ADDIS ABABA UNVERSITY
COLLEGE OF HEALTH SCIENCES

School of Allied Health Sciences

Department of Medical Laboratory Sciences

Treatment outcomes of HIV-infected patients on second line ART in selected health facilities of Addis Ababa

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II. Abbreviations

3TC	Lamivudine
AAU	Addis Ababa University
ABC	Abacavir
AIDS	Acquired Immunodeficiency Syndrome
ART	Antiretroviral Therapy
ARV	Antiretroviral
ATV/r	Atazanavir/ ritonavir
d4T	Stavudine
EFV	Efavirenz
EHNRI	Ethiopian Health and Nutrition Research Institute
EPHI	Ethiopian Public Health Institute
FHAPCO	Federal HIV/AIDS prevention and Control Office
FMOH	Federal Ministry Of Health
FTC	Emtricitabine
HAART	Highly Active Anti Retroviral Theraphy
HIV	Human Immunodeficiency Virus
LPV/r	Lopinavir/ritonavir
NNRTI	Non-Nucleoside Reverse-Transcriptase Inhibitors
NRTI	Nucleoside Reverse Transcriptase Inhibitors
NVP	Nevirapine
PI	Protease inhibitors
PLWHA	People Living with HIV/AIDS
RNA	Ribonucleic Nucleic Acid
TDF	Tenofovir
VL	Viral load
WHO	World Health Organization
ZDV	Zidovudine

III. Summary

Background: Ethiopian government launched free ART initiative in 2005, since then, there is an unprecedented effort to scale-up ART and access to HIV care. Following massive rollout of ART, large numbers of people are receiving first-line ART and as the cohort mature, the number of people living with HIV who will fail and switching will steadily increase. Identifying treatment failure in patients taking ART in order to propose early therapeutic switches to another available ART regimen is essential. In Ethiopia, there is no study on treatment outcome for the second line anti-retroviral therapy.

Objective: The aim of this study is to assess the clinical, immunological and virological treatment outcomes of patients on second line antiretroviral therapy among adult HIV/AIDS patients in selected public health facilities in Addis Ababa, Ethiopia.

Materials and Methods: A longitudinal study was conducted between July 2014 and June 2015.A total of 236 adult HIV patients who were on second line ART for more than six month were included. Clinical specimen were collected from each client during routine clinic visits. Viral load and CD4 cell count tests were done and basic clinical information were extracted from the medical record. Data analysis was performed using SPSS version 20 software. P values <0.05 was considered as statistically significant.

Result: Among the total of 236 HIV infected individuals received second line ART, 111(47%)were male and 125(53 %)were female. The mean age was 40± 10SD (18-78)years and the average time on second line treatment was 2.4± 1.17SD(0.5-7.5) years. The average CD4 count at switch to second line ART was 133 cells/mm^3(4-519)[95%CI:121.4-145] and there was significant increase in mean CD4 count to 338 cells/mm^3 after switch to second line ART. About 204 (86.4%)the of the patients had undetectable viral load.

Conclusion: In this study, we observed a significant improvement in clinical and immunological condition as well as good virological suppression in patients after starting second line therapy. Even though higher viral load suppression observed, 32(13.5%)of the study participants also have virological failure.

1. Introduction

1.1. Background

The Human Immunodeficiency Virus (HIV)/Acquired Immunodeficiency Syndrome (AIDS) pandemic is a major public health problem globally. Since the start of the epidemic in 1981 around 78 million have become infected with HIV and an estimated 39 million people have died due to HIV/AIDS. At the end of 2013 an estimated 35 million people were living with HIV and 1.5 million HIV-related deaths has occurred(1).

Sub-Saharan Africa is the most affected region, with 24.7 million people living with HIV, were women accounts for 58% of the total number of people living with HIV in 2013. In this year, there were an estimated 1.5 million new HIV infections in sub-Saharan Africa. Even though new HIV infections have declined by 33% from 2005 - 2013, Sub-Saharan Africa accounts for almost 70% of the global total of new HIV infections (1).

According to the EPP/Spectrum modeling in Ethiopia, there were an estimated 793,700 people living with HIV including 200,300 children in 2013. There were approximately 45,200 AIDS related deaths and about 898,400 AIDS orphans in the same year (2).

Scaling up of prevention, care and treatment for HIV/AIDS is important for the control of the disease. The introduction of highly active antiretroviral therapy (HAART) was the significant breakthrough in the battle against HIV/AIDS. Globally, a total of 10.6 million people were receiving antiretroviral therapy as of December 2012.The scaling up of ART has averted 6.6 million AIDS-related deaths worldwide, including 5.4 million deaths in low- and middle-income countries from 1995-2012 (3).

In Ethiopia, ART was rolled-out in 2005 and has since then expanded in a large scale and substantially decreased AIDS related deaths. The number of eligible patients getting access to the antiretroviral drug is increasing and there is also an increasing number of ART centers across the country(2).

The goal of ART is to achieve and sustain viral suppression among the people receiving ART. Early results from ART programs in developing countries have been promising, showing

virological outcomes similar to those obtained in industrialized settings. However, the growing expansion of these programs has revealed high rates of treatment failure in many countries, with reports >20% of virological failure after 12 or 24 months of ART (4).

ART can fail as a result of toxicity, pretreatment HIV-1 drug resistance, insufficient patient adherence or incomplete suppression of viral replication leading to the emergency of drug resistance viruses, and hence adequate clinical and laboratory monitoring can significantly improve treatment outcome and prevent rapid failure (5).

Monitoring individuals receiving ART is important to ensure successful treatment, identify adherence problems and determine whether and which ART regimens should be switched in case of treatment failure. Monitoring effectiveness of HAART in the developed world usually involves longitudinal measurement of viral load (3-4 times per year) to ascertain appropriate viral suppression to viral loads of less than 50 copies/ml, which typically occurs by the 6^{th} month of therapy. In these settings, resistance testing is typically recommended at baseline, and for patients with consistent viral load elevations (treatment failure) in the course of treatment, so that their ART regimen can be selected and/or modified according to the resistance profile . CD4 cell count measurements are usually performed concomitantly with the viral load (6, 7).

In resource-limited settings, however, viral load measurements and genotypic resistance testing are rarely available due to their high costs, complexity and stringent requirements for storage and transport of plasma. Therefore, as a substitute WHO recommends clinical criteria (new or recurrent WHO stage 4 condition) and immunologic criteria (CD4 count falls to the baseline (or below) or persistent CD4 levels below 100 cells/mm3) to be used by clinicians to diagnose ART failure and guide switches to second-line regimens; However several studies in Asia and Africa have reported on the failure of immunologic criteria to appropriately identify virologic antiretroviral treatment failure (8).

Treatment switches in patients who do not experience virological failure will increase treatment costs and might limit treatment options in the future. Unnecessary loss of treatment options is especially hazardous since only one second-line antiretroviral therapy regimen is available in most Sub-Saharan African countries. Additionally, continuation of a treatment regimen when

patients experience virological failure might compromise patient's immunological and clinical status and, because of ongoing viral replication can result in the selection of viruses with extensive resistance to antiretroviral drugs (9,10).

Following the massive rollout of ART, large numbers of people are receiving first-line ART, and over the coming few years an increasing number will be developing treatment failure and requiring second-line therapy (11).

To date, in the Ethiopian ART program, data regarding on the actual number of HIV patients failing their first line regimens and requiring second line regimens is very limited. Based on data from routine reports, 4,575 patients are on a second-line regimen as of 2013, but far greater number of patient are likely to be failing virologically but have not been switched to second line regimens(12).

In Ethiopia the preferred first-line regimen consists of nucleoside reverse transcriptase inhibitor (NRTI) backbone with one of the non-nucleoside reverse transcriptase inhibitor (NNRTI). Both NNRTIs are given equal preference; choice is based on patients' conditions. TDF(Tenofovir) and ZDV(Zidovudine) are preferred first line NRTIs in the treatment naïve patients. They can be combined either with 3TC(Lamivudine) or FTC(Emtricitabine) and given with one of the NNRTIs. Fixed dose combination, triple or double, are much preferred to lose compounds since they ensure patient convenience and adherence to ART. The other NRTIs ,d4T(Stavudine) and ABC(Abacavir) are used as alternative to TDF or ZDV in selected patient. Apparently, the selection of the second line regimen depends on the first line regimen that patient has been taking (13).

HIV- drug resistance in treatment experienced human immune deficiency virus (HIV) patients is a major cause to first line antiretroviral therapy (ART) failure, necessitating a switch to second line therapy(14).

In Ethiopia, clinico–immunological criteria are mainly used as monitoring tools for patient's health status. This results in late detection of treatment failure and continuation of a treatment regimen when patients experience virological failure might compromise the treatment outcome

of second line regimen. In addition, there is no information on the outcome of the second line ARV treatment(14).

It is therefore, critical to assess the clinical, virological and immunological outcomes and among patients' switched to the second line ART.

1.2. Statement of the problem

Highly active antiretroviral therapy has revolutionized the treatment of HIV infection and resulted in dramatic reductions in morbidity, mortality, and health care utilization. Effective ART has consistently resulted in sustained suppression of HIV-1 RNA replication, resulting in gradual increases in CD4 T-lymphocyte count. However, the long term use of ART might be compromised by the emergence of HIV drug resistance which may lead to treatment failure. HIV drug resistance can be caused by the virus factors, which is its high replication capacity and error-prone nature of the viral enzyme reverse transcriptase and host factors like poor adherence, low absorption and other pharmacokinetics factors(8).

Failure of ART is commonly monitored clinically, immunologically and virologically. Resource-poor countries mainly depend on clinico-immunological criteria only. This both insufficiently sensitive and specific criteria causes significant errors in the classification of patients. Due to this, many patients will remain on a failing regimen for a long time. This results in an increase in accumulation of drug resistance mutations, morbidity and mortality, and limited subsequent treatment options. In addition, numerous patients meeting the clinico-immunological criteria for therapeutic failure are, in reality, cases where the failure is actually a false positive that can inappropriately lead to a switch to second-line drugs too early. As a consequence, it has been recommended by numerous researchers and clinicians that systematic viral load confirmation prior to switching to second-line treatment and for treatment follow up is critical(8,9).

Viral load test is the most important indicator of treatment failure and earlier detection of virological failure allows better preservation of the efficacy of second-line regimens. Due to un-affordability of viral load monitoring in the majority of resource-poor settings, viral load test utilization is low. In Ethiopia, Clinico–immunological criteria are mainly used as monitoring

patient's health status which results in late detection of treatment failure. Continuation of a treatment regimen when patients experience virological failure might compromise patients immunological and clinical status and, because of ongoing viral replication can result in the selection of viruses with extensive resistance to antiretroviral drugs, in particular, the accumulation of mutations associated with cross-resistance within the

1.3. Significance of the study

The findings of this study will rebound mainly to the benefit of patients on second line ART in general and study participants in particular. Study participants benefit by getting viral load service which is not routinely done in the existing situation which help to know their treatment success. To our knowledge there is no study conducted in Ethiopia regarding second line treatment outcome. Thus, this study puts recommendations on the second line ART monitoring services and HIV program which improves health HIV care service in Ethiopia .

2. Literature review

The rapid scale-up of antiretroviral therapy (ART) in resource-limited settings over the past decades has resulted in substantial reductions in morbidity and mortality caused by HIV/AIDS in PLWHA (15-17).

More than eight million HIV-infected patients in resource-poor settings have initiated antiretroviral therapy ART since 2003, and as many as one million of these patients may have virologic failure with ongoing HIV replication (18-21).

A number of patients can be expected to develop drug resistance to first-line regimens, and a growing number of patients on ART in developing countries have switched to second-line therapy (22-24). Limited access to viral load monitoring and genotyping, and poor availability of second-line treatment options (25), has meant that failure is likely under diagnosed (26), with the consequence that some patients eligible for second-line therapy are not switched and many die as a result (27).

Whenever there is first line failure there should be on time switch to second line treatment. Low baseline CD4 count, Zidovudine-based ART ,imperfect adherence, virus related resistance and poor drug supplies are among factors associated with first- line treatment failure. Earlier initiation of ART, provision of treatment monitoring and as well as developing new strategies to enhance adherence are key priorities in sustaining the first-line and second line regimens (4).

For patients failing second-line therapy, treatment options are largely nonexistent. Current WHO guidelines provide some guidance for treatment in the case of second-line failure, but these are prefaced with the caution that many countries have financial constraints that will limit the adoption of third-line options (15,28,29).

In the event of first-line treatment failure, there is indication to start second-line regimens. Treatment failure is defined as, clinically, based on indication of clinical progression of HIV-infection like emergence or recurrence of OIs, or other HIV-related illnesses and new or recurrent WHO stage IV conditions. Immunologically, by decline in CD4 counts and virologically, rise in viral load (13)

Failure patients to both first line and second line ART is commonly monitored clinically, immunologically or virologically. It is well established that virological failure occurs earliest, followed by immunological failure, then clinical failure (30-32).

Although CD4 T-cell counting is essential in clinical practice, and even mandatory to initiate ART, it is becoming increasingly obvious that criteria for therapeutic failure (both immunological and clinical) as advanced by the WHO public health approach are not sufficiently sensitive and specific, causing significant errors in the classification of patients (33-35) .The sensitivity of these clinico–immunological criteria is in the range of 29–33% (36).Recent data from Uganda, South Africa and Kenya have confirmed that CD4 T-cell count monitoring does not accurately identify patients in virological failure (30)

Studies suggested that sole immunologic criteria failed to appropriately identify virologic ART failure. In a recent study in Kenya, immunological monitoring as a sole indicator of virological failure would have provided a premature switch to second-line regimens for 58 and 43% of patients experiencing a decrease in CD4 T-cell count of 25 and 50%, respectively (37).

Despite the successful roll out of first-line therapy across resource-limited settings, <3% of all patients undergoing treatment, a small proportion of the total number in whom treatment is failing, are receiving second-line therapy (38). Clinical and immunologic monitoring detects failure late, after the accumulation of more-complex mutations render standard second-line NRTI backbones less effective (30).

The outcomes of second-line therapy have been satisfactory and largely consistent across different settings. Among studies reporting outcomes of second-line treatment in low-income and middle-income countries, the proportion of patients for whom therapy had failed virologically was 21.8% at 6 months, 23.1% at 12 months, 26.7% at 24 months, and 38% at 36 months (15,31). Death was relatively uncommon across most studies, although some programs that used clinical monitoring to detect treatment failure reported high early mortality rates (10%) at the time of initiation of second-line treatment (39,40).

Reported virological failure rates are varying. A recent review and earlier studies describe relatively high proportions 30-40% of patients experiencing virological failure, mostly within the first six months after switch to a second-line regimen (15,41,43).

Among five second-line treatment studies reporting associations between adherence and treatment outcomes, all reported that poor adherence was associated with failure. Use of hair sampling to detect lopinavir (LPV) level as a measure of adherence found that those with treatment failure had the lowest levels of drug exposure (44).

Only small studies have evaluated Protease Inhibitors(PI) resistance at the time of second-line failure. PI resistance mutations are present in approximately 18%(0-50%) of genotyped viruses (45), with some variation according to region. Self-reported poor adherence, genotypic resistance profiles are also the most common factors for second line treatment failure(46).

3. Objectives

3.1. General Objective

To assess the clinical, immunological and virological treatment outcome of second line antiretroviral therapy among adult HIV patients who had been on the treatment for more than six months in four selected hospitals in Addis Ababa, Ethiopia.

3.2. Specific Objectives

- To assess clinical outcome of second line antiretroviral therapy among adult HIV patients
- To assess immunological outcome second line antiretroviral therapy among adult HIV patients
- To assess virological outcome of second line antiretroviral therapy among adult HIV patients
- To review major reasons and criteria used treatment for switching from first line to second line regimens

Hypothesis

- Using Clinical and/or immunological measurements as a criteria for switch to second line ART is the same as of viral load criteria to determine the second line ART out comes.
- There is higher rate of treatment failure among patient on second line regimen due to limited access to routine viral load monitoring

4. Materials and Method

4.1. Study design and period

The study was longitudinal that was conducted among patients switched on second line ART regimen at selected public health facilities in Addis Ababa from July 2014 to June 2015.

4.2. Study area and setting

The study was conducted in Addis Ababa city. Four hospitals were selected for this study; St. Paul's Hospital Millenium Medical College , Zewditu Memorial, Minilik II and ALERT hospitals. These sites are prominent sites giving ART services since its begun in Ethiopia in 2005.The facilities are selected purposely due to higher number of patients on second line ART they are serving. Zewditu and Minilik II hospitals are administered under Addis Ababa city administration health bureau whereas both St Paul's and ALERT are accountable to Federal Ministry of Health. These four sites have technical linkages with EPHI which oversees the laboratory quality assurance activities of the nation and serves as a backup laboratory during service interruptions at sites.

According to the report from ministry of health 4,575 patients were on second line ART as of 2013 in Ethiopia and among these an approximate of 123 clients were getting service in St. Paul's hospital millennium Medical college,250 in Menelik II ,300 in ALERT and 350 in Zewuditu Memorial hospitals during the study period according information from their ART clinics.

4.3. Source population

The source population was HIV patients on second line ART at the selected public health facilities in Addis Ababa.

4.4. Study Population

The participants of this study were adult HIV patients who had been on second line ART for more than six months at the selected ART sites, who visit the health facilities during the study period and who consented to be involved in the study.

4.5. Participant inclusion and exclusion criteria

4.5.1. Inclusion criteria

Were, individuals;

- Consented to participate in the study
- Age greater than 18 years and
- Who are on second line ART regimen for at least six months

4.5.2. Exclusion criteria

Were,

- Transfer in patient from different facilities
- Clients with incomplete data

4.6. Study variables

Independent variables

The following variables were considered as independent variables at switch to second line treatment; age, gender, WHO stage at start of treatment, weight at start of treatment, list of ARV drugs prescribed at the beginning and adherence.

Dependent variables

Patient's Clinical outcome improvement ,viral load suppression and increase in CD4 count.

4.7. Sample size

A total of 236 clients who switched to second line ART regimen and fulfilled the inclusion criteria were recruited using convenient sampling and proportional allocation to each facilities. Accordingly , from St. Paul's Millenium Medical College(N=73) , Zewditu Memorial (N=60), Minilik II(N=35) and ALERT (N=68) hospitals participants included. We aimed total sample size of 384 and due to limited number of patients during the study period, the total sample size was reduced.

4.8. Sampling procedures

All individuals who are on second line ART, greater than age of 18 and willing to participate in the study were recruited and convenient sampling method was used until the required sample number met.

4.9. Data Collection Method

4.9.1. Enrolment and data collection procedures

All patients who were on second line ART for at least six months and visiting the facility during the study period were approached and enrolled consecutively until the needed sample size of 236 reached. All patients were requested for their consent by physicians to be included in the study and they were included after written consent was obtained(Annexes 1-3). Basic socio-demographic information and clinical information were collected by trained physicians. Data on ART history prior to initiation of second line ART at the site and adherence assessment were collected using questionnaire by trained physicians. Other related data were extracted from the available record system physicians using data extraction checklist (Annex 4). Specimen for both CD4 and viral load tests were collected by the laboratory staff at facilities. Information on specimen collection and processing were recorded to characterize the specimen that were used for CD4 and viral load tests(Figure 4.1).

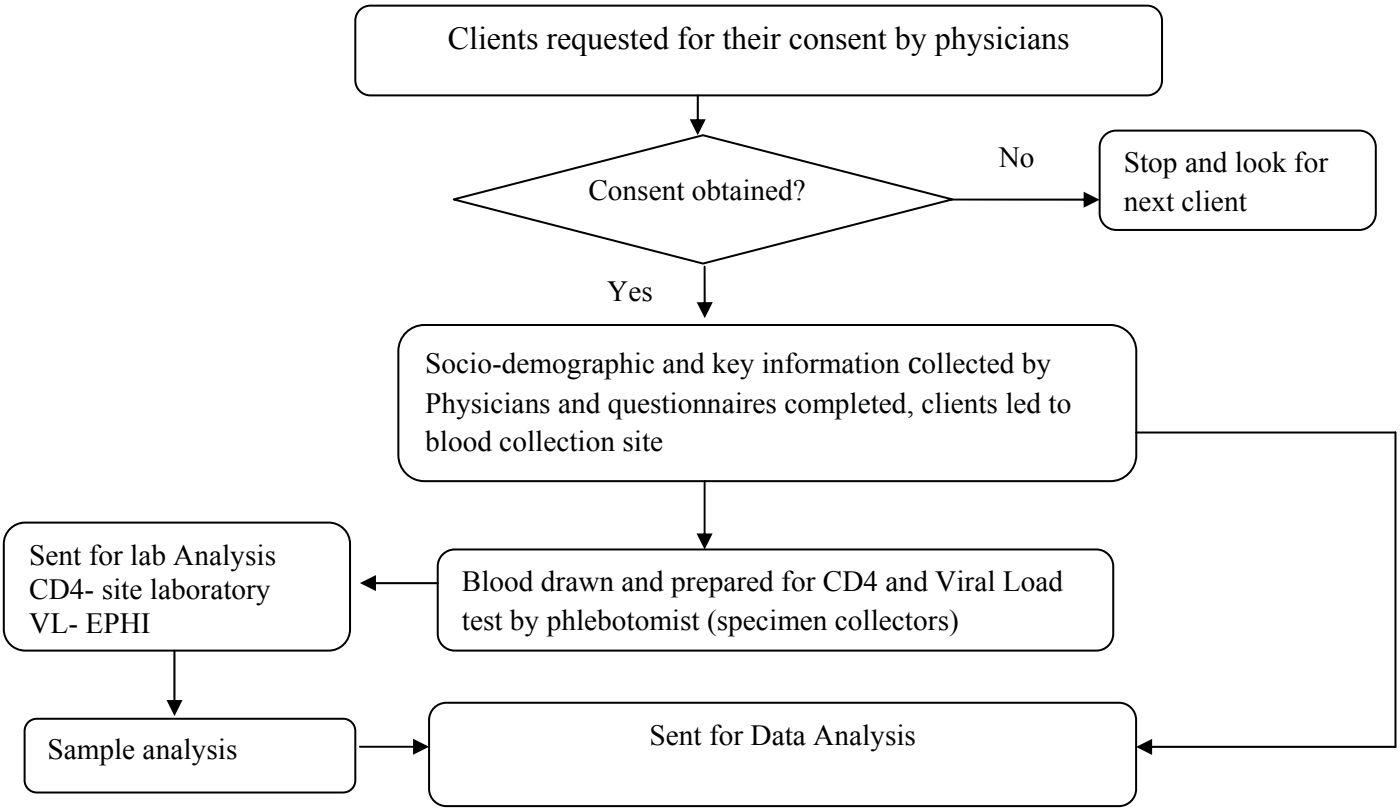

Figure 4.1. Specimen and data collection flow chart

4.9.2. Specimen collection and laboratory methods

4.9.2.1. Specimen collection and processing

About 10 ml of blood was collected from each patient for CD4 and Viral load tests on the same venipuncure. For both tests 4-5 ml of whole blood was drawn from each participant using vacutainer tube separately with anticoagulant (EDTA) following standard venipuncture protocols and plasma was separated and aliquots prepared for viral load testing. Specimens collected were labelled with ART , study IDs and date and transported directly to facility's laboratory for CD4 test and to the national HIV reference laboratory, EPHI for VL test .The storage temperature for CD4 specimen was at room temperature (20°C - 25°C) and specimen were only stored for a maximum of 48 hours before preparing & 48 hours after preparing. The CD4 test was performed

at site level along with daily QC run and results were given to the principal investigator for analysis and to the physician for routine treatment follow-up of patients .

For viral load testing, plasma was separated within 5 hours and two-three aliquots of cryo-vials (with capacity of 1ml each) prepared for transportation. Specimen transportation was on dry ice and stored at -80°C until the test is done. Centrifugation, pipetting, and aliquoting was performed following standard protocol and laboratory bio-safety precautions both at collection and testing sites. The specimen were handed over to the PI after coded at site level for analysis at national HIV reference laboratory (Molecular laboratory), EPHI.

4.9.2.2. Laboratory testing methods

Lymphocyte Immunophenotyping(CD4 Testing): Quantification of absolute counts of CD4+ T cells on whole blood specimens were determined using the FACSCalibur and FACs count systems (Becton Dickinson, San Jose, USA).Both instruments use whole blood which is added to the reagent, the fluorochrome –labeled antibodies in the reagent bind specifically to leucocytes surface antigens. During acquisition, the cells travel past the laser beam (488nm Argon and 635nm Red diode) and scatter the laser light and the stained cells fluoresce. These scattered and fluoresce signals, detected by the instrument, provide information about the cell size, internal complexity and relative fluorescence intensity(47) .

Viral Load Determination: HIV-1 viral load was determined by quantifying the amount of HIV-1 RNA in plasma sample. The Abbott Real Time HIV-1 assay was used, which uses RT-PCR to generate amplified product from the RNA genome of HIV-1 in clinical specimens (Abbott Molecular Inc. Des Plaines, IL 60018 USA) . An RNA sequence that is unrelated to the HIV-1 target sequence is introduced into each specimen at the beginning of sample preparation. This unrelated RNA sequence is simultaneously amplified by RT-PCR, and serves as an internal control (IC) to demonstrate that the process has proceeded correctly for each sample. The amount of HIV-1 target sequence that is present at each amplification cycle is measured through the use of fluorescent-labeled oligonucleotide probes on the Abbott m2000rt™ instrument. The amplification cycle at which fluorescent signal is detected by the Abbott m2000rt is proportional to the log of the HIV-1 RNA concentration present in the original sample. The lower detection

limit of the assay is 40 RNA copies per ml of plasma for 0.6 or 1ml sample volumes ,75 RNA copies per ml of plasma for 0.5 ml plasma sample volume and 150 RNA copies per ml of plasma for 0.2ml sample volume(48).

4.10. Quality Assurance

To ensure reliable data collection;

- Training was given on data collection procedures for physicians
- Continuous supervision of senior laboratory technicians to ensure that they apply standard operational diagnostic procedures.
- The data collection, application of standard procedure, accuracy of test results was supervised by principal investigator.
- Filled questionnaires were collected after checking for consistency and completeness

To ensure quality laboratory processes;

Quality Assurance measures were taken at different levels of laboratory process. At Pre Analytical stage appropriate patient identification was done. In Addition, standard collection, storage and transport of blood and plasma specimens were implemented. Appropriate containers were also used. At analytical stage daily QC were run, daily maintenance checks on the instruments were done and recorded to ensure the quality of tests. Appropriate reporting and record were done at post analytical stage.

In addition, standard operating procedures for all laboratory tests were employed uniformly throughout the study. Corrective actions were implemented immediately for laboratory works where any technical problems identified. Besides, performance of the laboratories (for CD_4 and viral load testing) is externally monitored by participation in the proficiency testing programs of international and national external quality assessment(EQA) schemes including that of CDC Atlanta and One World Accuracy programs. All laboratories scored acceptable EQA results in recent two rounds of participation for CD4 and VL tests.

4.11. Data Collection, Storage and Management

Confidentiality was insured through involvement of physicians and other professionals on regular ART clinic activities. All study participants were approached by their physicians. Basic information were collected after consent obtained and signed using prepared consent forms (Annexes 1-3). The clients were sent to laboratory for specimen collection and the data extraction checklist was used by physician for completion of previous clinical information. The laboratory staff collected specimen for both viral load and CD4 test. Finally completed checklist, CD4 test result and packaged viral load specimen were given to the PI.

Data entry quality assurance were maintained by undertaking double data entry as well as daily checking. No personal identifying information on participants were made available. Questionnaires, laboratory specimen tracking forms, survey logs, and results were kept secure places(locked drawers).

4.12. Data Analyses

The associations between factors of interest with the treatment outcomes was performed by SPSS version 20 software. Test results were considered significant when the $P<0.05$

4.13. Ethical consideration

Before the research work, ethical clearance was obtained from Departmental Research Ethics Review Committee (DRERC), Department of Medical Laboratory Science, School of Allied Health Sciences, Addis Ababa University, Scientific and Ethical review office of EPHI, St Paul's Millennium Medical College and AHRI/ALERT Ethics review committees (AAERC).Additionally, a formal letter of cooperation was acquired from Addis Ababa Health Bureau. Written informed consent was obtained from voluntary study participants. They were provided with all information about the study and assured about the confidentiality and

anonymity of data which are only used for research proposes. Clinicians were notified on the results of the tests and any abnormal findings were immediately reported.

4.14. Dissemination of results

This study on completion could serve as a reference material to researchers, experts or policy makers as an input. To reach these bodies the finalized paper will be submitted to School of Allied Health Sciences, Addis Ababa University. So it can serve as a reference in the library. In addition, a copy of this material will be given to EHNRI,HAPCO, Federal Ministry of Health, Addis Ababa Health Bureau, and respective hospitals. The result will also be communicated to clinicians and further disseminated through publication in peer reviewed local and international journals and through presenting it in relevant workshops and seminars.

4.15. Operational terms definition

Clinical failure	New or recurrent clinical event indicating severe immunodeficiency (WHO clinical stage 4 condition and certain WHO clinical stage 3 conditions (pulmonary TB and severe bacterial infections) may also indicate treatment failure) after 6 months of effective treatment
Immunologic failure	CD4 count falls to the baseline (or below) or Persistent CD4 levels below 100 cells/mm^3
Virologic failure	Plasma viral load above 1000 copies/ ml

5 . Result

5.1. Characteristics of the study subjects

A total of 236 HIV infected individuals who received second line ART were included in the study, of which 111(47%) of them were male and 125(53%) were female. The mean age of the patients at study time was 40 (18-78)years and the average time on second line ART was 2.4(0.5-7.5) years. The average duration on first line regimen before switch to second line for the study participants was 3.5(0.5-8) years**(Table 5.1.).** The average CD4 count at switch was 133.2 cells/mm3(4-519)[95%CI:121.4-145].At second line initiation the WHO treatment stage was mainly stage III with 98 (41.5 %) of patients, followed by stage IV= 62(26.3), stage II= 40(16.9%) and stage I= 36(15.3%).The two common opportunistic infections at time switch were tuberculosis(6) and oral candidacies(1). Self report showed that the majority of patients (99.5%) on second line ART were adherent to the treatment and significant change observed from first line treatment.

Table 5.1: Socio demographic characteristics of patients on second line ART at St. Paul's hospital Millennium Medical College , Menelik II ,ALERT and Zewuditu Memorial Hospitals, Addis Ababa Ethiopia, June 2015

Variables		Frequency (N)	Percent(%)
Gender	Male	111	47
	Female	125	53
Age(in years)	18-24	11	4.7
	25-34	60	25.4
	35-44	93	39.4
	45-54	52	22
	55+	20	8.5
Residence	Urban	233	98.3
	Rural	3	1.7
Living Arrangement	Own house	110	46.6
	With relatives	34	14.4
	Rented	68	28.8
	Kebele	24	10.2
Marital status	Never Married	56	23.7
	Married	113	47.9
	Separated	20	8.47
	Divorced	30	12.7
	Widowed	16	6.78
	Not specified	1	0.42
Educational level	No Education	32	13.6
	Primary	83	35.2
	Secondary	106	44.9
	Tertiary	15	6.36
Religion	Orthodox	188	80
	Protestant	25	11
	Muslim	21	8.9
	Catholic	2	0.8

Of all patients on the second line treatment,137(58.1%) received TDF+3TC+LVP/r regimen followed by AZT+3TC+ LVP/r 37(15.7%) ,ABC+ DDI+ LVP/r 22(9.3%) and 16.9% other regimens combined(Table 5.2.). The two most common reasons for drug substitution among patients on second line ART over course of treatment were toxicity/side effect related and availability of new drugs for substitution .

Table 5.2: Drug combination at switch to second line ART and at date of survey for patients on second line ART at St. Paul's hospital Millenium Medical College , Menelik II ,ALERT and Zewuditu Memorial Hospitals,Addis Ababa Ethiopia, June 2015

Regimen	At switch		At date of survey(After substitutions)	
	Frequency	Percent(%)	Frequency	Percent(%)
TDF+3TC+LVP/r*	137	58.1	127	53.8
AZT+3TC+ LVP/r**	37	15.7	41	17.4
ABC+DDI+LVP/r***	22	9.3	19	8.1
ABC+3TC+LVP/r	16	6.8	19	8.1
TDF+3TC+ATV/r	11	4.7	18	7.6
ABC+3TC+ATV/r	10	4.2	9	3.8
TDF+DDI+LVP/r	2	0.8	1	.4
DDI+3TC+LVP/r	1	0.4	0	0
ABC/TDF/LVP/r	0	0	1	.4
AZT/3TC/ATV/r	0	0	1	.4
Total	236	100	236	100

** TDF- Tenofovir disoproxil fumarate(Tenofovir)- belongs to the nucleotide reverse transcriptase inhibitor (NtRTI) class of drugs. It inhibits enzyme called reverse transcriptase, which is essential to the process of viral replication*

**3TC- Lamivudine- is one of nucleoside reverse transcriptase inhibitors (NRTIs). It disrupts an HIV protein or enzyme called reverse transcriptase, which is involved in making new viruses*

**LVP/r- Lopinavir /ritonavir (Kaletra,Aluvia)- is a protease inhibitor drug available in tablet and solution form. It blocks the activity of the HIV protease (or proteinase) enzyme to slow HIV replication and delay damage to the immune system*

***AZT- Zidovudine- belongs nucleoside reverse transcriptase inhibitors (NRTIs). It substitutes a defective version of one of the nucleosides, causing premature termination of the proviral DNA chain.*

****ABC- Abacavir- Abacavir belongs to NRTIs. An NRTI drug substitutes a defective version of one of the nucleosides, causing premature termination of the proviral DNA chain.*

****DDI- Didanosine- Didanosine belongs to NRTIs. An NRTI drug substitutes a defective version of one of the nucleosides, causing premature termination of the proviral DNA chain.*

Source: http://www.aidsmap.com/hiv-basics/Treatment/page/1412440/

Data were also collected to assess the major criteria for treatment switch from the first line regiment to second line regimen among the study participant. Based on this the major reasons for switch to second line treatment were combined Clinical, immunological and virological failure criteria 88 (37.3%),Clinical &Immunologic failure 62(26.3%), Clinical treatment failure only 37(15.7%), Immunologic & virologic failure 27(11.4%), Virological failure only 12(5.1%) and Immunological failure only 10(4.2%)(**Table 5.3)**.

Table 5.3: Criteria of switch to second line ART at St. Paul's hospital Millenium Medical College , Menelik II ,ALERT and Zewuditu Memorial Hospitals, Addis Ababa Ethiopia, June 2015

Criteria	Frequency(N)	Percent (%)
Clinical treatment failure only	37	15.7
Immunological failure only	10	4.2
Virological failure only	12	5.1
Clinical &Immunologic failure	62	26.3
Immunologic and virologic failure	27	11.4
Combined Clinical, immunological and Virological failure	88	37.3
Total	236	100.0

5.2. Treatment out comes on second line ART

5.2.1. Clinical Outcome

The second line treatment has improved the clinical condition of the patients. Based on this, the number of patients categorized as WHO treatment stage IV/III reduced from 160(67.8%) to 13(5.5%) during the survey (all patients were on second line ART fror ≥6 months). The mean body weight increment at 6 month was 1.32 KG, 1.12 KG at month 12 and 4.4 kg at date of

survey. All patients with opportunistic Infection at switch to second line ART were cured at during the first 6 month.

Table 5.4: Change in WHO treatment stage for patients on second line ART at St. Paul's hospital Millenium Medical College , Menelik II ,ALERT and Zewuditu Memorial Hospitals, Addis Ababa Ethiopia, June 2015

Treatment stage	At switch to 2L		At date of survey	
	Number (N)	Percent(%)	Number (N)	Percent(%)
I	36	15.3	167	70.8
II	40	16.9	56	23.7
III	98	41.5	11	4.7
IV	62	26.3	2	0.8
Total	236	100.0	236	100.0

5.2.2.Immunological outcome

Study participants were on second line ART for a minimum of 6 and maximum of 90 months with a median follow up time of 29 months .There was significant increase in mean CD4 count by 210cells/mm3 from the mean of 133.2cells/mm^3 during switch period to 338cells/mm^3(P=0.01)

Table 5.5 .CD4 Count at different periods of time for patients on second line ART at St. Paul's hospital Millenium Medical College , Menelik II ,ALERT and Zewuditu Memorial Hospitals, Addis Ababa Ethiopia, June 2015

	At Switch	Month 6	Month 12	Month 18	Month 24	Month 30	Month 36	Month 42	Month 48
N	227	152	116	89	42	36	29	17	14
CD4 Not done	9	80	89	77	42	29	15	12	9
Mean CD4 Count	133.2	240.25	264.3	305.9	358.7	330.6	381.3	391.2	489.6

5.2.3. Virological outcome

Out of 236 participants only 129(55%) received at least one viral load testing since start of ART. Participants were followed for different period and the total person-time of follow up was 558.4patient-years of follow up. Hence, the rate of virological failure was 1.2 per 100 patient-years of follow up. The mean plasma viral load level was 202,973.2 copies/ml(0-2,666,045copies/ml)(127 patients for which VL used as criteria for switch) and the overall average viral load count decreased to 23,854.1copies/ml. Overall switch to second line ART brought significant improvements to the patents(P=0.01).Among all the study participants , 32 (13.6%)of patients were found to have viral load count of >1000copies/ml which indicates treatment failure.

There was no overall significant relationship between different criteria used for switch to second line treatment and virological treatment outcome (p= 0.257).

Table 5.6: Relationship of reason of switch and virological treatment outcome for patients on second line ART at St. Paul's hospital Millennium Medical College , Menelik II ,ALERT and Zewuditu Memorial Hospitals, Addis Ababa Ethiopia, June 2015

	Virological Treatment outcome		
Reason of switch	Not improved (>1000cps/ml)	Improved (<1000cps/ml)	P-Value
Clinical treatment failure	4	33	.263
Immunological failure	0	10	.121
Virological failure	2	10	.134
Clinical &Immunologic failure	7	55	.213
Immunologic and virologic failure	5	22	.149
Clinical, Immunological and virological failure	14	74	.251
Total	32	204	

There was viral also higher viral suppression rate observed in patients after switch to second line treatment and 204(86.4%) of the patients had suppressed viral load(Table 5.7 shows higher viral

suppression rate for patients with viral load of >300,000copies/ml during switch to second line ART)

Table 5.7. Viral suppression of patients on second line ART after years of follow-up(Patients with viral load of >300,000copies/ml during switch to second line ART) at St. Paul's hospital Millennium Medical College , Menelik II ,ALERT and Zewuditu Memorial Hospitals, Addis Ababa Ethiopia, June 2015

ID	At switch (copies/ml)	At Date of survey VL(copies/ml)	Years on second line ART	Viral suppression (<1,000 copies/ml)
029	301,811	Not detected	1	Suppressed
027	322,680	178	1	Suppressed
155	327,027	78,033	2	**Not** suppressed
120	378,976	<150	2.5	Suppressed
144	380,411	161,869	2	**Not** suppressed
151	409,301	224	2	Suppressed
195	455,013	726,499	1.5	**Not** Suppressed
191	455,287	Not detected	1	Suppressed
083	470,770	Not detected	4.5	Suppressed
131	490,000	<150	3	Suppressed
138	500,000	204	3.5	Suppressed
088	510,456	336	2	Suppressed
134	561,564	Not detected	2	Suppressed
207	652,102	Not detected	1.5	Suppressed
218	660,245	Not detected	2.5	Suppressed
182	685,991	Not detected	1.5	Suppressed
122	726,224	<150	2	Suppressed
214	1,089,455	589	1.5	Suppressed
189	1,119,285	<150	1.5	Suppressed
090	1,600,000	<150	3.5	Suppressed
012	2,048,939	16,251	2	**Not** suppressed
213	2,666,045	<150	2	Suppressed

6. Discussion

As the extent of ART in developing countries continues, and the number of patients switching to second line therapy will unavoidably increase. In this study, of 236 patients, there were more female (53%) than men(47%) indicating higher first line ART failure among females. Clinic based study in Soweto, Johannesburg shows females had 28% higher risk of being switched to second line ART than males(49). In contrary to this, a multicentre study in Africa, Asia and South American settings(50) and two other studies in Brazil(51) and France (52)showed no sex differences in predicting switching(53).The socio-cultural dynamics of the society may also be contributing to such different observations. Issues surrounding disclosure, gender inequalities on the cultural strata and discordant couples may all play a role and make women more vulnerable in such situations (54).This study shown that the most common age group was 35-44 years followed by 25-34 years which indicates 64% of the patients belonged to the reproductive age group which is comparable to studies conducted in India, south Africa and Thailand indicating 52-72 reproductive age group(14,55,56).

Unlike findings from study conducted in India which shown the common cause of switch to second line ART was immunological and virologic failure criteria (51%), the most common cause to switch on second line ART among the study participants was combined clinical, immunological and virological failures 88(37.3%)(14).

This study has shown an overall increase of CD4 cells count by average of 210 cells/mm3 during course of second ART and the mean increment at month 6 and 12 were to 240.25cells/mm3 and 264.3cells/mm3 respectively. Study conducted in India supports this study where there was a significant increase in mean CD4 count at 6 months by 179.4 cells/mm3, and 12 months by 353.85 cells/mm3 as compared to baseline(14).Similar to this, a study conducted in Tanzania showed a significant increase in mean CD4 cells count at 6 months by 155.4 cells/mm3 (95% CI: 133.5-179.8) and 12 months by 226.2 cells/mm3(95% CI: 202.9-252.0) as compared to baseline (57). Another study done in China reported most patients respond well to ARTs with significant CD4 increase after initiation of second line ART (58).

The mean plasma viral load level at switch for 129 patients which VL was used as criteria for switch was 202,973.2 copies/ml(0-2,666,045 copies/ml). The mean viral load was decreased to 23,854.09 copies/ml (± SD 121743.7). During this study period, among the total of 236 participants, 204 of them had undetectable viral load (<150 copies/ml), giving an 86.4% viral suppression rate. Study conducted in Ahmedad, India shown 82% of patients with undetectable viral load after 12 months on second line ART showing high treatment success rate of second line ART regimen (14), other African region and south Asia studies also support this evidence with 68-85% virological suppression rate after 12 months on second line treatment(59,60) .

The two most common reasons for drug substation reasons after switch to second line ART where toxicity/side effects related and availability of new drugs for substitution. Studies conducted in Malawi and Italy showed concordant result with higher toxicity related substitutions(61,62).

In this study,self report showed that the majority of patients (99.5%) on second line ART were good adherent to the treatment overall during course of their treatment follow up and significant change observed when compared to first line treatment which was 72.7%(N=220)at 6 months and 82.4%(N=195) at12 months. In concordance to our finding, a study conducted in Tanzania shown this with higher level of adherence rate in second line ART than first line ART(57). Findings from studies conducted in south Africa and Georgia support this finding, showing the mean first 6 month adherence on second-line treatment 81%, with 47.5% of patients showing 100% adherence (63,64). High adherence can be related to intensive counseling from Physicians .

At second line initiation the WHO treatment stage was mainly stage III with 98 (41.5 %) of patients, followed by IV 62(26.3),II 40(16.9%) and I 36(15.3%). After initiation of second line ART treatment stages IV/III from 160(67.8%) reduced to 3(5.5%).This result is comparable with an study conducted in western India which shown significant changes after initiation of second line ART with patients categorized as WHO stage III/IV changed from 48% to 21 % after sixth months on therapy(14).

The two common Opportunistic infections at time switch were found to be Tuberculosis and Oral candidacies. A hospital based study conducted in India also showed the most common opportunistic infection was tuberculosis [18], followed by Candidiasis [2], herpes [1] and Mycobacterium avium complex (MAC) [1](14,59).

7. Conclusion and recommendation

7.1. Conclusion

The finding of this study showed that, second line ART regimen, has improved the clinical and immunological condition of patients and suppressed the viral load in most of the patients who were failing the first line ART regimen. This is significant achievement compared to the expected prolonged exposure of the patient on failing first line regimen due to the lack of use of the viral load for patient monitoring. The continuation of a treatment regimen when patients experience virological failure can result in the emergence of viruses with extensive resistance to antiretroviral drugs which will compromise the effectiveness of standard second-line regimens

The Ethiopian national ART program national has been successfully on ART roll-out, but to achieve and sustain the benefits of increased coverage, monitoring persons on ART is very essential. Patients need timely CD4 count, viral load, and drug resistance monitoring in order to maintain the efficacy of ART.

Increasing the accessibility of viral load testing as recommended by the recent WHO guidelines would improve the treatment success of the ART program. Virological monitoring will enable timely switches from first- to second-line therapy and minimize the prolonged exposure of patient on failing regimen.

To our knowledge, this is the first study to assess the treatment outcome of second-line therapy among adults on second-line ART in Ethiopia. In this study, we observed a significant improvement in clinical and immunological condition as well as good virological suppression in patients after starting second line therapy compared to that before drug change.

Maintaining the long-term efficacy of the available second-line regimen is paramount in order to fully and effectively utilize the limited second-line drug sources and obtain good clinical effect. In this study, 13.5%. of the study participant were with virological failure even though, this study did not assess the HIV Drug resistance associated with the virological failure among the study participant, this indicate that, there is a need for access to third-line ART medications, for which national ART program should be prepared. Furthermore, the national ART program should improve access to VL monitoring and HIV genotype testing for optimal management of patients failing on ART.

7.2. Recommendations

Based o the findings from this study it was observed viral load testing is prescribed when there is suspect of treatment failure. Routine viral load testing should be implemented as it is gold standard indicator of treatment failure and can limit the accumulation of HIV drug resistance mutation and improve the benefit from second line regimen.

This study indicated there is significant failure for second line treatment and it is better to look for third options for benefit of patients. This study has a limitation to identify why patients are failing virologically after switching to second line ART and capacity for drug resistance testing should also be well established to identify mutation for drug failure and for better intervention of disease progression .

This study has limitation of not following patients from the first start of switch to some time period to see clear figure of treatment out come. In future there should be prospective cohort study with more study participants and sites to fill the gaps seen .in .this. study.

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9. Annexes

Annex 1 : **INFORMATION SHEET**

ADDIS ABABA UNIVERSITY

DEPARTMENT OF MEDICAL LABORATORY SCIENCES

Title: Treatment outcomes of HIV-infected patients on second line ART in selected health facilities of Addis Ababa: Longitudinal study

Name of principal investigator: Adisu Kebede

Affiliations/ collaborating institute: This study is conducted as student project in collaboration with Addis Ababa University School of allied health sciences &Ethiopian Public Health Institute.

Background of the study: Studies shown that,CD4 test and clinical diagnosis are not good indicators of treatment failure compared to virological monitoring. In Ethiopia currently there is no study on the treatment outcome of second line ART and the study will identify gaps related to treatment outcomes and conducted from July 2014 and June 2015.

Purpose of the study: To assess the treatment outcome of second line antiretroviral therapy among patients.

Procedure of the study: You will be requested for your consent by your physicians. Your basic socio-demographic information and clinical information will be extracted from the medical record by your physicians/data clerk. Specimen for both CD4 and Viral load tests will be collected by the laboratory staffs.

Role of participants: You are expected to allow viral load and CD4 tests done and allow your clinical information collected.

Benefits and risks: The benefit of the study is to put recommendation on the second line ART services which improves health care service in Ethiopia and there may not be direct benefit to you. There is no observed major risk since blood is collected for viral load and CD4 tests for routine monitoring purposes. You will be provided with 80 ETB for transportation purpose as compensation.

Right to withdrawal: Participation is voluntary and individuals are not obliged to participate. Participation can be suspended if the participants are not comfortable anytime. This will not have any negative consequences on the service provided to you.

Confidentiality: Your name and any related data will be kept strictly confidential. You will be contacted with your physician and the PI will get coded specimen and checklist only.

For any information you can contact: Adisu Kebede (PI) Phone: 0913088587E-mail: adisukebede78@yahoo.com(Addis Ababa University/staff at Ethiopian Public Health institute)

Mr Kassu Desta (advisor) Phone: 0911 107099 E-mail: kassudesta2020@gmail.com AAERC: Phone:0113481285

Annex 1 : **የመረጃ ቅፅ (INFORMATION SHEET AMHARIC VERSION)**

ADDIS ABABA UNIVERSITY

DEPARTMENT OF MEDICAL LABORATORY SCHIENCES

የጥናቱ ርዕስ፡ የሁለተኛ ደረጃ ፀረ-ኤች አይ.ቪ/ኤ.ድስ ህክምና መቆጣጠሪያ ውጤት ጥናት

የጥናቱ መሪ/አስተባባበሪ፡ አቶ አዲሱ ከበደ

መግቢያ፡ ይህ የቃል ስምምነት፤በአዲስ አበባ ከተማ በተመረጡ የመንግስት ጤና ድርጅቶች ውስጥ በሚሰጡ የሁለተኛ ደረጃ ፀረ-ኤች አይ.ቪ/ኤ.ድስ ህክምና መቆጣጠሪያ ውጤት ለማጥናት የተዘጋጀ ነው፡፡ ጥናቶች እነደምሳዩት የቫያራል ሎደ ምርመራ ከሲዲ ፎርና ክልንካል መረጃ የተሸል የኤች አየ ቪ ህክምና ውጤት ለማሳየት ጠቀሜታ አለው፡፡በ አሁኑ ጊዜ የሁለተኛ ደረጃ ፀረ-ኤች አይ.ቪ/ኤ.ድስ ህክምና መቆጣጠሪያ ውጤትን በተመለከተ ጥናት የለም፡፡ጥናቱም የሚካሄደው ከ ጥቅምት-ታህሳስ 2007 ዓ.ም ነው፡፡

የሚሳተፉ አካላት፡ ይህ ጥናት የመካሄደው በአዲስ አበባ ዩንቨርሲቲ ህክምና ትምህርት ቤትናየኢትዮጵያ ህብረተሰብ ጤና እንስትትዩት ትብብር ነው፡፡

የጠናቱ አላማ፡ የዚህ ጥናት አላማ የሁለተኛ ደረጃ ፀረ-ኤች አይ.ቪ/ኤ.ድስ ህክምና መቆጣጠሪያ ውጤት ለማጥናት ነው፡፡

የጥናቱ አካሄድ፡ በመጀመሪያ ጥናቱ ላይ ለመሳተፍ የእርሶ ፈቃደኝነት በ ሃክሞ ይጠየቃል፡፡ፈቃደኛ ከሆኑ የ ህክምና መረጃዎ በሀክሞ/ዳታ ክሌረክ ይሰበሰባል፡፡ለ ሲዲ ፎር ና ቫይራል ሎድ ምርመራም በ ሰለጠኔ የ ላቦራቶሪ ባለሙያ አንዲሰጡ ይደረጋል፡፡

የጥናት ተሳታፊዎች ድርሻ፡ በጠናቱ ላይ ለመሳተፍ ፍቃደኛ ከሆኑ ለቫያራል ሎደና ሲዲ ፎር ምርመራ የደም ናሙና በመስጠትናና የክልንካል መረጃዎ እንዲሰበሰብ ትብብር ማድረግ ይጠበቅቦታል፡፡

የጥናቱ ጥቅምና ሊያስከትለው የምችለው ተፅዕኖ፡ የጥናቱ ጥቅም የጸረ ኤች አይ ቪ/ኤድስ ህክምና መቆጣጠሪያ ወሳኝ ጉዳዮች ለይቶ ለማወቅ ሲሆን፤ ይህም ለወደፊቱ ለተጠቃሚው የሚሰጠውን አገልግሎት የበለጠ ለማሻሻል ይጠቅማል፡፡ጥናቱም ለእርሶ ቀጥተኛ ጥቅም ላያስገኝ ይችላል፡፡ የከዚህ ቀደም ለ ቫይራል ሎድና ከሲዲ ፎር ምርመራ የደም ናሙና የመስጠት ልምዱ ስላለ በዚህ ጥናት የደም ናሙና በመስጠቶ በጤናዎ ላይ ሊያስከትለው የሚችለው የሚታይ የጎላ ጉዳት የለም፡፡ ለትራንስፖርት ወጭ የሚሆኖት 80 ብርም ይሰጥዎታል፡፡

ጥናቱ ላይ መሳተፍ መብት፡ በዚህ ጥናት ላይ መሳተፍ የእርስዎ ሙሉ ፍቃደኝነት ላይ የተመሰረተ ነው፡፡ ካልተስማሙ በማንኛውም ጊዜ ከጥናቱ ራሳቸውን ማግለል ይችላሉ፡፡

ሚስጢራዊነት፡ የግል መረጃዎ በምስጥር የሚጠበቁና ግንኝነትዎ ከሃክሞና ከሚመለከታቸው የጤና ባለሙያዎጻ ጋር ብቻ ነው የሚሆነው፡፡ ለበለጠ መረጃ

አዲሱ ከበደ (የጥናቱ መሪ)፡ **ስልክ ቁጥር ፡** 0913088587 **ኢሜል፡** adisukebede78@yahoo.com

አዲስ አበባ ዩንቨርሲቲ/የኢትዮጵያ ሕብረተሰብ ጤና ኢንስቲትዩት ባለደረባ

አቶ ካሱ ደስታ(አማካሪ) ፡ **ስልክ ቁጥር ፡**0911 107099 **ኢሜል፡** kassudesta2020@gmail.com

AAERC: **ስልክ ቁጥር ፡** 011348128 5

Annex 2 : **INFORMED CONSENT FORM**

ADDIS ABABA UNIVERSITY

DEPARTMENT OF MEDICAL LABORATORY SCIENCES

Title of the study: Treatment outcomes of HIV-infected patients on second line ART in selected health facilities of Addis Ababa, Longitudinal study. Please put "✓" mark

1. I have read/been read the information about the above study. I have also been given an opportunity to ask questions which have been answered to my satisfaction.

Yes ☐ No ☐

2. I freely agree to participate in this study and I understand that I can refuse to participate or withdraw from participation at any time without consequence to my present or future medical care and legal rights.

Yes ☐ No ☐

3. I confirm that no procedures associated with this study have been performed on me prior to my signing this consent.

Yes ☐ No ☐

4. I agree to provide blood sample for laboratory test for CD4 and Viral load test for the purpose of this study.

Yes ☐ No ☐

5. I understand that my personal data will be kept confidential. On the other hand, I understand that my medical notes and other study documents can be looked by the authorized personnel who are involved in this study. I give permission for these individuals to have access to my records.

Yes ☐ No ☐

6. I agree not to restrict the use of any data or results that arise from this study for scientific purpose(s)

Yes ☐ No ☐

7. I certify and voluntarily agree to take part in this study.

Yes ☐ No ☐

Signature of the client _____ Date_____

Witness (for those not reading and writing) 1_____sign_____ 2_____sign_____
Physician _____Signature_____Date _____

Annex 2: የመግባቢያ ቅፅ (CONSENT FORM AMHARIC VERSION)

ADDIS ABABA UNIVERSITY

DEPARTMENT OF MEDICAL LABORATORY SCIENCES

ይህ ቅፅ ጥናቱ ላይ ለመሳተፍ የመግባቢያ ቅፅ ነው፡፡

የጥናቱ ርዕስ፡የጥናቱ ርዕስ፡ የሁለተኛ ደረጃ ፀረ-ኤች አይ.ቪ/ኤ.ድስ ህክምና መቆጣጠሪያ ውጤት ጥናት

አባክዎ የተስማሙበትን የተስማሙበትን የ "✓"ምልክት በማስቀመጥ የሳዩ

1. ከላይ የተጻፈውን የመረጃ አንብቤ የጥናቱን ዓላማና ጥቅም በግልፅ ተረድቻለሁ፡፡ ጥያቄ የመጠየቅ ዕድሉንም አግኝቼ ነበር፡፡በቂም መልስ አግኝቻለው፡፡

   አዎ ☐ አይደለም ☐

2. በዚህ ጥናት ላይ ለመሳተፍ መሉ በሙሉ ፈቃደኛ መሆኔንና በማናቸውም ጊዜ ያለ ምንም ተፅዕኖ ከጥናቱ ራሴን ለማግለል እንደምችል ተረድቼ ተስማምቻለው፡፡

   አዎ ☐ አይደለም ☐

3. በዚህ ጥናት ላይ ከእኔ ጋር የተገናኜ ማንኛውም ነገር ካለእኔ ፍቃድና ዕውቅና የተፈጸመ አለመኖሩን አረጋግጣለው፡፡

   አዎ ☐ አይደለም ☐

4. ለ ሲዲ ፎርና ቫየራል ሎድ ምርመራ የሚሆን የደም ናሙና ለመስጠት ተስማምቸለሁ፡፡

   አዎ ☐ አይደለም ☐

5. የህክምና መረጃዬ በሚስጥር እደሚጠበቅናየተፈቀደላቸው ባለሙያዎች ብቻ ማየት እንዲችሉ ተስማምቻለሁ፡

   አዎ ☐ አይደለም ☐

6. የጥናቱ ውጤት ለታሰበለት ዓላማና በ ተለያዩ ሳይንቲፍክ መደረኮች ላይ መቅረብ እንዲችል ፈቅጃለሁ፡

   አዎ ☐ አይደለም ☐

7. እዚህ ጥናት ላይ ለመሳተፍ ሙሉ ፈቃደኝነቴን እገልፃለሁ፡፡

   አዎ ☐ አይደለም ☐

ፊርማ _____ ቀን_____

ምስክር (ማምበብ ለማይችሉ) 1. _____ፊርማ _____ 2. _____ፊርማ _____የሃኪሙ ሥም _____ ፊርማ _____ቀን_____ ሠዓት _____

Annex 3 : **CONSENT FORM(PROXY)**

ADDIS ABABA UNIVERSITY,DEPARTMENT OF MEDICAL LABORATORY SCIENCES

Proxy consent form (for clients not capable of filling the consent form) for data collection on the second line treatment outcome among HIV patients

This consent form is filled by clients' relative/family members for clients in comatose/disabled to give their consent

Title of the study: Treatment outcomes of HIV-infected patients on second line ART in selected health facilities of Addis Ababa: Longitudinal study. Please put "✓" mark

I hereby need to assure with my signature below that I, without any coercion or forceful act by the research team, have decided to voluntarily give my consent on behalf of the client

Yes ☐ No ☐

1. I have read/been read the information about the above study. I have also been given an opportunity to ask questions which have been answered to my satisfaction.

Yes ☐ No ☐

2. I freely agree to participate in this study and I understand that I can refuse to participate or withdraw from participation at any time without consequence to my present or future medical care and legal rights.

Yes ☐ No ☐

3. I confirm that no procedures associated with this study have been performed on me prior to my signing this consent.

Yes ☐ No ☐

4. I agree to provide blood sample for laboratory test for CD4 and Viral load test for the purpose of this study.

Yes ☐ No ☐

5. I understand that my personal data will be kept confidential. On the other hand, I understand that my medical notes and other study documents can be looked by the authorized personnel who are involved in this study. I give permission for these individuals to have access to my records.

Yes ☐ No ☐

6. I agree not to restrict the use of any data or results that arise from this study for scientific purpose(s)

Yes ☐ No ☐

7. I certify and voluntarily agree to take part in this study.

Yes ☐ No ☐

Signature of the consenter _____ Date_____ Witness (for those not reading and writing)
1_____sign_____ 2_____sign_____Physician
_____Signature_____Date _____

Annex 3: የመግባቢያ ቅፅ (CONSENT FORM)/ PROXY

ADDIS ABABA UNIVERSITY,DEPARTMENT OF MEDICAL LABORATORY SCIENCES

ይህ ቅፅ ጥናቱ ላይ ለመሳተፍ የመግባቢያ ቅፅ ነው::የሚሞላውም አቅም ላጡና መስማማታቸውን መግለፅ የማይችሉ ዘመድ/አሰታማሚ ነው

የጥናቱ ርዕስ:የሁለተኛ ደረጃ ፀረ-ኤች አይ.ቪ/ኤ.ድስ ህክምና መቆጣጠሪያ ውጤት ጥናት

አባክዎ የተስማሙበትን የተስማሙበትን የ "✓"ምልክት በማስቀመጥ የሳዩ

በሙሉ ፈቃደኝነት በዚህ ጥናት ለመሳተፍ ለፀረ ኤች አይ ቪ/ኤድስ ህክምና አገልግሎት መሻሻል በሚደረገውጥረት ውስጥ ደመበኛውን ወክዬ አስተዋፅኦ እንዲያበረክቱ መወሰኔን አረጋግጣለሁ

አዎ ☐ አይደለም ☐

1. ከላይ የተጻፈውን የመረጃ አንብቤ የጥናቱን ዓላማና ጥቅም በግልፅ ተረድቻለሁ:: ጥያቄ የመጠየቅ ዕድሉንም አግኝቼ ነበር::በቂም መልስ አግኝቻለው::

   አዎ ☐ አይደለም ☐

2. በዚህ ጥናት ላይ ለመሳተፍ መሉ በሙሉ ፈቃደኛ መሆኔንና በማናኛውም ጊዜ ያለ ምንም ተፅዕኖ ከጥናቱ ራሴን ለማግለል እንደምችል ተረድቼ ተስማምቻለው::

   አዎ ☐ አይደለም ☐

3. በዚህ ጥናት ላይ ከእኔ ጋር የተገናኜ ማንኛውም ነገር ካለእኔ ፍቃድና ዕውቅና የተፈጸመ አለመኖሩን አረጋግጣለው::

   አዎ ☐ አይደለም ☐

4. ለ ሲዲ ፎርና ቫየራል ሎድ ምርመራ የሚሆን የደም ናሙና ለመስጠት ተሰማምቻለሁ::

   አዎ ☐ አይደለም ☐

5. የህክምና መረጃዬ በሚስጥር እደሚጠበቅናየተፈቀደላቸው ባለሙያዎች ብቻ ማየት እንዲችሉ ተስማምቻለሁ፡

   አዎ ☐ አይደለም ☐

6. የጥናቱ ውጤት ለታመበለት ዓላማና በ ተሰያዩ ሳይንቲፍክ መደረኮች ላይ መቅረብ እንዲችል ፈቅጃለሁ::

   አዎ ☐ አይደለም ☐

7. እዚህ ጥናት ላይ ለመሳተፍ ሙሉ ፈቃደኝነቴን እገልፃለሁ::

   አዎ ☐ አይደለም ☐

   ፊርማ _____ ቀን_____

   ምስክር (ማምበብ ለማይችሉ) 1. _____ፊርማ _____ 2. _____ፊርማ _____

   የሃኪሙ ሥም _____ ፊርማ_____ቀን_____ሠዓት _____

Annex 4: **Data extraction checklist**

Record Review Form for Collecting ART Information

Part-1: Facility level information **Date** _____

Question		Response category	Remarks
101	Health facility	Name _____,	

2. Socio-Demographic Variables

Question		Response category		Remarks
201	Patient Unique ART number?	__ __/__ ___ / __ __ __ __ __ /__ __		2LTO code____
202	Age at the start of ART (ART	_____ years		
203	Sex	1. Male 2. Female		
204	Patient's residence	1. Urban 2. Rural		
205	Patient residence's distance from the Health Facility	_____kms		
206	Patient's living arrangement	1.Own house ☐ 2.With relatives ☐ 3.Rented ☐	4.Kebele ☐ 5.Other,specify _____	
207	Marital Status (for adult)	1.Never married ☐ 2.Married ☐ 3.Separated ☐	4.Divorced ☐ 5.Widowed ☐	
208	Educational level	1.No education ☐ 2.Primary ☐	3.Secondary ☐ 4.Tertiary ☐	
209	Religion	1.Muslim 2.Orthodox 3.Protestant	4.Catholic 5.Other specify _____	
210	Occupation	Specify_____, Not recorded		
211	Income of the patient	_____Birr per month		

3. HIV Care and ART Information

Question (Q)		Response category	Remarks
301	Date confirmed HIV positive	__ __/__ __/__ __ __ __	
302	Past TB treatment	1. Yes 2. No	
303	Date of eligibility	__ __/__ __/__ __ __ __	
304	Reason for eligiblity for ART	1. Clinical only 4.Clinical&CD4 2. CD4 3.VL 5.clinical,CD4&VL 6. Other(TB, HBV, Pregnancy)	
305	Date of first ART start	Date __ __, Month __ __, Year __ __	

3.1. **Parameters before second line**

Q	Parameters *	Pre ART	At first line ART start		Every Month						Every 3 Months				
				2 wks	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6	Month 9	Month 12	Month15	Month 18	Month 24
306	Weight (kg)														
307	WHO staging(1-4)/ treatment staging														
308	TB status (if Any)														
309	OIs or other problems														
310	Drug combination (regimen)														
311	If there is regimen substitution, what reason was considered?* *														
312	CD4 count														
313	Viral load test														
	ADHERENCE														
314	Adherence status (P,F,G)														
315	If poor /fair adherence reason ***														
316	Scheduled date of visit														
317	Actual date of visit														
318	Number of miss to follow ups														

* Months are dated to track information of patients on second line ART who stayed longtime before they shift. Data input can be stopped at any time

Q	Parameters *	Every 6 Month											
		Month 30	Month 36	Month 42	Month 48	Month 54	Month 60	Month 66	Month 72	Month78	Month 84	Month 90	Any time(beyond Month 90)
306	Weight (kg)												
307	WHO staging(1-4)/ treatment staging												
308	TB status (if Any)												
309	OIs or other problems												
310	Drug combination (regimen)												
311	If there is regimen substitution, what reason was considered?* *												
312	CD4 count												
313	Viral load test												
	ADHERENCE												
314	Adherence status (P,F,G)												
315	If poor /fair adherence reason ***												
316	Scheduled date of visit												
317	Actual date of visit												
318	Number of miss to follow ups												

3.2 Parameters After second line

319	Date of second line ART start	Date __ __, Month __ __, Year __											
	Criteria for switch to second line	1.Clinical Only 2.CD4 only 3.Virological only 4.Cinical and CD4 5. CD4 and virological 6.clinical,CD4 and virological											
320	Parameters	At first visit (during switch)	Month 6	Month 12	Month 18	Month 24	Month 30	Month 36	Month 42	Month 48	Month 54	Month 60	At date of survey
321	Weight (kg)												
322	WHO staging(1-4)												
323	TB status (if Any)												
324	OIs or other problems												
325	Drug combination (regimen)												
326	If there is regimen change, what reason was												
327	CD4 count												
328	Viral load test												
	ADHERENCE												
329	Adherence status (P,F,G)												
330	If poor /fair adherence reason ***												
331	Scheduled date of visit												
332	Actual date of visit												
333	Number of miss to follow ups												

**If there is regimen change/substitution/modification at d/t times, consider the following options for reasons (multiple response is possible)
1. Toxicity/side affects 2. Pregnancy 3. Risk of pregnancy 4. due to new TB infection 5. New drug available
6. Drug out of stock 7. Other reason 8. Clinical treatment failure 9. Immunologic failure 10. Virologic failure
***Possible reason for poor/fair Adherence.

1.Toxicity/side effects 2. Share with others 3. Forgot 4. felt better 5. too ill 6. stigma, disclosure or privacy issue 7. drug stock outs 8. patient lost/run out of pills 9. delivery/travel problems 10. inability to pay 11. alcohol 12. Depression 13. other

Declaration

I, the undersigned, declare that this MSc thesis is my original work, has not been presented for a degree in Addis Ababa University or any other universities. I also declare that all sources of materials used for the thesis have been duly acknowledged.

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Signature_____

Place: Addis Ababa University School of Medical Laboratory Sciences, Ethiopia

Date of submission_____/_____/_____

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