-7 loose stools per day OR diarrhea lasting >1 week	Bloody diarrhea OR orthostatic Hypotension OR >7 loose stools/ day OR intravenous Rx required	Hypotensive shock OR hospitalization required

	Grade 1	Grade 2	Grade 3	Grade 4
Fever (oral, >12 hours)	37.7 - 38.5 0C OR 100.0 - 101.5 0F	38.6 - 39.5 0C OR 101.6 - 102.9 0F	39.6 - 40.50C OR 103 - 105 0F	>40.5 0C OR >105 0F for >12 continuous hours
Headache	Mild; no Rx required	Moderate OR non-narcotic analgesia Rx	Severe OR responds to initial narcotic Rx	Intractable
Rash hypersesnitivity	Erythema, pruritus	Diffuse maculopapular rash OR dry desquamation	Vesiculation OR moist desquamation OR ulceration	ANY ONE OF: mucous membrane involvement, Suspected Stevens-Johnson (TEN), erythema multiforme, exfoliative dermatitis
Fatigue	Normal activity reduced by <25%	Normal activity reduced by 25-50%	Normal activity reduced by >50%; cannot work	Unable to care for self

Annex -II Data collection Form

Data collection form for Addis ababa university, MPH research project on Prevalence of ADRs among patients on ART

No.....

S.N	Variable	Categories	Code
Part I- Socio-demographic			
1.	Unique ART No.	14/08/001/ _____	
2.	Age in years	_____	
3.	Sex	1. Male 2. Female	
4.	Initial Wt in kg	_____ kg	
5.	Marital status	1. Single 2.Maried 3. Divorced 4. Widowed	
6.	Educational status	1. Illiterate 2. Read and write 3. Grade 1-8 4. Grade 9-12 5. High school Certificate 6. Diploma and above	
7.	Monthly income in Birr	_____ Birr	
8.	Religion	1. Orthodox 2. Islam 3. Catholic 4. Protestant 5. Other, specify	
Part II- Clinical and laboratory state at the beginning of ART			
9.	Date confirmed HIV+	_____/_____/_____E.C. _____/_____/_____G.C.	
10.	Reason for ARV	1, Treatment 2. PEP 3. Other specify	
11.	WHO stage	1. I 2. II 3. III 4. IV	
12.	Function	1. Work 2. Ambulatory 3. Bed ridden	
13.	Initial CD4 Count		
14.	Initial TL Count		
15.	HBsAg	1. Positive 2. Negative	
16.	HCVAb	1. Positive 2. Negative	
17.	Hemoglobin		
18.	Absolute Neutrophil count		
19.	ALT		
20.	Bilirubin		
21.	Creatinine		
22.	Amylase/Lipase		
23.	Triglycerides		
24.	Cholesterol		

S.N	Variable	Categories	Code
Part III- Anti Retroviral Treatment			
25.	Treatment Naive	1. Yes 2. No	
26.	Initial Regimen	1. D4T/3TC/ NVP 2. ZDV/3TC/NVP 3. D4T/3TC/ EFV 4. ZDV/3TC/EFV 5. Other _____	
27.	Date treatment started	_____/_____/_____E.C. _____/_____/_____G.C.	
28.	Dose and frequency		
29.	Current treatment status	1. On Initial Regimen 2. Only one drug changed 3. Changed other regimen 4. All drug stopped 5. Lost to follow up 6. Unknown 7. Other, Specify _____	
30.	If initial regimen changed, Reason for changing Regimen	1. Toxicity/ Side Effects 2. Pregnancy 3. Failure of treatment 4. Poor Adherence 5. Illness/ Hospitalization 6. Drug out of stock 7. Patient lack of finance 8. Other, Specify	
31.	Current Regimen started	_____/_____/_____E.C. _____/_____/_____G.C.	
32.	Current Regimen patients on	1. D4T/3TC/ NVP 2. ZDV/3TC/NVP 3. D4T/3TC/ EFV 4. ZDV/3TC/EFV 6. 8. Other, Specify	
33.	Dose and frequency		
34.	If Stopped, reason for Stopping ART	1. Toxicity/ Side Effects 2. Pregnancy 3. Failure of treatment 4. Poor Adherence 5. Illness/ Hospitalization 6. Drug out of stock 7. Patient lack of finance 8. Planned treatment interruption 9. Other, Specify _____	
Part IV- Drug used other than ARV drugs			
35.	Are there other drugs used when the patient develop ADRs 1. Yes 2. No		
36.	Number of drugs other than ARV drugs	1. 1-2 2. 3-4 3. 4-5 4. > 5	
37.	Cotrimoxazole prophylaxis	1. Yes 2. No	

S.N	Variable	Categories				Code
38.	INH prophylaxis	1. Yes 2. No				
39.	Is patient on TB treatment	1. Yes 2. No				
40.	If answer to Q.39 is yes	1. On intensive phase (DOTS) 2. Continuation Phase				
41.	Name of other drug on use during ADRs	Dose and frequency	Date started	Date stopped		
Part V: ADRs						
42.	Does patient develop ADR	1. Yes 2. No				
Clinical Description of ADRs Measures taken -1. Reassurance only 2. Supportive treatment only 3. One drug changed 4.Regimen changed 5.All drug stopped						
		Measures taken	Date ADR Dx	Duration Pt on ART Rx		
43.	Nausea					
44.	Vomiting					
45.	Diarrhea					
46.	Headache					
47.	Fatigue					
48.	Peripheral neuropathy					
49.	Rash					
50.	Other Specify					
Laboratory		Result	Measures taken	Date ADR Dx	Duration Pt on ART Rx	
51.	Hemoglobin					
52.	Absolute Neutrophil count					
53.	ALT					
54.	Bilirubin					
55.	Creatinine					
56.	Amylase/Lipase					
57.	Triglycerides					

S.N	Variable	Categories	Code
58.	Cholesterol		
59.	Outcome of reactions	1. Deceased 2. Recovered with sequelae 3. Recovered with out sequelae 4. Not yet recovered 5. Unknown	
Part IV: Compliance			
60.	Counting remaining pills doses missed	1. Good (<= 3doses missed) 2. Fair 5-8 doses missed 3. Poor >= 9 doses missed	
61.	Reason for poor adherence	1. Financial constraints 2. Substance Abuse 3. Forgetfulness 4. Drug out of stock 5. Drug side effects 6. Inadequate adherence counseling 7. lack of motivation	

N.B. Measures taken

1. Reassurance only = Mild (Grade I) 2. Supportive treatment only = Moderate (Grade II)

3. One drug changed & 4.Regimen changed = Severe (Grade III) 5. All drug stopped = life-threatening (Grade IV)

Declaration

I, the under Signed, declare that this is my original work and has never been presented in this or any other university and that all the source materials used for the thesis have been duty acknowledged.

Name Assegid Tassew Mengistu

Signature _____

Place Addis Ababa University, Ethiopia

Date of submission _____

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

Name Professor Ahmed Ali

Signature _____

Date _____