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FIRST LINE ANTIRETROVIRAL TREATMENT FAILURE AND FACTORS ASSOCIATED WITH IT IN ADDIS ABABA, 2009

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Acronyms

3TC:	Lamivudine
AIDS:	Acquired Immune Deficiency Syndrome
ART:	Antiretroviral Therapy
ARV:	Anti RetroViral
CD4 cells:	Cells with CD4 marker
D4T:	Stavudine
ddi:	Didanosine
E.C.:	Ethiopian Calendar
EFV:	Efavirenz
G.C.:	Gregorian Calendar
HAART:	Highly Active Anti- Retroviral Therapy
Hgb:	Hemoglobin
HIV:	Human Immunodeficiency Virus
NNRTI:	Non-nucleoside Reverse Transcriptase Inhibitor
NRTI:	Nucleoside analogue Reverse Transcriptase Inhibitor
NVP:	Nevirapine
OI:	Opportunistic Infection
PCP:	Pneumocystis pneumonia
PEP:	Post Exposure Prophylaxis
PI:	Protease Inhibitors
PLWHA:	People Living With HIV/AIDS
PMTCT:	Prevention of Mother-to-child Transmission
TLC:	Total Lymphocyte Count
UNAIDS:	United Nations' Program on HIV/AIDS
WHO:	World Health Organization

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Abstract

Background

Monitoring patient response with viral load, which is the gold standard, is not feasible in resource limited settings. Therefore it's essential to look for factors that can be used to identify those patients at higher risk of treatment failure in these settings.

Objective

To explore factors that can be used to identify those at a higher risk of treatment failure.

Method

A Nested case-control study from a cohort of HIV patients on ART at government hospitals in Addis Ababa was conducted through review of medical records. A total sample size of 423 with 141 patients with failure of their first line regimen (cases) and 282 patients without failure (controls) is used. Base line socio-demographic and clinical information were collected. Comparison of survival times were made through Kaplan Meier and Log-rank tests. Independent predictors of treatment failure were identifies using multivariate COX regression analysis.

Results

The mean survival time (without treatment failure) was 53 months (95% CI, 50 – 57). Females were found to have a higher survival time of 57months (95%CI, 52-62, P= 0.01) and males have a significantly higher risk of developing treatment failure with an adjusted HR of 1.518 (95%CI, 1.084-2.125, P=0.01). Those with two or more episodes of poor adherence during their follow-up have a significantly higher adjusted hazard ratio of 4.02 (95% CI, 2.71, 5.96, P=<0.001) compared to those with no episode of poor adherence. Missed appointment is another independent predictor of treatment failure with adjusted HR of 1.77 (1.11, 2.96, P= 0.03).

Conclusion

This study has shown that non- adherence to medication and clinic visits are independently associated with treatment failure. Following patients closely for their level of adherence and their trend of missing clinic visits can be used to help identify those at higher risk of treatment failure. Providing intense adherence counseling for these patients may prevent occurrence of failure.

1. Introduction

1.1 Background

According to the UNAIDS' report, at the end of 2007 there were 33.2 million people living with HIV globally. During the same year 2.5 million new infections and 2.1 million deaths have also occurred. Of these, 22.5 million people living with HIV (68%), 1.6 million deaths (76%) and 1.7 million of new infections, were in Sub-Saharan Africa (1).

Through the advent of Highly Active Antiretroviral Therapy (HAART) in 1996 HIV/AIDS, which was once an infectious disease with an almost universally fatal outcome, has been transformed into a manageable chronic infectious disease. Antiretroviral drugs are drugs which act against viral replication through different mechanisms. These drugs have dramatically reduced rates of mortality and morbidity and have improved the quality of life of people with HIV/AIDS (2- 4).

Considering the fact that the majority of PLWHA are found in resource poor countries where access to antiretroviral treatment was very much limited due to high drug cost, need for trained personnel and sophisticated laboratory monitoring of patients, WHO (in collaboration with other partners) launched the three-by-five initiative in 2003, treating 3 million people by 2005 (5). Although the initiative failed to reach the target of 3 million by 2005, at the end of 2006, it was estimated that there were over 2 million HIV-infected individuals in low and middle-income countries accessing ART. This number improved to about 3 million [2 700 000–3 280 000] at the end of 2007, nearly 950 000 more compared with the end of 2006 (6).

In sub-Saharan Africa the initiative was able to increase the number of individuals on ART from approximately 100,000 (2% out of 4.4 million in needed of treatment) in 2003 to 810 000 by the end of 2005 and to 1,340 000 (28%out of the 4.8 million in need) by

the end of 2006. Despite progress, antiretroviral therapy coverage remains low, only 31% [27–34%] of people in need were receiving antiretroviral therapy in 2007 (6-8).

ART is a treatment to be taken for life. The fact that some of these drugs are prone to cause short and long-term toxic effects and the need for high level of adherence rate, ideally more than 95%, makes compliance difficult for patients. This in turn affects the effectiveness of the treatment leading to treatment failure (9, 10).

There are three different types of antiretroviral treatment failure namely clinical, immunological and virological failures. The WHO 2006 global guidelines define each as:

• Clinical failure when there is a new or recurrent WHO stage III or IV condition;

• Immunological failure when CD4 falls to the pre-therapy baseline (or below) or there is a 50% fall from the on-treatment peak value (if known) or CD4 levels are persistently < 100 cells/mm3; and

• Virological failure when plasma VL > 400 copies/ml.

First Virologic failure appears then immunologic failure follows and at last clinical failure occurs.

Ethiopia is among the countries most heavily affected by the HIV epidemic. The cumulative number of PLWHA is a little more than 1 million (11). Since 2004, there were an estimated 105,453 and 27,226 new AIDS cases in the adult and children population respectively. Some 90,000 adults and 25, 000 children have died of AIDS. About 265,000 PLWHA were in need of antiretroviral treatment, and of this, only 2% could afford to pay for it (12). Considering this the Government of Ethiopia has launched its free ART initiative in 2005 in collaboration with WHO. As a result of this initiative at the beginning of March 2009, there were 339,635 patients ever enrolled in the HIV care

and ART services. The cumulative number of those ever started on ART was 189,267 and of these 139,494 were still on ART (13).

1.2 Statement of the Problem

Even though the introduction of antiretroviral therapy is a breakthrough in the management of HIV/AIDS, the need for close follow-up of patients with different laboratory investigations in addition to the drug cost has made it difficult especially for resource limited settings to give optimal care for patients. Antiretroviral drugs are medications to be taken for life and they need follow up to make sure they are still helping to achieve maximal viral suppression so that in the event they failed to do so the regimen could be changed immediately. Failure to achieve optimal viral suppression will lead to the development of drug resistant virus. In resource limited settings, routine monitoring of patient's progress with viral load measurement which is the gold standard for the detection of early treatment failure is near impossible (5,7). This is because of the sophisticated and expensive laboratory facility and training of personnel needed for determining viral load. As a result, in resource limited settings treatment failure is often diagnosed based on the clinical or immunological criteria which occur way after the occurrence of virologic failure. Keeping patients on a failing regimen leads to the reversal of clinical conditions of patients to the pre-treatment state and development of drug resistant strains (14). Once drug resistant virus starts transmitting in the population the consequences will be devastating.

Therefore, for resource limited settings it would be best to look for ways of predicting treatment failure early. Knowing factors that can help to predict treatment failure will help to identify those clients that are at a higher risk of failure. Armed with this information, clinicians could give such patients special attention during their follow-up and the limited resources available for diagnosing treatment failure can be used for them.

Ethiopia being one of the resource-limited countries has similar problems. However, no study is done to assess treatment failure and factors that are associated with it in the Ethiopian context. Since viral load determination is not used in the management of HIV, the lack of this kind of study will affect the effective follow-up and management of patients. With no routine viral load monitoring and unaware of factors that predict treatment failure early, health providers are forced to keep patients on a failing regimen for a longer duration, which leads to development of drug resistant HIV strains. Furthermore, in the absence of predictive factors, the scarce resources available may be wasted unnecessarily by using it for patients that are less likely to develop treatment failure (15). This study will assess factors associated with first line antiretroviral treatment failure and it will provide information for clinicians to use in the follow-up and management of patients. Public health professionals will use the information generated in the design of ART related programs and care and support endeavors.

2. Literature Review

2.1 General Overview of the Use of Antiretroviral Therapy

The advent of potent Highly Active Antiretroviral Therapy (HAART) in 1996 led to a revolution in the care of patients with HIV/AIDS in the developed world. These treatments have dramatically reduced rates of mortality and morbidity and have improved the quality of life of people with HIV/AIDS. Most importantly, through antiretroviral therapy, HIV/AIDS which was once an infectious disease with an almost universally fatal outcome has been transformed into a manageable chronic infectious disease (2).

A study in US that evaluated Twelve hundred fifty-five study participants who were on different ART regimens found that mortality among these patients declined from 29.4 per 100 person-years in 1995 to 8.8 per 100 person-years in the second quarter of 1997. There were reductions in mortality regardless of sex, race, age, and risk factors for transmission of HIV. The incidence of major opportunistic infections also declined from 21.9 per 100 person-years in 1994 to 3.7 per 100 person-years by mid-1997 (3).

Another study from Canada has demonstrated a similar finding of significant improvement in mortality and AIDS-free survival for men and women who received initial therapy with combination antiretrovirals (4). A report from WHO European Region countries also shared this result of increased survival; decreased HIV associated mortality and vastly improved quality of life (16). Antiretroviral drugs give these results by way of suppressing viral replication which then leads to the restoration of number and quality of CD4 cells.

Despite these beneficial effects, antiretroviral therapy is not an easy task both for the service providers and the patients. For optimal use it needs highly qualified personnel and sophisticated laboratory services in addition to high level of commitment from patients, which is difficult since it’s a treatment to be taken for life. In controlled clinical trials,

different combinations of antiretroviral drugs have reduced plasma HIV-1 RNA levels to less than 500 copies/mL in 60 to 90% of patients (17-19). However, since such therapy involves complicated dosing schedules, side effects in a substantial number of patients, and a need for high degree of adherence (> 95%) to maintain viral suppression, studies out side of the clinical trials have shown that between 10–50% of patients who start HAART fail to achieve adequate virological control (20,21). This in the long run affects the effectiveness of the drugs and leads to the development and transmission of drug resistant strain (9, 10). Failure to achieve adequate virological control will also cause recurrences of illness and with it the inevitability of decreased quality of life and premature death from the disease.

In developing countries where most of the 33 million people living with HIV/AIDS reside, the transformation brought to the care of patients with HIV/AIDS through ART was unthinkable for a long period of time. This is as a result of lack of trained human resource and well equipped laboratory facility in addition to the high cost of the drugs (1, 16). According to an assessment by WHO in 2003, of the 6 million people from developing countries in immediate need of life-sustaining ART, only about 400,000 patients, which was about 8%, were being treated. Over a third of these were in Brazil, a country that produces ART, and another 100, 000 (2% of those in need) in Africa (16). Taking this into consideration WHO, in collaboration with UNAIDS, Global Fund to Fight AIDS, Tuberculosis and Malaria, the United States Presidential Emergency Plan for AIDS Relief and other bilateral programs, launched the 3 by 5 initiative (Treating 3 million people in need of ART by 2005) in September 2003 (5,22). The goal of the Initiative was for WHO and its partners to make the greatest possible contribution to prolonging the survival and restoring the quality of life of individuals with HIV/AIDS, advancing toward the ultimate goal of universal access to antiretroviral therapy for those

in need of care, as a human right and within the context of a comprehensive response to HIV/AIDS.

Pilot studies done prior to the launch of the initiative, have demonstrated the clinical feasibility and effectiveness of HAART in a range of resource-poor settings, including Cameroon, Cote d'Ivoire, India, Kenya, Malawi, Senegal, South Africa and Uganda. The results from the pilot studies have shown positive outcomes for patients that compare with those found in rich countries, in terms of decrease in viral load, increase in CD4 cell count, decrease in morbidity associated with opportunistic infections (OIs), and similar rates of side effects (23).

A cross-sectional, observational study conducted on 137 HIV-infected patients who were receiving antiretroviral therapy in Uganda reported that a total of 93% of patients were unable to hold a job when HAART was initiated, yet 85% reported feeling "good" to "excellent" following at least 12 weeks of treatment, and 96% reported better performance at home or work. None of the patients felt weaker while receiving HAART. These short-term clinical results in economically disadvantaged individuals with HIV infection are comparable with the outcomes observed in larger cohorts of less severely immune-compromised individuals in industrialized nations (24). Another paper from the same country also showed that, those who survived and remained on therapy derived long-term virologic and immunologic responses to ARV drugs in a manner similar to that observed in western countries (25).

In a review- article, where twenty-eight articles and abstracts involving studies from 14 African countries were reviewed to assess lessons learnt from provision of ART in Africa, it was found that many studies have reported positive health outcomes, including high levels of treatment adherence that were comparable to those of industrialized countries leading to a conclusion that provision of ART in resource-limited settings is

feasible (26). These and other preliminary results from the limited African HAART experiences were encouraging and appear to be comparable to those seen in Western countries (27-31). However, most of them relate only to short-term follow-up (mostly 12 months), whereas experience in Western countries shows that HAART management becomes more difficult with time (because of increasing toxicity, decreasing adherence, treatment failure & switches and emergence of drug resistance). One study, that compared responses in European and African patients, reported better virologic responses in European than African patients after 21 months of treatment, despite similar initial responses (32).

2.2 First Line Treatment Failure

Triple combination antiretroviral therapy for HIV infection has been in use for more than a decade globally. The primary initial goal of treatment is to suppress viral replication. Viral suppression enables recovery of the number of CD4 lymphocyte cells and hence CD4-mediated immune responses, and thereby reduces risk of opportunistic infections and death.

The first-line antiretroviral regimen usually consists of two nucleoside reverse transcriptase inhibitors (NRTIs) (D4T, 3TC & ZDV) and one non-nucleoside reverse transcriptase inhibitor (NNRTI) (Nevirapine or Efavirenz), i.e. 2NRTIs (either D4T-3TC or ZDV-3TC) plus 1NNRTI (either Efavirenz or Nevirapine).

Once a patient has initiated the first-line regimen, there are various reasons to change this regimen. These can be generally classified into two groups:

1. Substitution

This refers to the replacement of antiretroviral drug by another in the same regimen.

The various indications for substitution include:

Toxicity: Substituting a safer drug for an offending agent e.g. Stavudine for Zidovudine induced anemia

***Pregnancy*:** substitution of a safer drug during pregnancy e.g. Substituting Nevirapine in place of Efavirenz to prevent vertical transmission of HIV and avoid teratogenicity.

Drug-drug interactions: For example, a patient on a Nevirapine-based regimen developing TB being shifted to an efavirenz-based regimen to avoid the rifampicin-associated drug interactions.

2. Switching

This refers to changing an entire regimen, when patients fail their first-line ART regimen, to a second-line regimen.

Treatment failure is often associated with virologic failure, immunologic failure, and/or clinical failure. There are many factors that may lead to treatment failure, such as: inadequate adherence, drug side effects and toxicity leading to poor adherence, drug-drug interactions between the antiretroviral drugs and other concomitantly administered drugs resulting in sub- therapeutic antiretroviral drug concentrations and suboptimal potency of the antiretroviral regimen.

Virologic failure, immunologic failure and clinical failure have distinct time courses and may occur independently or simultaneously. In general, virologic failure occurs first, followed by immunologic failure, and finally by clinical failure. These events may be separated by months to years. The delay between virological and immunological failure carries the risk of exposing HIV to a failing regimen. This can lead to development of further cross resistance, which compromises the efficacy of the second-line regimen. Thus, viral load monitoring offers the advantages of detecting treatment failure early and preventing accumulation of further resistance mutations. Hence plasma viral load

determinations are recommended every six months to identify virological failure early (3, 4, 7, 14).

The decision on when to switch from first-line to second-line therapy is critical. If the decision is made too early the months and years of potential further survival benefit from any remaining first-line effectiveness is lost; if it is made too late, there will be accumulation of resistance mutations. (14)

Treatment failure is an increasing concern in the use of ART. Despite the reduction in morbidity and mortality, a considerable proportion of patients fail to achieve a sustained virologic response to therapy due to different reasons (33-35). A study from South Africa that assessed prevalence of HIV-1 drug resistance after failure of a first line HAART regimen reported that out of a total of 124 antiretroviral-treated adults who experienced virologic failure 83.5% of participants carried ≥1 significant drug resistance mutation (36). A similarly high prevalence of ARV drug resistance was reported among samples from patients who experienced treatment failure of first-line regimens in Zimbabwe and Uganda (33, 37, 38).

2.3Predictors of first line treatment failure

Monitoring the efficacy of treatment in countries with limited resources is difficult. In these settings, inadequate laboratory facilities, shortage of trained staff, and costly laboratory reagents prohibit the assessment of treatment failure through viral load monitoring, which is the gold standard (39). Therefore, it is important to look for alternative factors that can be used as predictor of treatment failure. Several studies are conducted, both in the high and low income countries, to assess the different factors that can predict the risk of developing subsequent treatment failure.

A prospective multicenter study from Germany reported that antiretroviral drug resistance and inadequate plasma concentration were risk factors for treatment failure (35).

A retrospective cohort study from Johns Hopkins HIV Clinic in Baltimore, Maryland identified that among the different factors analyzed for 273 patients, higher rates of missed clinic appointments was found to be independently associated with failure to suppress viral load at 1 year with OR 0.27 (Confidence Interval (CI): 0.16-0.47, P < 0.001) (40). Another retrospective analysis of 829 patients from the Massachusetts General Hospital HIV out patient clinic, found that 614 of them had at least 1 HIV RNA measurement of ≤400 copies/mL during the study period. Of these, 167 (27.2%) experienced treatment failure. Baseline characteristics independently associated with treatment failure were: poor adherence (hazard ratio [HR] = 3.44; 95% confidence interval [CI]: 2.34 to 5.05), absolute neutrophil count <1000/mm3 (HR = 2.90, 95% CI: 1.26 to 6.69), CD4 count <200 cells/mm3 (HR = 1.90, 95 % CI: 1.31 to 2.76) and >1 missed visit in the prior year (HR = 1.56, 95% CI: 1.13 to 2.16) (41).

The EuroSIDA study, a prospective observational study of HIV-1–infected patients from 70 centers in 27 countries across Europe, plus Israel and Argentina and another study from Thailand found pre-HAART (baseline) CD4 count of less than100 cells/mL to be an independent predictor of immunological failure (relative hazard [RH], 2.05; 95% CI, 1.83–2.31; p< 0.0001) and [hazards ratio (HR) 0.20; 95% confidence interval (CI) 0.17–0.23] respectively (42,43).

A Brazilian study that evaluated 454 patients reported virologic failure in 127 (28%) of them. Analysis of a subset of 158 patients with baseline CD4 count ≤ 200 cells/μL who started therapy after 1999 showed that factors independently associated with virologic failure were non-adherence (OR: 8.78; 95% CI: 1.49 to 51.80) and number of years of formal education (OR: 6.05 for those with <5 years of formal education; 95% CI: 1.02 to 35.99) (44).

A study done in India to assess predictors of failure of first-line antiretroviral therapy reported that the cumulative incidence of treatment failure in the 1370 adult patients included in the study was 3.9% (95% confidence interval [CI] 2.9 to 4.9). Male patients had a 3.5 (95% CI 1.6 to 7.4) times significantly greater hazard ratio for treatment failure compared with female patients ($P < 0.001$). Patients from urban areas had 1.9 (1.1 to 3.2) significantly greater hazard ratios for treatment failure compared with those from rural areas ($P = 0.021$). Those patients who exhibited a negative change in absolute lymphocyte count during follow-up had 3.2 (1.6 to 6.2) times significantly greater hazard ratios than those in whom the change was positive over time ($P < 0.001$). Patients exhibiting a negative change in hemoglobin concentration had 3.1 (1.6 to 6.2) times significantly greater hazard ratio values for treatment failure compared with those in whom there was a positive change ($P < 0.001$). Similarly, patients who had a negative change in body weight over time had 3.5 (1.9 to 6.4) times significantly higher hazard ratio for treatment failure compared with those with a positive change in body weight ($P < 0.001$). In the analysis of association of treatment regimen and treatment failure, compared to other regimens, the percentage of treatment failure (15.8%) was significantly greater ($P < 0.05$) in the regimens that included efavirenz, which were mostly given to patients receiving rifampicin as part of their treatment for concomitant

tuberculosis. These results show that monitoring of hemoglobin concentration, absolute lymphocyte count, and body weight during follow-up can be used as inexpensive predictors of treatment failure in a resource-poor setting (45).

A cross-sectional study conducted in Tanzania to assess predictors of virologic failure among 150 adults, who have been on ART for more than 6 months, reported that forty-eight (32%) of 150 subjects had plasma HIV RNA levels >400 copies/mL and met the definition for virologic failure. The analysis showed that virologic failure was significantly associated with incomplete adherence (AOR, 3.6; p<.03). Disclosure of HIV infection status to someone other than health care providers (AOR, 0.10; p<.04) and higher weekly house- hold expenditures (AOR, 0.96; p<.03) were found to be protective (46).

In Uganda a 12 months follow up study of five hundred twenty-six adults and 250 children (0 to 18 years of age) who were started on first-line ART regimens found that compared with adults with viral suppression, a greater proportion of those with viral failure at 12 months were taking the d4T/3TC/NVP regimen versus ZDV/3TC/EFV and this was found to be an independent baseline predictor of viral failure (odds ratio [OR] = 2.59, 95% confidence interval [CI]: 1.20 to 5.59; P = 0.02) (47). Another paper from Uganda compared characteristics of patients with detectable viral load with those of patients with undetectable viral load. And in the result, treatment-naïve patients had a greater likelihood of viral suppression than did treatment-experienced patients (OR, 2.6; 95% CI, 1.1–6.1), and a history of unplanned treatment interruption was significantly associated with virologic treatment failure (OR, 0.2; 95% CI, 0.1–0.6) (24).

A study from Lusaka, Zambia demonstrated that, those with poor adherence appeared to have an attenuated CD4 response at 18 months (185 cells/µl vs. 217 cells/µl; $P < 0.001$), 24 months (213 cells/µl vs. 246 cells/µl; $P < 0.001$), 30 months (226 cells/µl vs. 261 cells/µl; $P < 0.001$) and 36 months (245 cells/µl vs. 275 cells/µl; $P < 0.01$) when compared with those with optimal adherence (48).

According to a study from Seoul, South Korea, among other factors, longer total elapsed time without clinical visits for 1 year after HAART initiation was a significant risk factor for the occurrence of new AIDS-defining illnesses (clinical failure) or death. Compared with no missed visits, the hazard ratio adjusted by clinical stage and number of new drugs in HAART was 2.87 (95% confidence interval [CI], 1.34-6.16, $P = 0.007$) for one missed appointment, 4.37 (95% CI: 1.74-10.98, $P = 0.002$) for two, and 8.19 (95% CI: 2.95-22.78, $P < 0.001$) for three or more, leading to a conclusion that adherence to clinic visits early after initiation of HAART is an independent predictor for long-term clinical progression in HIV patients (49).

3. Objectives

3.1 General Objective:

→ To explore factors associated with first line antiretroviral treatment failure in HIV positive patients taking ART in Addis Ababa

3.2 Specific Objectives

→ To determine survival time for failure of first line treatment failure

→ To compare survival time with out treatment failure among different groups

→ To assess factors associated with first line treatment failure

4. Methodology

4.1 Background information of study Area – The study was conducted in Addis Ababa, the capital city of Ethiopia. It has an area of 450 square kilometer with an estimated population of 2.7 million. Currently ART service is being given at 49 sites (9 public, 11 private and 3 uniformed forces hospitals plus 26 health centers) in the city. Of these sites, all public hospitals providing free ART service to the general public were selected for the study. These hospitals are Black Lion; Zewditu Memorial, St. Paul's, Ras- Desta, Yekatit 12, Minilik II, St. Peter's and ALERT. As of March 2009 there were a total of 76703 patients ever enrolled for the HIV care and ART services at the public health care facilities in Addis Ababa and there were 44414 ever started on ART and 33363 of these were still on ART.

Hospitals are sites which are equipped for close follow-up of patients who are failing their first line ART and are capable of provision of second line antiretroviral treatment. For these reasons only hospitals were considered for the study, not health centers. Once patients were started on ART, after thorough baseline assessment, they were appointed every two weeks for the first month to assess for tolerability of the drugs, presence of any side effect and for adherence counseling, and then every month till the third months then after every two to three months for follow-up. During the visits different follow-up investigations were done to assess patients' response. However, as it was noticed during the data collection, other than the baseline investigation, there was no uniformity across patients and hospitals with regard to time for follow-up investigations.

4.2 Study design: A Nested case-control study from a cohort of HIV patients on ART at government hospitals in Addis Ababa was conducted through review of medical records.

4.3 Source population: All HIV positive patients started on First line antiretroviral treatment at Addis Ababa public hospitals with age above 18 were source population.

4.4 Study subjects: HIV positive patients started on first line ART between 1/1994 and 1/ 2001 E.C. [9/2001 and 9/2008 G.C.] and have complete information on important parameters.

End point;

For Cases: Failure of first line regime

For Controls: Last date of visit for those who have withdrawn from the follow-up, and 30 April, 2009 for those who are still on follow up

4.5 Sampling method:

- All public hospitals providing free ART service for the general public were included in the study.
- All cases in the selected hospitals with full baseline information and fulfilling the inclusion criteria were included in the study
- Simple random sampling was used to identify controls. And in order to make the duration on ART for cases and controls comparable controls were selected from those who started ART on the same day as cases.

4.6 Sample size determination: Sample size was determined for two population proportions, taking type one error to be 5%, power 80%, and by using the following formula

$$n_1 = \frac{Z_{\alpha/2}\sqrt{[1 + 1/r]p(1-p)} + Z_{\beta}\sqrt{p_1(1-p_1) + p_2(1-p_2)/r}}{(p_1 - p_2)^2}$$

Where; n_1 = the required sample size for the cases

n_2 = the required sample size for the controls

$n_1:n_2$ = 1:2

p_1= Proportion of exposure in case

p_2= Proportion of exposure in controls

$P = \frac{p_1 + rp_2}{1+r}$

α= Type-I error (0.05)

$Z_{\alpha/2}$= Critical value at 95% level of confidence

Z_{β} = standard normal distribution value corresponding to power

Sample size was calculated for exposure status in different variables. Since there was no study in this area in Ethiopia, proportions of exposure status in these variables were taken from studies done in other countries (24, 41, 42, 45) (Table 1).

Table 1: Sample Size Determination

Variables (exposure)	Proportion of exposure in cases (%)	Proportion of exposure in controls (%)	Sample size for case (no.)	Sample size for controls (no.)	Total sample size (no.)
≥1 Missed visit	53.3	32.4	71	142	213
Poor Adherence	24	4	38	76	114
CD4< 200	29.9	15.7	109	218	327
ART interruption	43	13	29	58	87

Taking the largest calculated sample size, 327, and adding 10% for incomplete data, 33, the resulting minimum sample size was 360. To increase the power of the study, all cases in the selected hospitals fulfilling the inclusion criteria were included. The final total sample size was 423, 141 cases and 282 controls.

4.7 Data collection procedure

Data collection format that will help to extract all the necessary information with regard to the variables of interest was prepared by the principal investigator. ART nurses in the selected hospitals were recruited as data collectors and supervisors for their respective hospitals and were given training on how to extract information from the patients' medical records. Then pre-testing of the data collection format was done and modifications were made based on the findings. Identification of cases was done by the principal investigator through the help of the ART registers and patient medical charts and controls were selected with a ratio of one- to- two.

For those study subjects whose dates of appointment fail within the data collection period, the data collectors explained about the study and asked for verbal consent directly. If the dates of appointment were out of the data collection period, patients' consent was sought via telephone, using phone numbers registered on the charts. Then after, data collectors reviewed medical records of the selected cases and controls and filled the data collection format.

4.8 Operational Definitions:

4.8.1 Treatment Regimens:

- First-line ART: the initial regimen prescribed for patients fulfilling national clinical and laboratory criteria for starting ART. Current WHO

treatment guidelines recommend two NRTIs and one NNRTI for initial treatment. This includes one of the following combinations d4T/3TC/NVP, ZDV/3TC/NVP, d4T/3TC/EFV, ZDV/3TC/EFV and this is what is used as first line regimen in Ethiopia

- Second-line ART: is the regimen used immediately after first-line therapy has failed (clinically, immunologically or virologically). Current WHO treatment guidelines recommend that the PI class be reserved for second-line ART, preferring ritonavir-boosted protease inhibitors (bPIs) supported by two agents from the NRTI class. In this study for most of the cases regimens used as second line were Kaletra/TDF/3TC and in some cases there was an addition of ddI to the above regimens

4.8.2 Treatment failure:

- Clinical failure when there is a new or recurrent WHO stage 3 or 4 condition
- Immunological failure when CD4 falls to the pre-therapy baseline (or below) or there is a 50% fall from the on-treatment peak value (if known) or CD4 levels are persistently < 100 cells/mm3
- Virological failure when plasma VL > 400 copies/ml
- In this study treatment failure is considered when, due to at least one of the above criteria, first line regimen is changed to second line regimen

4.8.3 Adherence

- Good Adherence: > 95% of doses are taken(less than three doses are missed during the month)
- Fair Adherence: 85 – 94% of doses are taken (three to nine doses are missed during the month)

- Poor Adherence: <85% of doses are taken (more than nine doses are missed)

4.8.3 Inclusion criteria:

- HIV positive patients on ART in Addis Ababa who are 18 years and above
- HIV positive patients who started ART at the site
- Those who took treatment for more than 6 months

4.8.4 Exclusion criteria:

- HIV positive patients who started ART at another site (Transferred-in)
- Those who didn't allow for information to be taken from their medical records

4.8.5 Study Variables

Dependent variable:

- Treatment failure
- Time of occurrence of first line treatment failure

Independent variables:

- Age
- Sex
- Marital Status
- Educational Status
- Disclosure of HIV infection status
- Substance abuse
- Base line neutrophil count
- Base-line CD4 count
- Stage at initiation of medication
- Type of regimens

- Adherence
- Number of missed clinical appointments
- Presence of OI at base line

4.9 Data analysis technique

Data was entered, cleaned and analyzed using SPSS software version 15. Frequencies and proportions are used to describe the study population in relation to relevant variables. Life table analysis is used to show the probabilities of failure at different intervals. Kaplan Meier and Log Rank tests were used to estimate survival time, to compare survival time among different groups and to assess the significance of the difference in survival time among the groups respectively. Bivariate COX regression analysis was done to analyze the association between dependent and independent variables and multivariate COX regression analysis was performed to see the significance of the associations by controlling for covariates.

4.10 Data quality management

Data collectors were given training on how to extract data from patient medical records using the data collection format. Frequent supervision was made by supervisors and principal investigator. Data was checked for completeness and corrections were made on those that were found to be faulty.

4.11 Ethical Consideration

The proposal was reviewed by the Institutional Review Board (IRB) of the AAU, Faculty of Medicine and also by AHRI/ALERT Ethics Review committee, AHRI/ALERT. The selected hospitals were informed about the objective of the study through a supporting letter from the School of Public Health and written permission was obtained from the

hospital administration. Since the study is conducted through review of medical records, there was no harm done to the individual patients. In order to maintain confidentiality, patients' information was collected from patient charts and ART registers by ART nurses of the respective hospitals and there was no direct contact of principal investigator with patients. In addition no information that identifies individual patients was filled on the data collection format. The recorded data was kept in a secured place with strict confidentiality and no third person had access to the data. Those patients from whose records it was found out that they have problem of adherence and compliance were given appropriate counseling through the ART nurses or counselors.

4.12 Dissemination of Results

Finding of this study will be disseminated to the Hospitals were the study was done, to the School of Public Health and to the Federal HAPCO.

5. Results

Socio-Demographic Characteristics

The number of patients with treatment failure was 144, of these 3 were excluded due to incomplete base line information. Hence a total of 423 medical records were reviewed with a response rate of 98%. Of the total patients 33.3 %(141) were cases and 66.7% (282) were controls.

Minimum age of participants was 19 and the maximum was 73, with the mean being 36.8 years. More than half of the participants, 52.5 % (222), were females. The majority 62.2 % (263) were single (never married, divorced or widower) and 36.6% (160) were married. When we see the educational status of participants, 26.7 %(113) of them have attended primary education and 46.8 %(198) of them have completed high school and only 16.1 % (68) have some form of higher education the rest 10.4%(44) were illiterates. Higher proportions of the participants, 80.1 % (339), have disclosed their sero-status to a close family member or a friend.

Most of them, 87 % (368), have no history of substance abuse and the remaining 13% (55) have history of use of different combinations of cigarette smoking, chat chewing and alcohol consumption.

Clinical Characteristics

A Higher proportion, 75.9 %(321), of the participants had no OI at baseline and 24.1 %(102) of them had different OIs, the commonest ones being TB (17.3%) and oral-candidiasis (4.7%). Baseline CD4 was 200 or less in 86.1 %(364) of the participants, the mean being123. Mean CD4 of patients with treatment failure at the time of failure was 140. More than half, 56.3 %(238), of the participants were working at baseline and 35.4 %(150) were ambulatory while 8.3 %(35) were bed ridden. After at least six months of follow-up on ART, 94.6% had functional status of working. At baseline 51.1 %(216)

were classified as WHO clinical stage III and 30% (127) were started on NVP/3TC/D4T, fig.1 & 2 show the WHO stage and ART regimen distribution among participants. The majority, 77.1 %(326), had no episode of poor adherence during their follow-up and the remaining 22.9 %(97) had one to five episodes of poor adherence. When we consider the occurrence of missed appointments, 91.5 %(387) had less than 15 days of missed appointments during their entire follow-up and 8.5 %(36) had more than fifteen days of missed appointments. Patients are given two days' of reserve medication for every month when they came for refill, since the minimum duration of follow-up in this study is seven months every patient who is taking medication properly should have drug that's enough at least for fourteen days and considering the fact that up to 2 missed doses is still good adherence, missed appointment is categorized as less than and more than fifteen days. Table 2 shows distribution of common socio-demographic and clinical characteristics among cases and controls

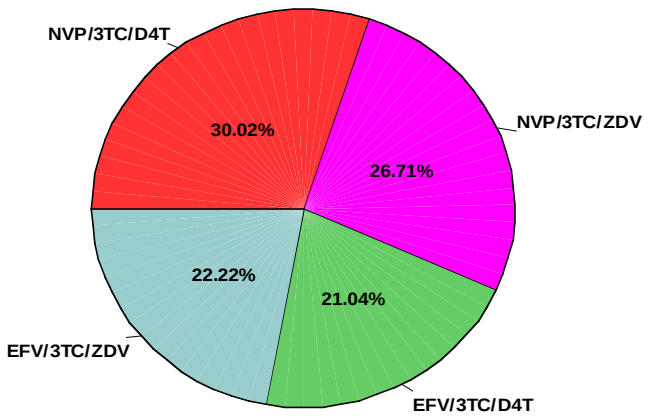

Fig.1: Distribution of First Line ART Regimen among Participants at initiation of ART, Addis Ababa, 2009

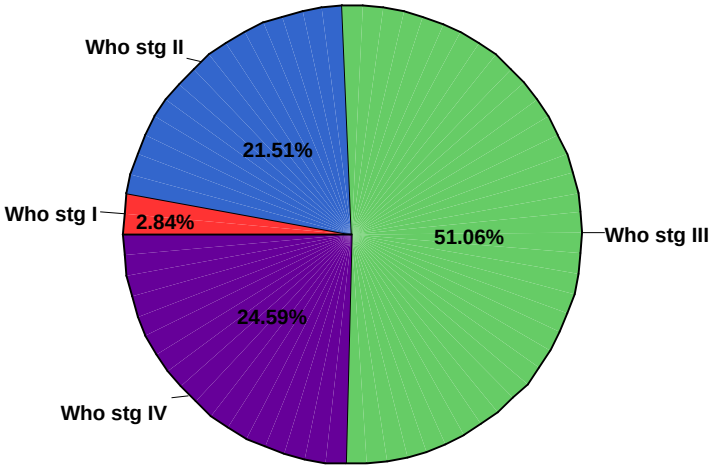

Fig. 2: WHO clinical stage of participants at initiation of ART, Addis Ababa, 2009

Table 2: The Distribution of Important Socio-Demographic and Clinical Characteristics among Cases and Controls, Addis Ababa, 2009

Variables	Total (Percent)	Frequency(percent)	
		Cases	Controls
Sex			
Male	201 (47.5)	84 (59.6)	117 (41.5)
Female	222 (52.5)	57 (40.4)	165 (58.5)
Disclosure			
Yes	339 (80.1)	119 (84.4)	220 (78.0)
No	84 (19.9)	22 (15.6)	62 (22.0)
Regimen			
NVP/3TC/D4T	127 (30.0)	39 (27.7)	88 (31.2)
NVP/3TC/ZDV	113(26.7)	32 (22.7)	81 (28.7)
EFV/3TC/D4T	89 (21.0)	36 (25.5)	53 (18.8)
EFV/3TC/ZDV	94 (22.2)	34 (24.1)	60 (21.3)
WHO Stage			
I	12 (2.8)	3 (2.1)	9 (3.2)
II	91 (21.5)	26 (18.4)	65 (23.0)
III	216 (51.1)	78 (55.3)	138 (48.9)
IV	104 (24.6)	34 (24.1)	70 (24.8)
Age			
18 – 40	305 (72.1)	91 (64.5)	214 (75.9)
41 – 60	118 (27.9)	50 (35.5)	68 (24.1)

Baseline CD4			
< 50	88 (20.8)	35 (24.8)	53 (18.8)
51 – 100	105 (24.8)	36 (25.5)	69 (24.5)
101 – 200	171 (40.4)	52 (36.9)	119 (42.2)
> 200	59 (13.9)	18 (12.8)	41 (14.5)
Adherence			
No episode of Poor Adh.	326 (77.1)	87 (61.7)	239 (84.8)
One episode	41 (9.7)	12 (8.5)	29 (10.3)
Two and more episodes	56 (13.2)	42 (29.8)	14 (5.0)
Baseline OI			
Yes	109 (25.8)	36(25.5)	73 (25.9)
No	314 (74.2)	105(74.5)	209 (74.1)
Missed Appointment			
≤ 15 days	387 (91.5)	122(86.5)	265 (94.0)
> 15 days	36 (8.5)	19(13.5)	17 (6.0)
Baseline Neutrophil			
≤ 1000	12 (2.8)	5 (3.5)	7 (2.5)
> 1000	411 (97.2)	136 (96.5))	275 (97.5)

Survival Status

Of the total 423 study subjects, 33.3 %(141) had treatment failure and 66.7% (282) were censored at 30 April 2009. Minimum duration of follow up was 7 months and the maximum 80, the median being 33 months. The median Survival Time for the whole data, using the Kaplan Meier analysis is 54 months (95%CI, 47-61). Table 2 shows the life table distribution for the data set and fig. 3 shows the survival function.

Table 3: Life Table distribution of probability of failure, Addis Ababa, 2009

Interval	No. Entering interval	No. Withdrawn during interval	No. Exposed to risk	No. of Terminal Events	Proportion Terminating	Proportion Surviving	Cumulative Proportion Surviving at the End
0 - 7	423	0	423	0	.0000	1.0000	1.0000
7 - 14	423	32	407	17	.0418	.9582	.9582
14 - 21	374	32	358	26	.0726	.9274	.8886
21 - 28	316	33	299	28	.0935	.9065	.8056
28 - 35	255	37	236	25	.1057	.8943	.7204
35 - 42	193	60	163	25	.1534	.8466	.6099
42 - 49	108	38	89	13	.1461	.8539	.5208
49 - 56	57	28	43	3	.0698	.9302	.4845
56 - 63	26	9	21	3	.1395	.8605	.4169
63 - 70	14	10	9	1	.1111	.8889	.3706

Of those who develop treatment failure only 4.18% of them do so in the first 7 to 13 months. The large proportion of failure, 15.3%, occurred in the 35 to 42 months interval and Survival is good up to 27 months and it starts to decline after that.

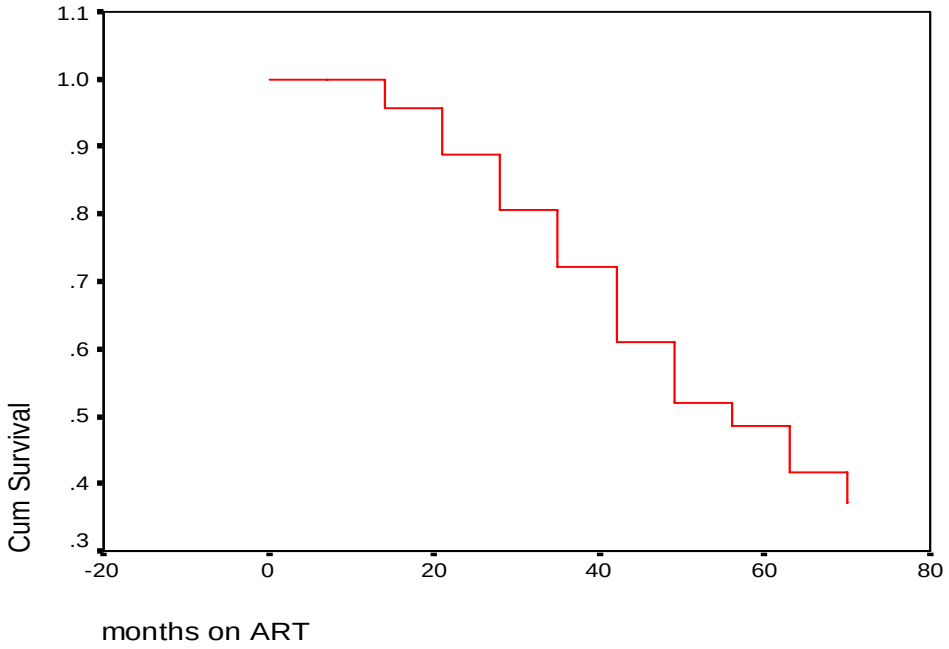

Fig.3: Cumulative probability of not developing treatment failure for patients after initiation of ART, Addis Ababa, 2009

Comparison of survival time using KM analysis showed difference among different groups as shown in Table 3. But follow up analysis using log rank test showed significant difference in survival time only in three of the variables. When survival time for sex is compared, females happened to have a better mean survival time of 57months (95%CI, 52-62) than males whose mean survival time is 47 months (95%CI, 43-51)the difference is significant with p-value of 0.01. The other significant difference is noticed between those who have a lesser number of missed appointment days (≤15) and those who have higher number of missed appointment days (>15), the first ones having a longer survival

time with P-value of 0.003. Survival time difference between those who had fewer episodes of poor adherence and those who had multiple episodes is also significant at p-value < 0.0001. Survival time gradually decreasing as we go from those who had no episode of poor adherence, 58 months(95% CI,54-62)to those with five episodes,21 months(95%CI,21- 21)the survival time decreasing by more than half (Table 4).

Table 4:Kaplan Meier and Log-rank analyses of survival time for patients on antiretroviral treatment according to important socio-demographic and clinical characteristics, Addis Ababa, 2009

	Mean survival time (95%CI)	P-value
Sex		
Male	47(43, 51)	
Female	57(52, 62)	0.01
Missed Appointment		
≤ 15 days	54(51, 58)	
>15 days	36(31, 41)	0.003
Adherence (No. of poor adherence episodes)		
None	58(54, 62)	
One	48(40, 56)	
Two	32(28, 35)	
Three	32(26, 38)	
Four	25(25, 25)	
Five	21(21, 21)	< 0.0001
Base Line CD4		
< 50	49(43, 55)	
51 – 100	46(42, 50)	
101 – 200	56(51, 61)	
> 200	43(39, 48)	0.4837

Age		
18-40	55(50, 59)	
41-80	47(43, 52)	0.1435
Regimen		
NVP/3TC/D4T	54 (49, 59)	
NVP/3TC/ZDV	49 (45, 54)	
EFV/3TC/D4T	45 (40, 50)	
EFV/3TC/ZDV	51 (44, 58)	0.3661
Base line OI		
NO	53 (49, 57)	
Yes	47 (43, 52)	0.8264
Base Line Neutrophil		
<=1000	42(32, 52)	
>1000	54(50, 57)	0.6227
Base Line Lymphocyte		
<=1200	51(45, 57)	
>1200	53(49, 56)	0.8539
Educational Status		
Illiterate	49(41, 56)	
Write & Read	48(25, 72)	
Primary	47(41, 54)	
Secondary	55(50, 60)	
Tertiary	48(42, 53)	0.6997
Disclosure		
Yes	51(47, 55)	
No	57(50, 63)	0.1267

Predictors of Failure

Bivariate Cox proportion model was used to analyze the relationship between important socio-demographic and baseline clinical characteristics and risk of treatment failure. According to the results of this study, Compared to females, males have a significantly higher hazard (HR= 1.518, 95%CI, 1.084-2.125, p=0.01) for treatment failure (Fig. 4).

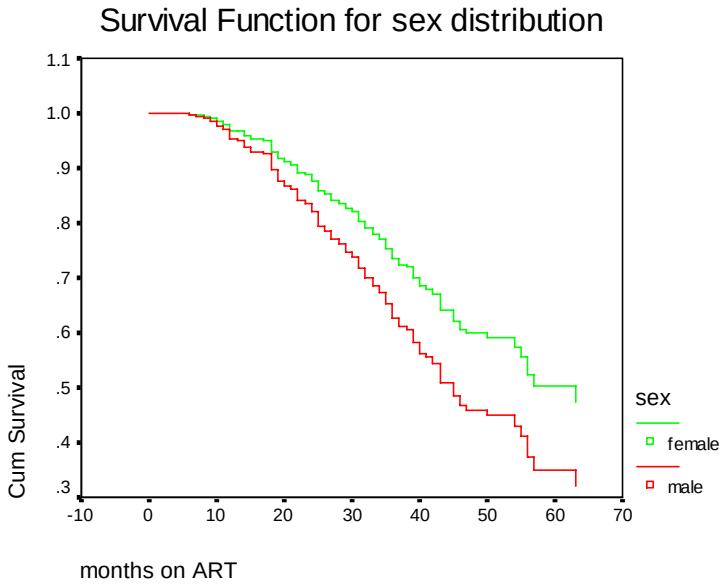

Fig. 4: Cumulative probability of not developing treatment failure according to sex of patients on ART in Addis Ababa, 2009.

Analysis of association between episodes of poor adherence and treatment failure showed that those with higher episodes of poor adherence are more likely to develop treatment failure than those who have no episode of poor adherence. The association is significant and there is persistent increase in the hazard ratio as the number of poor adherence episodes increased from one to five with respective HR of 3.782(p<0.0001), 3.710(p<0.0001), 7.541(p=0.046), 11.708(p=0.015). The difference is more pronounced

as we go from one episodes of poor adherence to two and three and from three episodes to four and then to 5 episodes (Fig. 5).

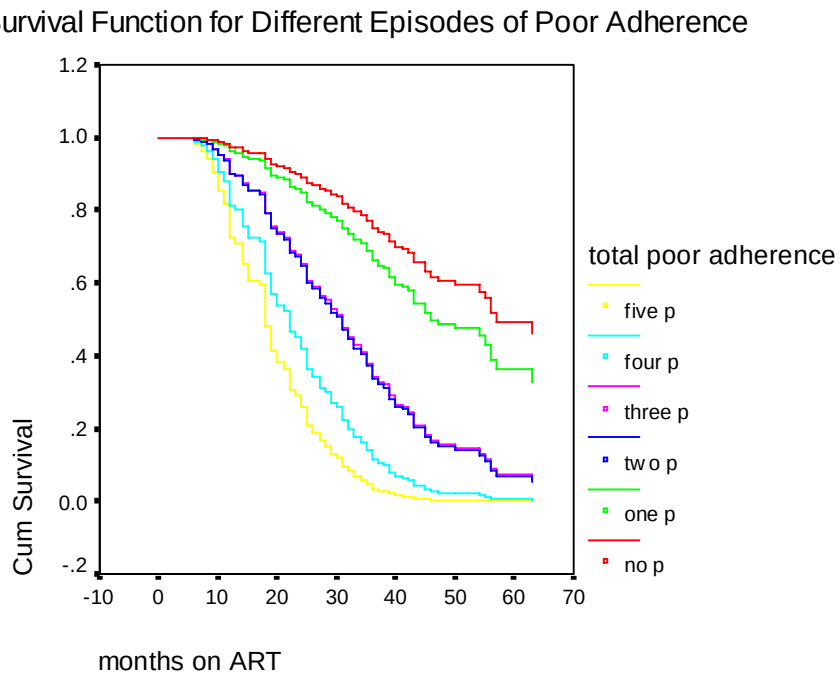

Fig. 5: Cumulative probability of not developing treatment failure for the different adherence categories, Addis Ababa, 2009

Another significant association was demonstrated between different categories of missed appointment days. when compared to those who have less than fifteen days of missed appointment, those who have more than fifteen days have a higher risk for treatment failure (HR 2.046,95% CI, 1.255 - 3.335, p=0.004)(Fig. 6).

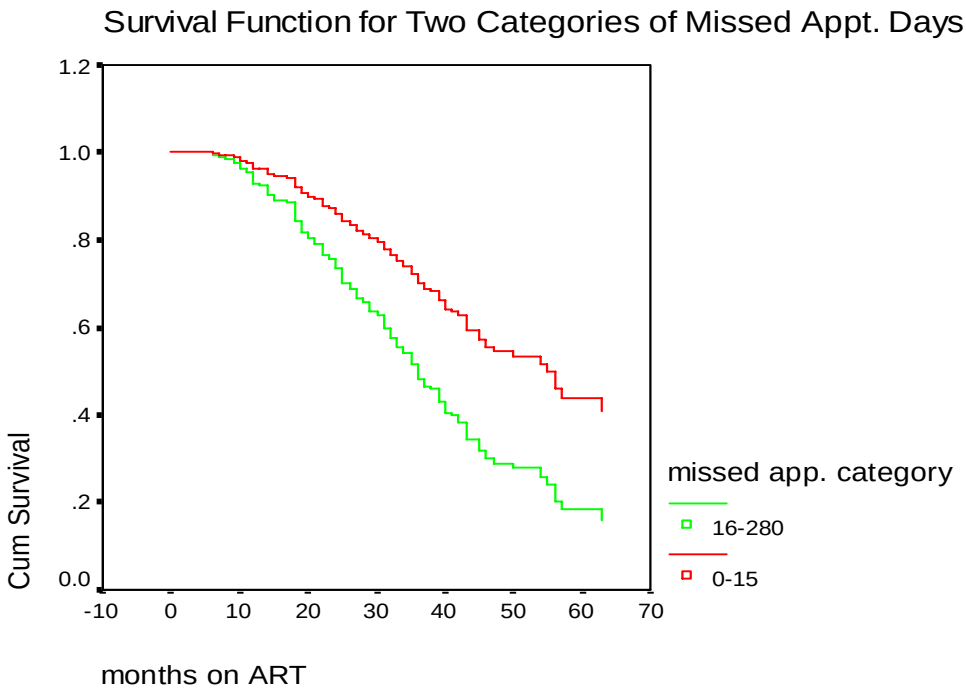

Fig. 6: Cumulative probability of not developing treatment failure for the different categories of missed appointments

Analysis for relationship between different categories of baseline CD4 levels and treatment failure has shown no significant association. The hazard ratios are 1.222 (95% CI, 0.690, 2.164) for baseline CD4 < 50, 1.091 (0.619, 1.925) for CD4 51-100, 0.882 (0.515, 1.510) for CD4 101-200 respectively when compared to baseline CD4 of more than 200.

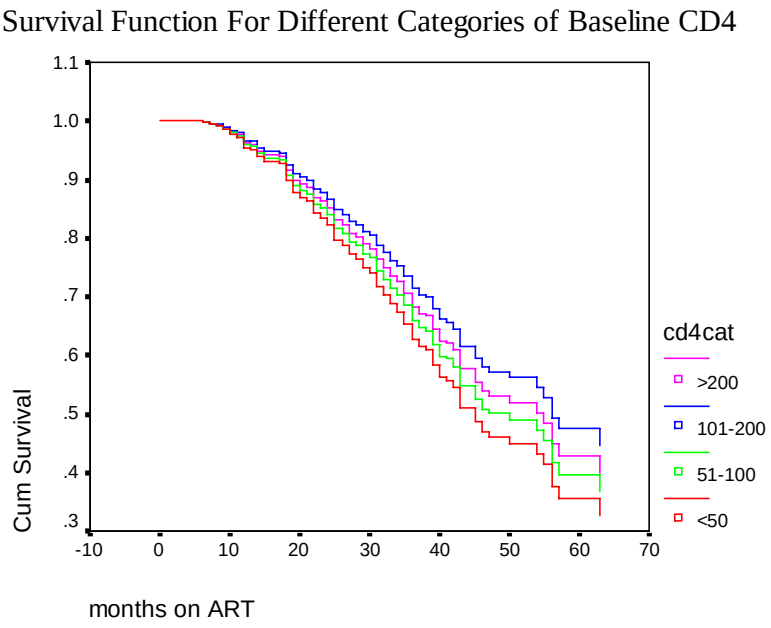

Fig.7: Cumulative probability if not developing treatment failure for different baseline CD4 categories, Addis Ababa, 2009

In this study there was no significant association between the different ART regimens patients were taking and risk of treatment failure. Different combinations of comparison such as comparing all the different regimens, comparing those on nevirapin based regimens with those on efavirenz based regimens and those with d4t based and zdv based regimens was done by using bivariat COX regression but still the association was not significant at α value of 0.05. Even though the difference was not statistically significant, When compared to Efavirenz based regimens, Nevirapin based regimens seems to be associated with a better survival (HR= .751, 95%CI .540-1.045, p=0.089) figure8 & 9

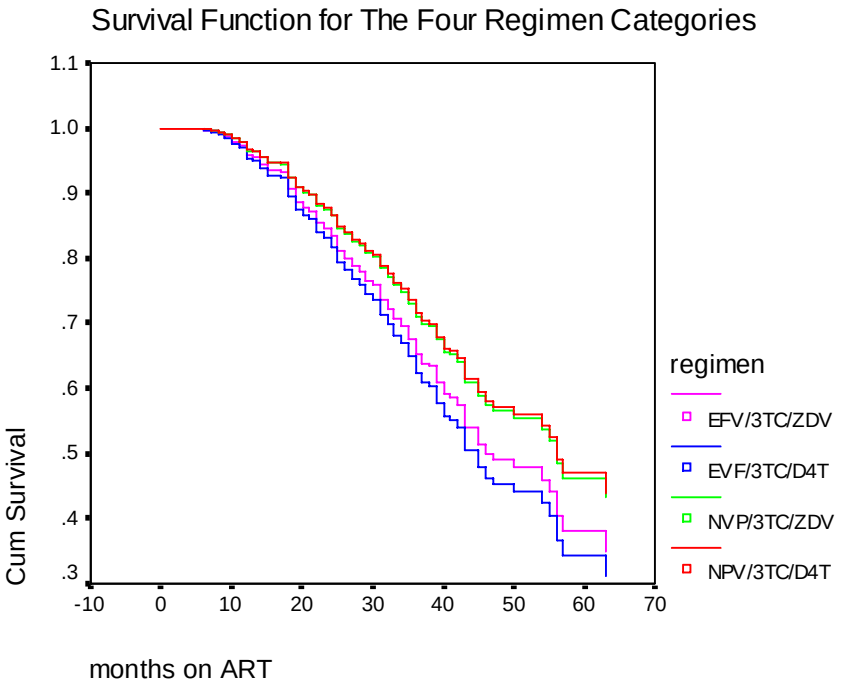

Fig 8: Cumulative probability of not developing treatment failure for the different ART Regimens

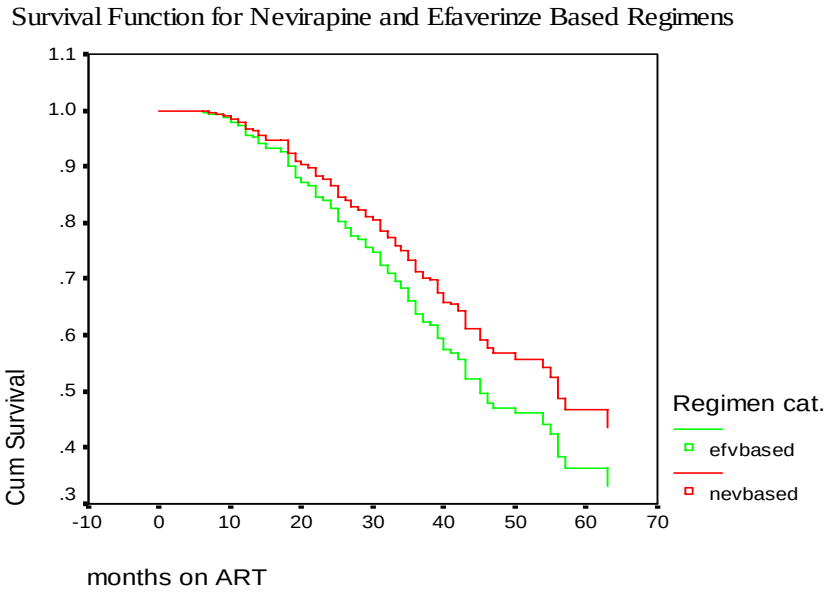

Fig. 9: Cumulative probability of not developing treatment failure for Efavirenz and Nevirapine based regimens, Addis Ababa, 2009

The Cox regression analysis for the relation between disclosure of sero-status and treatment failure showed no significant association at 5% significant level, rather it showed that compared to those who have disclosed their sero-status, those who haven't disclosed their sero-status have a lower hazard(HR=.703, 95%CI, .445-1.111, p=.131) (Fig 10).

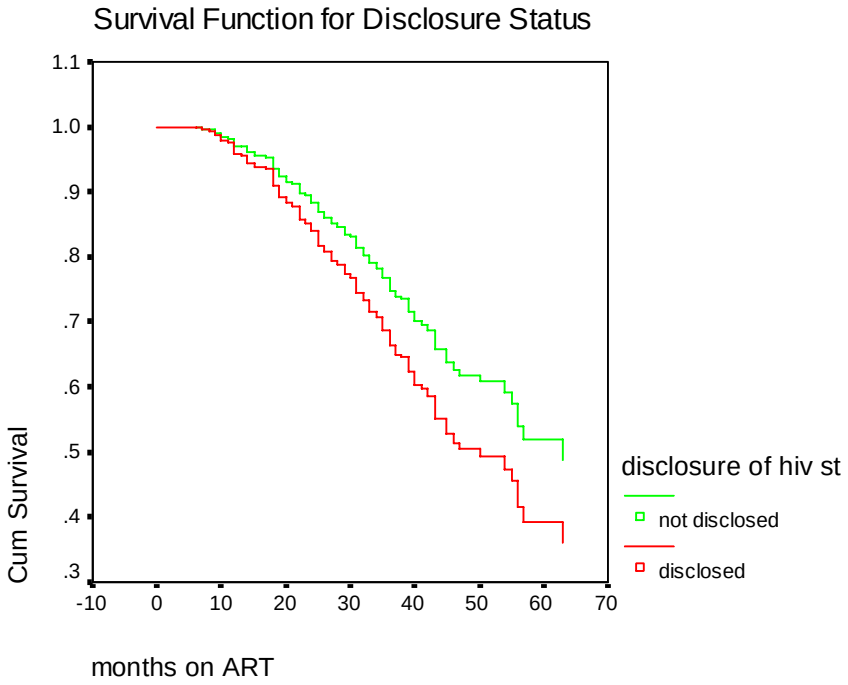

Fig. 10 Cumulative probability of not developing treatment failure for different Disclosure status

Variables such as History of substance use, educational and marital status, WHO stage at baseline, baseline hemoglobin, lymphocyte and neutrophil counts and presence of opportunistic infection at baseline, were found not to be significantly associated with treatment failure at 5% significance level.

A multivariate COX proportional hazard adjusted model was fitted with the predictor variables that were found to be significantly associated with treatment failure at $P \leq 0.05$ in the bivariate analysis and only three of them namely sex, number of poor adherence episodes and number of missed appointment days were retained in the final model (Table 5).

Table 5: Results of the Multiple COX- regression model, Addis Ababa, 2009

Covariates	Total N0.	No. failed	No. not failed	Adjusted HR	95% CI for AHR	P-value
Sex						
Male	201	84	117	1.58	(1.11, 2.27)	0.01
Female	222	57	165	1.00		
Disclosure						
Yes	339	119	220	1.00		
No	84	22	62	0.87	(0.54, 1.41)	0.58
WHO Stage						
I	12	3	9	1.00		
II	91	26	65	1.15	(0.34, 3.95)	0.82
III	216	78	138	1.40	(0.42, 4.67)	0.59
IV	104	34	70	1.30	(0.37, 4.59)	0.68
Missed Appointment						

≤ 15days	387	122	265	1.00		
> 15 days	36	19	17	1.77	(1.11, 2.96)	0.03
Regimen						
NVP Based	240	71	169	1.00		
EFV Based	183	70	113	1.20	(0.85, 1.70)	0.29
Age						
18-40	305	91	214	0.79	(0.54, 1.15)	0.22
41-60	118	50	68	1.00		
Base Line Neutrophil						
≤ 1000	12	5	7	0.99	(0.38, 2.53)	0.98
> 1000	411	136	275	1.00		
Base line OI						
Yes	109	36	73	0.96	(0.62, 1.49)	0.85
No	314	105	209	1.00		
Base line CD4						
<50	88	35	53	1.27	(0.70, 2.29)	0.43
51 - 100	105	36	69	1.17	(0.64, 2.14)	0.61
101 - 200	171	52	119	0.95	(0.55, 1.65)	0.86
> 200	59	18	41	1.00		
Adherence						
No episode of Poor adh	326	87	239	1.00		
One episode	41	12	29	1.44	(0.76, 2.70)	0.26
Two or more episodes	56	42	14	4.02	(2.71, 5.96)	<0.001

6. Discussion

This study has tried to assess variables that are significantly associated with increased risk of first line treatment failure. Follow-up of patients with routine viral load measurement is currently not feasible in our setting. Therefore identifying factors that are associated with increased risk of treatment failure is advantageous. These can be used to identify patients at a higher risk so that due attention will be given during their follow-up to try and delay development of failure.

Result from this study has shown that most of the diagnoses of treatment failure (69.5%) are made by immunologic criteria, the rest 13.4% and 17% being diagnosed by clinical and virological criteria respectively. This shows the lack of widespread use of viral load determinations in the follow-up or diagnosis of first line treatment failure of patients on ART. Using clinical and immunological criteria to diagnose treatment failure means keeping patients on a failing regimen unnecessarily this in turn results in the development and accumulation of drug resistant strains of the virus (14). This is particularly harmful in low-income settings like ours where drugs used as first line antiretroviral treatment regimens consist of NNRTIs and NRTIs which have low genetic barrier and resistant mutations can develop quite easily.

At base line 43.7% of the patients had functional status of either bed-ridden or ambulatory and only 56.3% had functional status of working. After at least six months of follow-up on ART this was changed and 94.6% had functional status of working. This is comparable with a study from Uganda where 96% of patients have reported better performance at home and work place after at least 12 weeks of treatment (24). Median CD4 count at base line was found to be 110 and this has shown improvement to 265 after at least 6 months of follow-up on ART the difference being 155, this is comparable to

that reported from a study done in Senegal which has reported median CD4 increase by 147 at 12 months and by 180 at 18 months from a base line CD4 of 108 (27). These results show that ART response in the Addis Ababa HIV patients is comparable with findings from other African settings (23, 26).

Comparison of survival time (to treatment failure) has shown significant difference in favor of females i.e. the mean survival time for females is 57 months while for males its 47months. Results from this study showed that males are at a significantly higher risk of treatment failure than females. This finding is consistent both in the bivariate and multivariate COX regression analyses with a higher hazard ratio in the multivariate analysis. This finding is similar to that of an Indian study which has found males to be at a significantly higher risk of treatment failure (45).

In this study adherence is another factor found to be associated with first line antiretroviral treatment failure. When compared to those with no episode of poor adherence who have mean survival time of 58 months, those with five episodes of poor adherence have a survival time shortened by more than half, almost one-third, which is only 21 months. Those who have poor adherence episodes ranging from one to four have mean survival time of 48, 32, 32 and 25 months respectively. This difference is statistically significant. Both the bivariate and multivariate analyses showed that a higher rate of poor adherence episode is significantly linked with increased hazard for treatment failure. The hazard ratio has shown gradual increment with increasing numbers of poor adherence episodes, showing the important relation of adherence with response to treatment. This result is consistent with studies from Massachusetts General Hospital (41), Brazil (44), Tanzania (46) and Zambia (48) which has also shown poor adherence to

be independently associated with increased risk of treatment failure. Thus, for many patients who fail to respond to initial therapy, inability to take their drug regimen properly (non-adherence) is the primary reason for failure.

It is well recognized that complete suppression of viral replication is critical for long-term durability of antiretroviral therapy and this is achieved only in the face of optimal adherence. Suboptimal adherence is a primary factor responsible for the emergence of resistant strains of the HIV virus which in turn results in treatment failure, reduction of future treatment options and potential transmission of drug resistant virus in the population. (29, 50-52).

Another important factor found to be associated with treatment failure in this study is higher number of missed appointment days. Survival time is higher for those with less than fifteen days of missed appointment when compared to those with more than fifteen days, mean survival being 54 months versus 36 months respectively. This difference was statistically significant. Further Bivariate and multivariate COX regression analyses also confirmed that higher numbers of missed appointment days are significantly associated with higher risk of treatment failure. A study from John's Hopkins HIV clinic has similar finding, that high rates of missed clinic appointments are independently associated with failure (40). A paper from Uganda has shown history of unplanned treatment interruption to be significantly associated with treatment failure (24). The Massachusetts study also showed the significant association between treatment failure and more than one missed clinical visit (41). Another paper from University of Alabama at Birmingham showed a significant relation between appointment non-adherence (missed clinic appointments) and virologic failure (53). Adherence to clinic visits early after initiation of HAART was also

found to be an independent predictor for long-term clinical progression in HIV patients in Seoul, South Korea (49).

ART interruption is problematic for patients treated with combination regimens of NNRTIs and NRTIs. This is because of the long half- life of NNRTIs and the comparatively short half- life of NRTIs. Patients who experience interruption of these regimens are exposed to functional mono-therapy with NNRTIS this then leads to development of drug resistance due to the low genetic barrier of these regimens.

These findings altogether support the finding from the German study which showed that inadequate plasma concentration of antiretroviral drugs is one of the risk factors for treatment failure. Whether it's poor adherence or missed clinical appointments the ultimate effect is sub-optimal concentration of drugs in the blood which in turn leads to sub-optimal suppression of viral replication which finally leads to treatment failure (35).

These findings of the association between treatment failure and adherence and missed appointments provide important information to clinicians and public health practitioners. These are variables that can be modified by proper follow-up and intensive and continuous adherence counseling of patients before and after the initiation of therapy. Once patients are made aware of the importance of adherence and the grave consequences of non-adherence to the medication and to clinic visits they will be more motivated to abide by the advice. This has been demonstrated in Uganda by one study which has demonstrated intensive counseling to lead to subsequent increase in CD4 in 65% of patients who were found to have clinical or immunological failure (15).

In this study, unlike that of the EuroSIDA (43) and the Thailand (44) studies which have found base line CD4 level of less than hundred to be significantly associated with risk of developing treatment failure, baseline CD4 level was not found to be significantly associated with treatment failure, both in the bivariate or multivariate Cox regression analyses. This result is shared by studies from Uganda and India which found no significant association between base line CD4 and risk of treatment failure (46, 24, 45).

In this study, even though not significant, patients who haven't disclosed their sero-status appears to have better survival than those who have disclosed their status, the difference being 6 months more for those who haven't disclosed their sero-status. This is contrary to the findings from the Tanzanian study which found disclosure of HIV status to someone other than health professional to be protective from treatment failure (46). Another study from the US has also shown disclosure to have a favorable effect on CD4 progression by relieving potential psychological distress (54). The reason could also be that information in this study was obtained at baseline this might have changed during the subsequent follow-up time.

In this study no significant association was found between the different antiretroviral regimens and treatment failure which is contrary to the study form Indian which demonstrated significant association between treatment failure and Efavirenz based regimens and that from Ugandan which has reported significant association between d4T/3TC/NVP and treatment failure when compared to ZDV/3TC/EFV (45, 47).

7. Strength and Limitation of The Study

Strengths

- This is the first study in Ethiopia that explored treatment failure
- Inclusion of all public hospitals in the study makes it more representative
- Data quality was assured by using ART nurse as data collectors
- It has included patients with longer time of follow-up giving it advantage of exploring variables effectively

Limitations

- Its being retrospective study has limited the number of variables that can be explored
- Lack of uniform follow-up investigation time has made it difficult to compare changes during follow-up
- Limitations of using secondary data like relaying on past information which can be changed subsequently

8. Conclusion and Recommendations

Conclusion

- The median survival time without treatment failure was 54 months
- Females have longer survival time than males
- Patients with multiple episodes of poor adherence have a very short survival time
- Large number of missed appointment days are associated with lower survival time
- Baseline CD4 levels, WHO stage at initiation of ART, first line ART regimen and disclosure of HIV status doesn't have significant effect on the probability of development of treatment failure
- Male sex, non-adherence and missed appointment are independently associated with increased risk of treatment failure

RECOMMENDATIONS

- Strengthen education/counseling on the advantage of adherence to medication and clinic appointments and consequences of non-adherence
- Entire treatment team should be involved in reinforcing adherence messages
- Investigate underlying causes of non-adherence, and design counseling and support programs that are relevant to our context
- Mechanisms should be put in place to contact patients who are missing their clinic appointments
- Special attention and intensive counseling should be given to patients identified as having problem of adherence
- There should be standard time for follow-up investigation across service provision sites
- Further prospective studies should be done to explore treatment failure and occurrence of drug resistance in our setting
- Strategies should be devised to make viral load monitoring available, accessible and affordable

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Annexes

Annex 1

Data Collection Format

Data collection format for Addis Ababa University, MPH research project on First-line Treatment Failure and factors associated with it among patients on ART in Addis Ababa, 2009

no	Variable	Description/Categories
Part I: Socio-demographic Characteristics		
1	Age (years)	
2	Sex	1. Male 2. Female
3	Marital-Status	1. Single 2. Married 3. Divorced 4. Widowed
4	Educational Status	1. Illiterate 2. Write & Read 3. Primary 4. Secondary 5. Tertiary
5	Occupation	
6	Date of 1st HIV test	____/_____/_____ (E.C) ____/_____/_____ (G.C)
7	Disclosure	1. Disclosed HIV status (To_____) 2. Not Disclosed
8	Substance	1. Chat Chewing 2. Cigarette Smoking 3. Alcohol Consumption

	Abuse	4. Other, Specify _____ 5. None
9	Drugs Patient is taking	
Part II: Antiretroviral Treatment		
1	Previous ART exposure	1. Yes 2. No
2	If yes to the above question How?	1. PEP 2. PMTCT Regimen _____
3	Did pt. had partner taking ART	1. Yes 2. No
4	Date ART started	_____/_____/_____ (E.C) _____/_____/_____ (G.C)
5	Regimen	1. D4T/3TC/NVP 2. ZDV/3TC/NVP 3. D4T/3TC/EFV 4. ZDV/3TC/EFV 5.Other, Specify_____
6	WHO stage at start	
7	OI at baseline	

Part III: Clinical Characteristics

		Base Line	1st	3rd	6th	9th	12th	18 1t	24th	At time of failure/last visit
1	Weight									
2	Functional Status									
3	Anti-TB R_x									

	(yes/no)									
4	Adherence									
5	No. of missed apt									
6	New OI (specify if any)									
Part IV: Laboratory Findings										
		Base Line	1st	2nd	3rd	4th	5th	6th	7th	At time of failure/last visit
1	CD4 count									
2	Hemoglobin									
3	WBC count									
4	Total Lymph count (%)									
5	Absolute Neutrophil count (%)									
6	Viral Load									
Part V: Treatment Failure										
1	Has the patient developed failure	1. Yes 2. No								

2	Date of diagnosis of failure/last visit	_____/_____/_____(E.C) _____/_____/_____ (G.C)
3	Duration on ART at time of failure	_____Weeks or _____Months
4	Type of Failure	1. Clinical 2. Immunological 3. Virological
5	The Changed regimen	_____/_____/_____

Annex 2

English Patient Information Sheet

ADDIS ABABA UNIVERSITY
FACULTY OF MEDICINE
SCHOOL OF PUBLIC HEALTH
Participant Information Sheet and Consent Form

Description of the study

Title of the study: First Line Antiretroviral Treatment Failure and Factors Associated with It

Objective of the study: Assessing factors associated with failure of first line antiretroviral treatment

Introduction

Antiretroviral treatment is used to control multiplication of the HIV virus in the human body. By doing so it improves the health status of people infected with HIV virus. However, sometimes due to different reasons the ability of ART to suppress multiplication of the virus will be compromised and this time the ART is said to have failed. Different studies have shown that the first line ART regimens will fail in 10- 50% of HIV infected patients

Rationale for doing this study and its benefits

One of the reasons for conducting this study is that there is no study done in Ethiopia on the subject. As the number of patients taking ART and the duration they are on the medication increases first line antiretroviral treatment failure will be a problem. Another reason is that Ethiopia, being one of the low-income countries, can't afford to implement follow-up of patients on ART with viral load measurement, which is the gold standard for diagnosing ART failure. Therefore knowing factors associated with ART failure will help to identify those at higher risk of developing failure earlier so that appropriate measures will be taken during their follow-up to try and avoid development of failure. This study is planned to identify those factors that are associated with antiretroviral treatment failure. The proposal for the study has been approved by Institution Review Board of Addis Ababa University and AHRI/ALERT Ethics review committee.

Information which is necessary for the study will be taken from your chart. Since the study will be conducted by taking appropriate information from your medical chart it will not inflict any harm on you and the information will be taken only when you give permission, participation is totally voluntary. You will not face any problem if you don't allow the information to be taken from your chart and there will also be no negative consequences on your treatment. Similarly you will not get any incentive for agreeing to participate in the study. Your name or any other identifying information will not be recorded on the questionnaire and all information taken from the chart will be kept strictly confidential and in a safe place plus it will only be used for the study purpose.

Annex 3
Amharic Patient Information Sheet

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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 properly acknowledged.

Name Selamawit Ejigu

Signature _____

Date of Submission _____

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

Name Dr. Alemayehu Worku

Signature _____

Date _____