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Patterns and Predictors Of Immuno-Virologic Outcomes Among Adult Hiv/ Aids Patients Receiving Highly Active Anti-Retroviral Therapy in Felege Hiwot Referral Hospital, Bahir Dar, Northwest-Ethiopia:-A Retrospective Cohort Study

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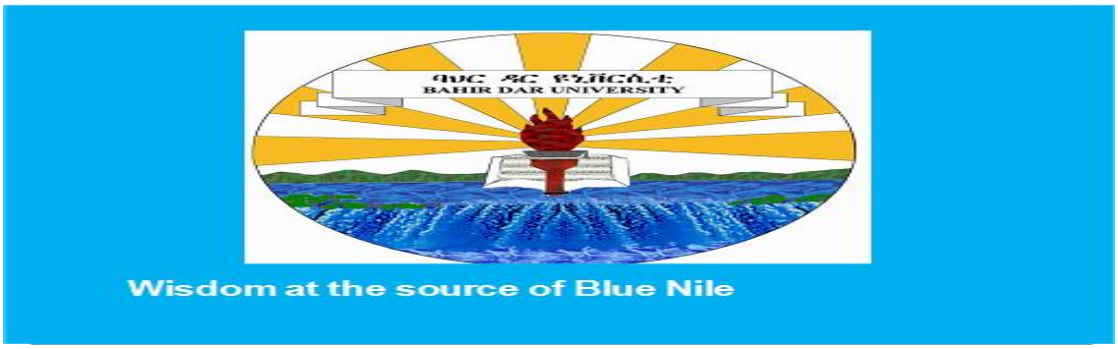

BAHIRDAR UNIVERSITY
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DEPARTMENT OF EPIDEMIOLOGY AND BIOSTATISTICS

PATTERNS AND PREDICTORS OF IMMUNO-VIROLOGIC OUTCOMES AMONG ADULT HIV/ AIDS PATIENTS RECEIVING HIGHLY ACTIVE ANTI-RETROVIRAL THERAPY IN FELEGE HIWOT REFERRAL HOSPITAL, BAHIR DAR, NORTHWEST-ETHIOPIA:-A RETROSPECTIVE COHORT STUDY

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Abstract

Background: With the federal scale-up of antiretroviral therapy (ART) in Ethiopia, survival and quality of life for people with HIV/AIDS has increased. However, some patients do not respond to antiretroviral therapy (ART). Failure to suppress viral replication leads to increased morbidity and mortality, making early diagnosis of treatment failure is imperative for the reduction of negative outcomes for patients.

Objective: The aim of this study was to characterize the success to failure patterns and determine predictors of Immuno-virologic outcomes among Adult HIV/ AIDS patients receiving Highly Active Anti-retroviral Therapy in FelegeHiwot Referral Hospital Northwest Ethiopia 2017.

Methods: A retrospective cohortstudy design was followed at antiretroviral Therapy follow up clinic of FelegeHiwot Referral Hospital. Data were extracted from medical records of adults commenced on HIV treatment since January 01, 2013using a standardized extraction tool. The data were entered in Epi-info version7, and exported to SPSS Version 23 for analysis. In descriptive analysis, variables were summarized using frequencies, and summery measures.

Results: Among the total of 350 participants, 61.1% were females, 71.1% were younger than 40 years. About 91.7% were orthodox Christian in religion & 82.3% were urban residents. The number of study participants who resulted in immune - virologic failure were 176 (50.3%) from which 107 were those who started medication late with baseline CD4 count less than 100 CD4 per mm^3.Patients with shift in ART were at higher risk of developing Immuno-virologic failure (AHR =2.164, 95% CI: 1.447–3.171) than patients stayed on baseline ART regimen. In addition, Baseline CD4 count and types of ART regimen 2 significantly associated with the immune-virologicfailure.

Conclusion: With a maturing HIV treatment program in Ethiopia, monitoring of patients on first line treatment to identify those who are more likely to develop immune-virologic failure is highly crucial.Clinicians should exert their effort to maintain patients on their initial regimen for as long as possible duration with appropriate care and close follow-up.

Key words: *HIV, ART, Immuno-viorologic outcome, Survival Analysis, Retrospective Cohort.*

ABBREVIATIONS AND ACRONYMS

3TC	Lamivudine
ABC	Abacavir
AIDS	Acquired Immunodeficiency Syndrome
ARV	Antiretroviral
ART	Antiretroviral therapy
AUROC	Area Under Receiver Operating Curve
AZT	Azidothymidine / Zidovudine
CD4	Cluster of differentiation 4 T-helper cells
D4T	Stavudine
EFV	Efavirenz
EDHS	Ethiopia Demographic Health Survey
EPHI	Ethiopian Public Health Institute
FTC	Emtricitabine
HAART	Highly Active Antiretroviral Therapy
HIV	Human immune-deficiency virus
LPV/r	Lopinavir boosted with ritonavir
MAP	Multi-country AIDS Program of the World Bank
MTCT	Mother-To-Child Transmission of HIV
NNRTI	Non-nucleoside reverse transcriptase inhibitor
NRTI	Nucleoside reverse transcriptase inhibitor
NtRTI	Nucleotide reverse transcriptase inhibitor
NVP	Nevirapine
OI	Opportunistic Infections
PI	Protease inhibitor
TDF	Tenofovir
PLHA	People Living HIV /AIDS
UNAIDS	Joint United Nations Agency for AIDS
WHO	World Health Organization/Woreda Health Office

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1. Introduction

1.1 Back ground

The natural course of HIV infection is characterized by progressive and, ultimately, profound loss of CD4+ T lymphocytes, the primary target of this virus is that it essentially infects the immune system. Human immune deficiency virus (HIV) is responsible for aworldwide pandemic, and it is the cause of acquired immune deficiency syndrome (AIDS).

The goal of antiretroviral therapy in HIV treatment is to maximize HIV viral suppression, preserve and restore immune function, reduce HIV-related morbidity and mortality and improve the quality of life**.** Combination therapy using three or more antiretroviral drugs from at least two different classes in therapeutic doses is termed Highly Active Antiretroviral Therapy (HAART). HAART has been associated with sustained virologic suppression**,** improvement in CD4 counts**,** increased survival and quality of life(1).

In response to antiretroviral therapy, some patients experience what has been termed a discordant response, characterized either by a sustained CD4+ cell count rise despite persistent viraemia or by HIV-1 RNA plasma levels below the limit of detection accompanied by a blunted CD4+ cell count response.Little is known about the pathogenesis of discordant responses, which seems to depend on the interaction of a multitude of viral, host and treatment-related factors

Treatment failure is considered when a person who has taken ART for at least 6 months presents with clinical, immunological or virologic evidence of unsuccessful treatment. In the absence of viral load monitoring treatment failure is diagnosed using immunological and clinical parameters following the WHO guidelines. Viral load testing is the gold standard for monitoring ART. However, this test is expensive and technique demanding. HIV treatment failure occurs when patients develop negative virologic, immunologic andclinical outcomes while still on therapy. Treatment failure normally progresses fromvirologic, to immunologic and then clinical failure(2).

Time to treatment failure frominitiation of ART appears to depend onseveral factors, including genetics, adherence, previous ART exposure, transmitted HIV resistance; and it can occur from 6 months to many years(3).

1.2 Statement of the problem

According to UNAIDS report 2017 on the Global AIDS Epidemic in 2016, there were 36.7million people living with HIV, 1.8 million people became newly infected with HIV and around 1.0million people died from AIDS-related illnesses in the same year.

Sub-Saharan Africa, contribute to only 12% of the global population, but accounts for 71% of the global burden of HIV infection. Ten countries, mostly in southern and eastern Africa, with South Africa (25%), Nigeria (13%), Tanzania (6%), Mozambique (6%), Zambia (4%), Zimbabwe (6%), Uganda (6%), Kenya (6%), Malawi (4%) and Ethiopia (3%), account for almost 80% of all people living with HIV (4).

Ethiopia is one of the sub Saharan African countries affected by HIV and AIDS with a prevalence of 1.5% of the population age 15-49. HIV prevalence in urban areas was approximately five times as high as in rural areas (5.2% and0.8% respectively). Among regions HIV prevalence is highest in Gambella (6.5 percent) and in Addis Ababa (5.2 percent). In 2016in Ethiopia around 710,000 peoples (570,000-880,000) were found living with HIV from which nearly half 420,000 people get ART treatment (5).

The HIV epidemic in Ethiopia is primarily associated with areas of urban concentration (5.1% in cities above 50 thousand compared to 3.1% in smaller cities and 0.6% in rural areas) and proximity to major transport corridors. Those living within five kilometers of a major road have HIV prevalence rates that are four-times higher than those who live further away. The two exceptions to this general pattern include Gambella region, a small and sparsely populated region that has the highest regional prevalence in Ethiopia (6.4%) (6).

The use of HAART in HIV patients reduces the viral load and increases the CD4+ counts in the usual trend, however, some patients do not respond to ART. Global scale-up of antiretroviral therapy has been the primary contributor to a 48% decline in deaths from AIDS-related causes, from a peak of 1.9 million (1.7 million-2.2 million) in 2005 to 1.0 million (830 000-1 2 million) in 2016(7).

InEthiopia, immunological treatment failure has been reported to be 4–17.5% amongadults,8–10% in children who are on firstline ART, 5.9% clinical and 6.7% immunological treatment failure. The immunological failure rate in Ethiopia a study conducted in Debremarkos Hospital was found to be high(8).The timing and accuracy of identifying treatment failure in resource-limited settings are fundamental but challenging.

The study gives an important relationship between baseline CD4 cell count and patterns of immunovirologic outcome and the discordant cases to clinicians and other stakeholders so that they do give great attention for baseline CD4 count and early detection of the discordant cases which in turn help them in caring for patients and maintaining their ambitious plan.(9).

1.3 Significance

Despite all efforts, HIV/AIDS remain to kill many in Ethiopia in re-emerging form. As to the recent national report's HIV spread is alarming. Unlike to the previous cases, patients are advised to start medication regardless of CD4 count which again necessitates reconsideration of the patterns of immunovirologic outcomes and number of CD4 counts compared to the baseline CD4 counts. Patients with poor baseline CD4 count and inactive immunity must be diagnosed as early as possible so that we can safeguard the community. Some patients do not respond to ART. Failure to suppress viral replication leads to increased morbidity and mortality, making early diagnosis of treatment failure imperative for the reduction of negative outcomes for patients. The health care providers do not have enough awareness on the discordant cases so the study may give certain concepts which they not only include in the diagnosis and treatment but also address the cases to the decision makers and health planners to enforce a strong focus on it.Failure of CD4+ cell reconstitution during receipt of virologically suppressive HAART indicates the need for alternative treatment strategies, so this study may initiate researchersfor further study the reality of the cause of discordant cases and develop solution.

Moreover, due to the re-emerging pattern of HIV/AIDS in Ethiopia, there is a need of national baseline data on the level of treatment failure which will aid the third target achievement the ambitious plan of 90-90-90 treatment target by 2020 and ending the AIDS epidemic by 2030. Therefore, this study assessed the patterns and predictors of immunovirologic outcomes among

adult HIV/AIDS patients in Felegehiwot Referral Hospital, Bahir Dar, Northwest Ethiopia to give supportive evidence for the national HIV treatment/ prevention programs.

2. Literature Review

2.1 Global HIV epidemiology

Based on the 2017 HIV/AIDS key facts (WHO), HIV continues to be a major global public health issue, having claimed more than 35 million lives so far. In 2016, 1.0 million people died from HIV-related causes globally. There were approximately 36.7 million people living with HIV at the end of 2016 with 1.8 million people becoming newly infected in 2016 globally. 54% of adults and 43% of children living with HIV are currently receiving lifelong antiretroviral therapy (ART) (10).

WHO African Region is the most affected region, with 25.6 million people living with HIV in 2016. The African region also accounts for almost two thirds of the global total of new HIV infections (11).

The HIV epidemic varies globally across geographical areas and can be categorized as low, centralized or generalized. The African epidemic is generalized unlike most other regions of the world where it is concentrated in high risk groups like injecting drug users, men who have sex with men and commercial sex workers and also characterized by a predominant heterosexual mode of transmission (12).

2.2 Epidemiology of HIV in Ethiopia

Ethiopia is in a low generalized HIV epidemic with significant heterogeneity among regions and population groups. According to UNAIDS 2015 report, estimated 753,100 people are living with HIV in Ethiopia with a declining national HIV prevalence ‑ in 2011 it was estimated to be 1.5% (DHS 2011) and 1.1% in 2015 (2014 Spectrum projection); urban are more affected than rural areas while females are twice affected than male population with HIV (2).HIV prevalence in urban areas was approximately five times as high as in rural areas (5.2% and0.8% respectively). Among regions HIV prevalence is highest in Gambella (6.5 %) and in Addis Ababa (5.2%. The prevalence of HIV is about 1.8% in Tigray, in Amhara 1.6%, Afar 1.8%, BenishangulGomez1.3%, Dire Dawa 4%, Harari 2.8%, Oromia 1%, Somali 1.1% and 0.9 % in SNNPR (13).

Studies on immune-virological response after HAART in Ethiopian patients on HAART report CD4 increment to be the greatest in the first six to twelve months with a pattern of slight decrease in mean CD4 count in later years of follow-up(14).

2.3 HIV Virology and Immunology

HIV is an enveloped RNA retrovirus that infects T-cells. Once HIV DNA isintegrated into host DNA, a state of latency in several tissues develops complicating attempts ateradication (14).

The natural history of HIV infection is divided into three: acute infection, chronic asymptomatic infection and terminal HIV infection. Acute infection is characterized by high viremia, CD4 decline, raised transaminases, flu-like clinical symptoms (acute viral syndrome) and typical spontaneous resolution with the development of a cytotoxic T-cell response (15). The chronic phase is characterized by continued viral replication with progressiveCD4 decline with later appearances of opportunistic infections. The terminal phase of HIV infection is characterized by pronounced depletion of CD4 cells, susceptibility to severe opportunistic infections resulting in AIDS and inevitable death if untreated (16).A Natural history study show three patterns of HIV disease progression from infection to AIDS: rapid progressors (median of 3-4 years), typical progressors (median of 8-10 years), and long term non-progressors (> 12 years) (17).

The CD4 T-cell count and theplasma HIV RNA viral load are two surrogate laboratory markers for monitoring diseaseprogression. While the CD4 count is a marker for immune competence, the viral load is a markerfor disease progression (18).

2.4 Patterns of immune-virologic failure

Generally, it is assumed that patients taking HAART decrease their viral load and parallaly increase CD4 cell count; however some patients experience what has been termed a discordant response, characterized either by a sustained CD4+ cell count rise despite persistent viraemia or by HIV-1 RNA plasma levels below the limit of detection accompanied by a blunted CD4+ cell count response(19). Immunological monitoring (CD4 cell count test) is expected at baseline just before starting HAART. A patient must be followed for a minimum of six months before assessment is made for treatment failure.

Discordant virological and immunological responses are observed during ART suggesting a complex interaction between virological response and the CD4 cell count change](20, 21)There are limited data on discordant responses in patients being treated in developing countries. In industrialized countries, discordant responses have been reported to occur in 20–30% of patients 6 months to 2 years after starting therapy(22). It is not surprising that, given the lack of universally accepted definitions of virological and immunological failure, published estimates of the frequency of discordant responses vary considerably.

Little is known about the pathogenesis of discordant responses, which seems to depend on the interaction of a multitude of viral, host and treatment-related factors. A blunted CD4 response despite suppression of viral replication has often been attributed to host characteristics, particularly older age(12).

2.5 Anti-retroviral Therapy

2.5.1 Overview

HIV is known to be associated with a wide range of immunological and hematological changes.The immunological changes include depletion in CD4+ T cell, cytokine deregulation, and immune dysfunction (23). The goal of antiretroviral therapy in HIV treatment is to maximize HIV viral suppression, preserve and restore immune function, reduce HIV-related morbidity and mortality and improve the quality of life (24). Combination therapy using three or more antiretroviral drugs from at least two different classes in therapeutic doses is termed Highly Active Antiretroviral Therapy (HAART). The use of HAART brought significant advantage in regard to the expected outcomes but data on immunovirologic monitoring during the treatment is not available (1).

2.5.2 Classes and modes of action

The main classes of antiretroviral agents include nucleoside reverse transcriptaseinhibitors (NRTI), non-nucleoside reverse transcriptase inhibitors (NNRTI), proteaseinhibitors (PI) and Fusion (entry) inhibitors (2).The NRTIs work by competitivelyantagonizing HIV replication by incorporating their synthetic analogues into viral DNAand inhibiting reverse transcriptase while the NNRTI work by non-competitive inhibitionof HIV reverse transcriptase. NNRTIs are not active against HIV (25)and easilysuccumb to rapidly emerging resistancethrough single point mutations (26) . Tenofovir-

disoproxilfumarate (TDF) is the only nucleotide reverse transcriptase inhibitor (NtRTI)and competitively incorporates into viral DNA inhibiting viral replication. PIs areexcellent inhibitors of HIV by inhibition of viral protease. Different combinations of drugs areavailable to reduce pill burden and simplify dosing (2).

2.5.3 Treatment guidelines and schedules (WHO and Ethiopia)

The WHO recommends the following as preferred regimens (listed in order of FDA approval) for antiretroviral (ARV)-naïve patients .(27) .includes regimens such as Efavirenz/ tenofovir disoproxilfumarate/emtricitabine (EFV/TDF/FTC); Ritonavir-boosted atazanavir + tenofovirk disoproxilfumarate/emtricitabine (ATV/r + TDF/FTC); Ritonavir-boosted darunavir + tenofovirdisoproxilfumarate/emtricitabine (DRV/r+ TDF/FTC); and the regimen Raltegravir + tenofovirdisoproxilfumarate/emtricitabine (RAL + TDF/FTC).

2.6 Adherence to Antiretroviral Therapy

Adherence which is defined as the degree of consistency between the providersprescribed medication and the patients' behavior is complex and difficult to measure inclinical and epidemiological studies, but has been associated with sustained viralsuppression, reduction in onset of resistance,and favorable clinical (28). Initial skepticism and reluctance to scale up ART in Africa was mainly founded onfears of prohibitive costs and medication non-adherence. However, numerousstudies have shown that medication adherence in Africans is good and sometimes betterthan that obtained in developed countriesm (29). Predictorsof medication adherence may include patient-related, regimen-related, provider-relatedand health systems-related factors (30) .In the absence of ideal adherence measurement tools and in the context of lackof routine viral load measurements and resistance testing, widespread treatment failurewith drug resistance is a grave possibility, thus efforts must be made to improveadherence measurements tools, and adherence counseling and treatment preparationactivities (31).

2.7 HIV treatment failure

2.7.1 Definitions and progression

Immunological monitoring (CD4 cell count test) is expected at baseline just before starting HAART. After starting treatment CD4 cell count should be measured every six months for the first year, then once yearly in line with the health management information system (HMIS) guidance for cohort reporting(32).Although the WHO recommends three types of criteria to define antiretroviral treatment failure, namely clinical, immunological, and virologic, the focus of this study was on immunological criteria which the WHO defines as either a fall of follow-up CD4 count to baseline (or below), orCD4 levels persisting below 100 cells/mm3, or50% fall from on-treatment peak value (33).These same criteria were used in this study to identify patients with immunological failure according to the WHO 2010 guidance. A patient must be followed for a minimum of sixmonths before assessment is made for treatment failure.

2.7.2 Measures and Predictors of Immuno-virologic treatment failure

Sustained virologic suppression on first-line therapy is the goal of treatment, sincepotency of subsequent regimen is affected by accumulated resistance mutations.Numerous studies in some settings in Africa havedemonstrated good rates of survival in ART patientshigh CD4 countrestoration,(34).sustained viral suppression and good clinical outcomes. However, failure rates on first line therapy is still high in some settings and numerousstudies demonstrate that this may be due to late presentation (35).

advanced disease, low baseline CD4 count level, malnutrition, low body mass index, presence ofopportunistic infection especially tuberculosis,co-infection with hepatitis B&C, long distance from treatment sites, HIV non-disclosure, stigma, low baseline hemoglobin count, low socio-economic status, prior non-HAARTexperience, WHO stages 3 &4, alcohol and drug abuse, clinical depression, perception of treatment efficacy and self-medication efficacy (36). Studies in Ethiopia regarding immune-virologic outcome is scarce, this study, therefore, investigated the patterns of immune-virologic outcome, the level of immunological response, both in the form of CD4 cell counts, as well as the viral load and its determinants among adult HIV/AIDS patients in Felegehiwot Referral Hospital, Bahir Dar, Northwest Ethiopia

2.8 Conceptual Framework

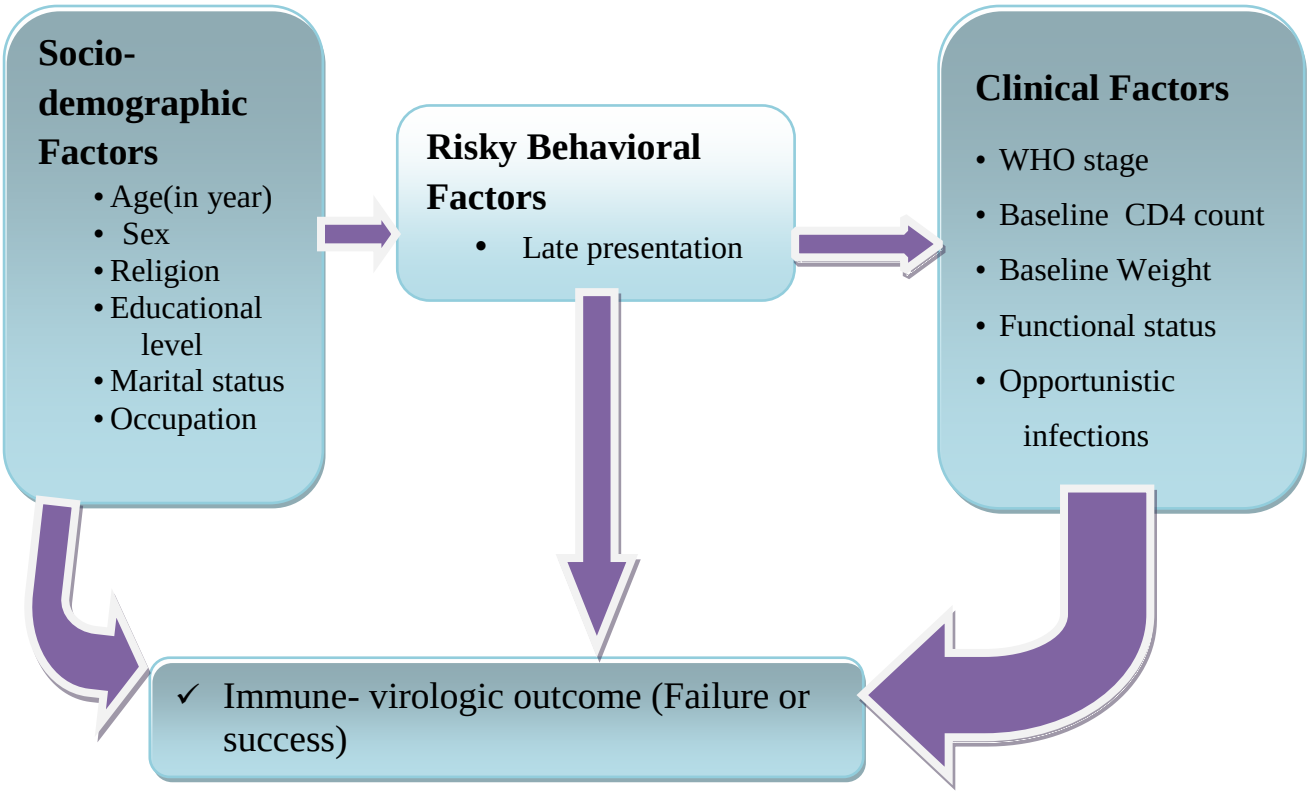

Figure 1Conceptual framework for the study of Patterns and Predictors of Immuno-virologic Outcomes Among adult HIV/ AIDS Patients Receiving Highly Active Anti-retroviral Therapy in FelegeHiwot Referral Hospital, Bahir Dar, Northwest-Ethiopia 2017: Based on the literature Review.

The above conceptual framework illustrated the types of independent variables considered to characterize the desired outcome; accordingly we tried to see sociodemographic variables such as age, sex, religion, marital status and level of education. Among risky behavioral factors late presentation was considered. The last factors considered were clinical factors and some of these include baseline CD4 count, baseline weight, functional status, presence of opportunistic infection and WHO stages.

3. Objective of the study

3.1 General Objective

- To characterize the immune-virologic outcome patterns and identifyits predictorsamong Adult HIV/ AIDS patients receiving Highly Active Anti-retroviral Therapy in FelegeHiwot Referral Hospital Northwest Ethiopia.

3.2 Specific Objectives

- To determine the proportion of immune-virologic outcomes among HIV Patients with a baseline CD4 count below and equal or above 100 cells/mm^3
- To describe patterns of immune-virologic outcomes among HIV Patients with a baseline CD4 count below and equal or above 100 cells/mm^3
- To identifyPredictors of immune-virologic outcomes among adult patients with a baseline CD4 count below and equal or above 100 cells/mm^3

4. Methods

4.1 Study Area

This study was conducted in FelegeHiwot Referral Hospital. Bahir Dar is the capital city of Amhara National Regional state, North Ethiopia. Situated at the Southern part of Lake Tana, Source of Blue Nile, Which is located at 564km from Addis Ababa (the capital city of Ethiopia). It is divided into 10 administrative subCities. It has a population of around 251,309.Bahir Dar Administrative Health Bureau is responsible for both curative and preventive health care of the city under which there are 2 public hospitals, 1 public health Institute (laboratory) and10 health centers in the city. There are 742 health care workers in government health institutions in Bahir Dar city, among those 373 were nurse, 53 were GP, 80 were laboratory technician, 63 were midwifes and 45 were Health officer, 128 were others (pharmacy, emergency surgeon, anesthetics and specialists).

4.2 Study Design

This study followed a clinic-based retrospective cohort study design using a secondary data extracted from medical records of adult HIV infected patients receiving HAART from January 01, 2013 to June 30, 2017. This study involved patients whose baseline exposure predictor variables were measured and collected before the occurrence of the outcomes of interest. A cohort of all patients commenced on ART between January 01, 2013 and June 30, 2017 was followed until December 30, 2017 and assessed at a maximum of 54 months and a minimum of 6 months post ART visit for Immuno-virologicfailure.Data extraction was done with a standardized tool and information was retrieved by medical record chart abstraction, and review of laboratory, clinical, pharmacy and follow-up records.

4.3 Source and Study Population

The sourcepopulation was all HIV infected Adults attending routine care in a single government owned public Referral Hospital in North West, Ethiopia. Those patients all tested positive for HIV, commenced to HAART fromJanuary 01, 2013 to June 30, 2017 and were being routinely followed up at the recommended three month intervals or sooner as the clinical providers or patients deem fit was included to the study.

4.4 Eligibility criteria

i. HIV infected Adults on HIV/AIDS care follow upfrom January 01, 2013to December 30, 2017.
ii. Aged 15 and above years old
iii. HIV patients with complete intake, registers and follow up form
iv. Women who were not pregnant at the time of ART initiation or PMTCT
v. Patients transferred out and transferred in after the cohort is started, Patient card not found, ART status not determined, out come not registered will beexcluded from the study

4.5 Operational definition

- Immunno-virologic success:When the Viral load less than or equal to 400 copies/ml and a change of greater than 50 CD4 cells from baseline to 12 months while on HAART
- Immunne-virologic failure: when the Viral loadgreater than400 copies/ml and a failure of CD4 lymphocyte count to improve by at least by 50 cells /mm3 or Discordant immune-virologic results or worsening to or below baseline pre-HAART CD4 level at 12 months after HAART initiation.

4.6 Sample Size Determination

Since the investigation is cohort study, the sample size required for achieving statistically significant results were determined by taking into account the major exposure variables and using Open Epi version 3.04 statistical package. Among exposure variables,the low baseline CD4 count (CD4 cell count less than100 cells/mm3) was chosen since it gave optimal sample size and most significant result. In this regard, 5%level of significance (two sided), a power of 80%, and a ratio of unexposed to exposed of 1:1, estimated proportion of immunne-virologic failure among patients with CD4 cell count less than100 cells/mm^3in Ethiopia was taken to be 4.1%.(37)Hence, with this assumption, the calculated sample size was 242 but the sample size used here was 350. The other two specific objective variables were used to calculate the sample size but resulted in lower sample size compared to the baseline CD4. Then, simple random sampling method was used to sample individuals from the eligible patients in the records by two recruited and trained nurses.

4.7 Sampling Procedures

There were 2378 adults on ART by the end of December 30, 2017. Of these,308 weretransferred in from other health facilities, 190 were transferred out, and 212 were whose outcome was not registered so only 1558 were eligible for the study. From these eligible ones, 680 were subtracted because 358patients card were not found and 322were ART status not determine. Therefore, only 878 were enrolled in the study from which350 were selected by simple random sampling method.

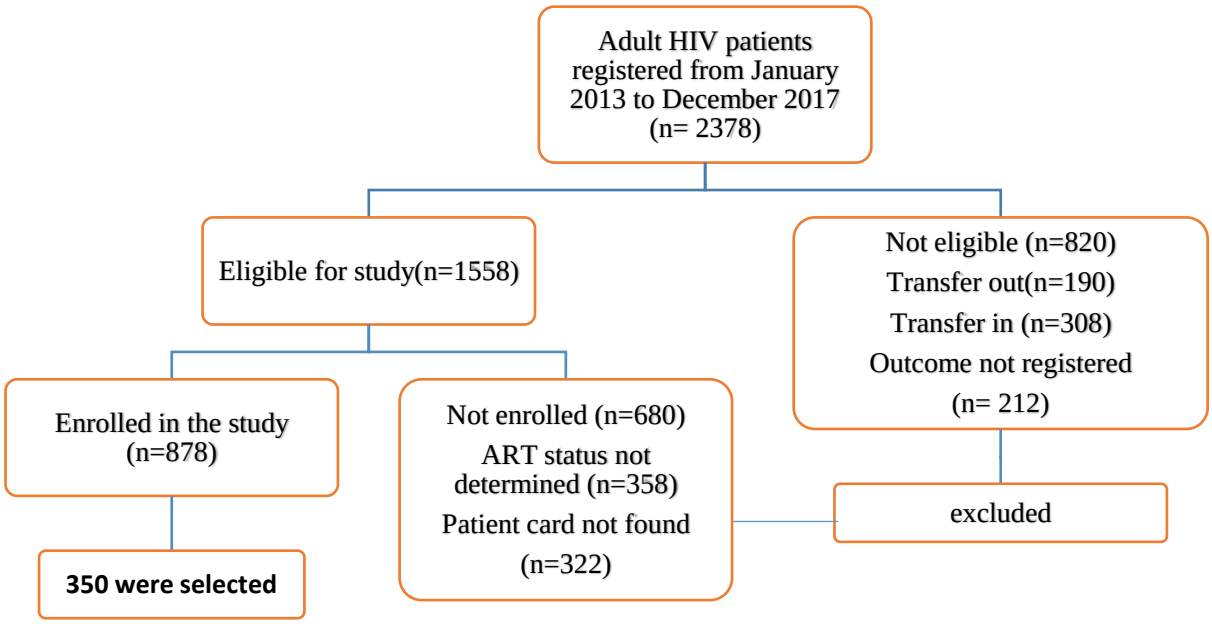

Figure 2 Sampling procedure for the study of Patterns and Predictors of Immuno-virologic Outcomes Among adult HIV/ AIDS Patients Receiving Highly Active Anti-retroviral Therapy in FelegeHiwot Referral Hospital, Bahir Dar, Northwest-Ethiopia 2017: Based on the literature Review

4.8 Study Variables

Dependent Variables: Immuno-virologic outcomes (Failure or success)

Independent Variables:age, religion, educational level, ethnicity, marital status, employment status, residence, number of rooms, post opportunistic infection, TB infection, functional status, baseline CD4 cells count, baseline weight, drug regimen, WHO clinical stage, risk behavior and substance use were predictors.

4.9 Source and Method of data collection

A data extracting checklist was prepared based on routine data registration protocol using standardized HIV care and followup forms employed by the ART clinics in healthfacilities of Ethiopia. Data was extracted from records bytwo ART staff nursesusing the data-collecting checklist after receiving 2 days training on how to extract data from the records. Datameasured during enrollment of patient or, if not available,data measured within 4 weeks of enrollment wasextracted as baseline data. To assure quality of data extraction, the researcher routinely monitored data extractors and moreover a pretestwasconducted in 5% (18 patients) of the sampled individuals from FHRH.

4.10 Method of data analysis

The data were entered, coded, and recoded using Epi-info version7. Thenexported to SPSS Version 23 and analysis was started. In descriptive analysis, proportions, frequencies, and numerical summery measures of patient characteristics were summarized.Kaplan-Meier approach was used to describe the cumulative proportion of survival and immune-virologic failure as of particular time in the follow-up. The bivariableregression model was used toverify the effect of variables on immunovirologic failure and other independent predictors of immune-virologic failure. Independent variables with $p < 0.2$ in thebivariable analysis were included in the multivariable analysis. The assumptions, multicollinearity, normality,and proportionality of hazards over time were checked.The Survival function was used to plot the probabilities immune-virologic failure and survival function over time.

The median of immuno-virologic failure and survivaltime across the categories of specific patient characteristics was evaluated with the log-rank test. Unadjusted Cox proportional hazards models was used to evaluate independent associations between each of the independent studyvariables and immuno-virologic failure. The final model was selected after checking for collinearity between covariates, the fulfillment of proportional hazards assumptions, and existence of extreme influential records.

The magnitudes of the associations summarized with hazard ratios and 95% confidence intervals. A multivariable Cox proportional hazards modelswas used to identify independent predictors and

develop a prediction models of the hazard rate of immune-virologic failure. Statistical significance was established with P-value of 0.05.

4.11 Ethical consideration

This document submitted to Bahir Dar University College of health science, school of public health for ethical approval. Following the approval, Official letter of co-operation was written to concerned bodies by the School of Public Health of Bahir Dar University. The study was conducted through review of medical records, the individual patients not subject to any harm as far as the confidentiality is kept. To preserve the confidentiality, nurses working in ART clinic in the study area. During data extraction, no personal identifier was used on data collection form.

5. Results

5.1 Socio-demographic characteristics of the study participants

The socio-demographic and clinical characteristicsof study participants were consistent with many other studies conductedin poor resource settings. Among the total of 350 participants, 61.1% were females, 71.1% were younger than 40 years, orthodox (91.7%), 56.6% were unemployed and 82.3% are of urban residents (Table 1).

Table 1 Socio-demographic Characteristics of adult HIV/ AIDS Patients Receiving Highly Active Anti-retroviral Therapy in FelegeHiwot Referral Hospital, Bahir Dar, Northwest-Ethiopia.

Variables	Category	Frequency	percent
Sex	Male	136	38.9
	Female	214	61.1
Age (years)	<40	249	71.1
	40-60	98	28
	>60	3	0.9
Religion	Orthodox	321	91.7
	Muslim	23	6.6
	Protestant	6	1.7
Educational status	illiterate	91	26
	Primary school	118	33.7
	Secondary school	76	21.7
	tertiary	65	18.6
Marital status	Single	83	26.8
	Married	118	38
	Divorced	90	29
	Widowed	19	6.2
Residence	Urban	288	82.3
	Rural	62	17.7
occupation	employed	152	43.4
	unemployed	198	56.6

5.2 Baseline clinical and immunologic characteristics

Regarding thebaseline clinical and laboratory characteristics of patients during HAART commencement, almost all (98%) participants were working by their functional status,65% of the

participants useTDF-3TC-EFV as base line ART regimen, 85% did not have Tb infection, 76% did not shift their regimen and 89.7% had baseline viral load above 400RNA copies/dl.

Table 2 Base line clinical, laboratory and ART information of HIV positive adults at initiation of HAART at FelegeHiwot Referral Hospital, (n = 350)

Variables	Category	Frequency	percent
functional status	working	343	98
	Ambulatory	3	0.9
	Bed ridden	4	1.1
Base line WHO staging	Stage I	97	27.7
	Stage II	134	38.3
	Stage III	33	9.4
	Stage IV	87	24.6
Base line ART regimen	d4t(30)-3TC-NVP	5	1.4
	d4t(30)-3TC-EFV	1	0.3
	AZT-3TC-NVP	53	15
	AZT-3TC-N-EFV	36	10.3
	TDF-3TC-EFV	227	65
	TDF-3TC-NVP	21	6
	ABC-3TC-EFV	6	1.7
	ABC-3TC-EFV	1	0.3
TB infection	No	298	85
	yes	52	15
ART shift	No	265	75.7
	yes	85	24.3
Base line viral load	<400	36	10.3
	= > 400	314	89.7
Current ART regimen	d4t(30)-3TC-NVP	12	11.9
	d4t(30)-3TC-EFV	12.6	12.6
	AZT-3TC-NVP	59.7	59.5
	AZT-3TC-N-EFV	6.3	6.3
	TDF-3TC-EFV	2.6	2.5
	TDF-3TC-NVP	0.6	0.7
	ABC-3TC-EFV	6.3	6.3
CD4 Cell count	<100	107	30.6
	=>100	243	69.4
Immune Failure	No	243	69.4
	yes	107	30.6
Virologic Failure	No	36	10.3
	yes	314	89.7
Immune-virologic failure	No	174	49.7
	yes	176	50.3

89.7% of the patients had baseline viral load greater than or equal to 400cells per ml and 69.4% of them had a baseline CD4 count of greater than or equal to 100cells per ml. Patients with baseline CD4 greater than or equal to 100cells per mlshowed higher median survival time of 39 months with CI(36.96-41.04) and SE of 1.041.The median survival time of patients who stayed on their first line ART was higher around 40 months with CI(37.825-42.175) and the overall failure cumulative probability is significant. The overall failure commutative probability with different types of second line ART regimen is high with p-value of 0.027.

Overall, most patients (69.4%) in our study experienced, a favorable immune response(CD4+), but most of the participants (89.7%) experienced virologic failurity(VL-) after initiating HAART, whereas nearly half of the patients (50.3%) experienced discordant responses. The median survival time of immune-virologic failure was around 23 months with CI(20.828-25.172) and SE of 1.108. The number of study participants who resulted in immune-virologicfailure were 176 from which 107 were those who started medication late with baseline CD4 count less than 100 CD4 per mm^3.

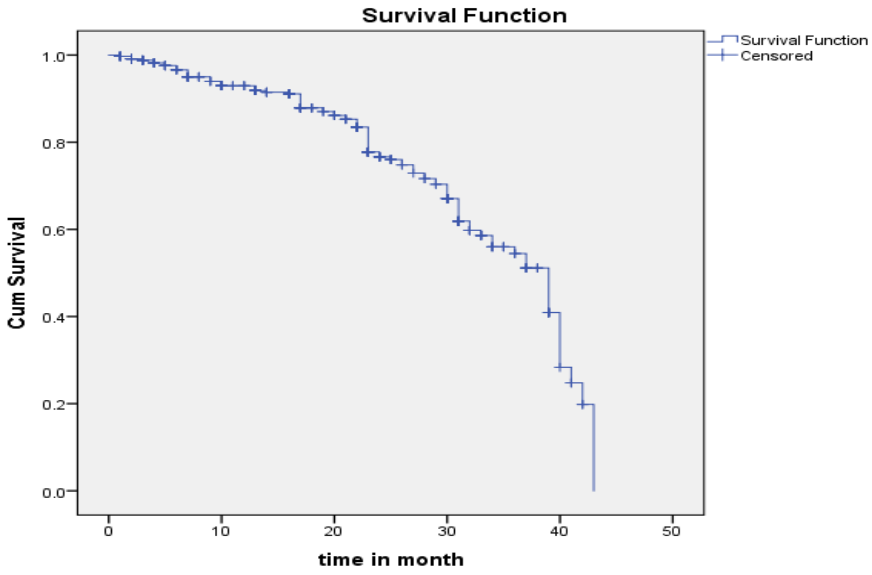

Fig 3. Kaplan Meier Cumulative survival curves for time to the pattern of immune-virologic failure among HIV patients on ART, Felege Hiwot Referral hospital

5.3 Predictors of immune-virologic failure among HIV infected adults

The bivariate analysis showed that most of thevariables like baseline CD4 count less than 100cells/mm3, ART shift, Base line WHO stage and ART regime were associated with immune-virologicfailure.

Table 3Cox regression analysis between different predictor variables and time to immune-virologic outcomes failure among adult HIV positive patients on HAART regimen at FelegeHiwot Referral Hospital, Jan. 2013 to Dec. 2017 (n = 350)

Variable	Catagory	Survival status		CHR (95% CI)	AHR (95% CI)	P-value
		Event	Censored			
Base line CD4	<100cells/mm3	81	26	0.817(0.63-1.05)	1.17(1.03-1.96)	0.042
	≥100cells/mm3	154	89	1	1	-
ART shift	yes	85	7	1.48(1.06-2.06)	2.16(1.47-3.17)	0.00
	No	265	75	1	1	-
Follow up ART regimen type	d4t(30)-3TC- NVP	4	1	1	1	-
	d4t(30)-3TC-EFV	1	0	1	1	-
	AZT-3TC-NVP	42	11	1	1	-
	AZT-3TC-N-EFV	24	12	1	1	-
	TDF-3TC-EFV	174	53	1	1	-
	TDF-3TC-NVP	17	4	1.09(0.99-1.19)	1.17(1.06-1.30)	0.001
	ABC-3TC-EFV	5	1	1	1	-
	ABC-3TC-EFV	1	0	1	1	-
sex	Female	103	111	1.186(0.91-1.53)		0.193
	Male	97	39	1	1	-
Base line HGB	<11	77	12	0.17(0.49-1.01)	-	0.062
	≥11	202	59	1	1	-
Base line WHO stage	I	75	22	1.12(0.99-1.27)	-	0.058
	II	103	31	1	1	-
	III	24	9	1	1	-
	IV	70	16	1	1	-

In the multivariate analysis, sex,baseline Hgb, baseline WHO stage and baseline ART regimen typewere not significant while baseline CD4 count, ART shift and follow up ART regimen type, were independent predictors of immune-virologicfailure after controlling for other factors.

6. **Discussion**

This retrospective Cohort study was carried out to assess the patterns of immune-virologic failure among HIVpatients after initiation of ART and the effect of baseline CD4 cell count response.Baseline CD4 cell count was evaluated whether it was a risk factor associated with immune-virologic failure and those patients with baseline CD4 count less than 100cells/mm^3 are more likely to develop immune-virologic failure than those patients with baseline CD4 greater thanor equal to 100cells/mm^3 with AHR1.17 and CI 1.03-1.96.Generally, it is supposed that lower CD4 counts are important contributor for virologic failure or higher baseline CD4 counts result in virologic reduction but there are discordant cases where virologic reduction may not be accompanied by increase in CD4 count and vice versa(38).the reason for discordant case is not well defined but studies reported that older age, concurrent viral hepatitis and genetic polymorphisms involved in CD4 T cells homeostasis were postulated as factors contributing to discordant case.

In this study around 50.3% (176) of the study participants resulted in immunovirologic failure of which 107(61%) had a baseline CD4 count less than 100 cells per mm^3, this directly show the influence of late starting of the therapy (below 100 CD4 cells per mm^3). This could be a reason to consider initiating HAART before the CD4 cell count decreases to less than 100 cells/mm3. Patients experienced immune-virologic failure or discordant cases in our study are much higher than previous studies which may be due to inconsistent cut off point for baseline CD4 count and immune-virologic failire. Discordant virological and immunological responses are observed during ART suggesting a complex interaction between virological response and the CD4 cell count change (39, 40)The gold standard for determining antiretroviral treatment failure is viral load testing, which is not routinely available in Ethiopia.

Another comparison of effect of ART shift with those who maintained on first line regimen, those who shift ART regimen were 2.16 times more likely to develop immune-virologic failure than those who did not change their ART regimen with CI of (1.47-3.17) and this is may be due to increased side effects of second line ART regimen.Follow up ART regimen type is another associated factor with immune-virologic failure with AHR 1.17, CI (1.06-1.30) and P-value of 0.001. This result is supported by different previous studies. A study byAlemie GA etal, 2017 and Moore DM. etal, 2005 showed the association between different ART regimen and immunovirologic failure and

patientds who were on their first line regimen for longer period, appeared to have low risk of treatment failure (41).

Various studies have reported on the prevalence of immunological failure. A study in northern Ethiopia reported a prevalence of 22% (n = 89) among adults, which was lower than the finding from the present study.(42).

Although different cutoff points are used to define virologic failure according to the national guidelines, one study done at Jimma, Southwest Ethiopia, reported a 5.3% virologic failure at 6 month of treatment (defined as viral load greater than1000 copies per milliliter of plasma)(15).A 21% of immunologic failure was reported from a study at Debremarkos hospital, Ethiopia; but in a more recent study in northern Ethiopia that used a CD4 cell count of 200 as cut off point among 100 adults and 100 children, there was no association observed between baseline CD4 count and immune virologic failure(42).Meanwhile, studies in Nigeria, Kenya and Cameroon have found 23.4%, 24.6% and 23.2% virologic failure respectively (defined as viral load greater than400 copies per mililiter of plasma).

Different studies have found that men were more likely to develop treatment failure as most men are diagnosed and present to health care .(6). But in this study the association of sex with treatment failure was not statistically significant. Our study did not show significant association between age, sex and educational status of the patients but a study done in Nigeria, poor immune-virologic outcomes were associated with younger age at ART initiation, male sex, lowhemoglobin leveland low educational status. Treatment failure is found to be significantly associated with young age&anemia in Kenya and Nigeria(3, 6, 38, 40).

Different studies in some settings in Africa have demonstrated good rates of survival in ART patients high CD4 count restoration, sustained viral suppression and good clinical outcomes(22). However, in other sub-Saharan African countries, studies point to an overall higher prevalence of immunological failure, at a range of 10%-32%, even when the follow-up duration was shorter compared to that of this study[(11). A large observational cohort study byDragsted et al have found that a gradual and significant decline in the rate of immunologicfailure over time. The trend over

time showed a 28% decrease with each additional yearssince the initial immunologic response (33). A cross sectional study fromIndia by Prabhakar et al found that duration of more than 3 years on ART was significantlyassociated with immunological failure(7).

Presence of opportunistic infection was not significantly associated with immune-virologic failure in this study but different previous studies in this area showed high significance of opportunistic infection with immune-virologic failure and this could be due to variation in the study participants' characteristics like environmental factors, immunity and nutritional status of the patients and the like.

Advanced disease stage was not significantly associated with immunovirologic failure in this study but various studies have shown that low baseline CD4 count and advance disease stage were significant predictors of immunovirologic failure explained by the frequent occurrence of opportunistic infections that leads to disease progression subsequently increased risk of failure (18, 36).

Despite the overall positive contributions of this study for clinical practice and program implementation, there werecertain limitations. Even if we tried to avoid bias; enrolling only 37% (878) patient cards out of 2378 adult patient cards from which 350 study population cards were selected may signify certain selection bias and this may be due to large number of cards not eligible for the study.Since this was a retrospective study based on existing medical records, the effect of possibly erroneous entries as well as incomplete entries of data should not be underestimated. For instance, these reasons have led us to drop the variabletreatment adherence. Also, since only one hospital was selected for the study; the overall\ prevalence of immune-virological failure couldn't be generalized for the whole region.(29).

7. Conclusion and Recommendation

7.1. Conclusion

Patients with baseline CD4 greater than or equal to 100 showed higher median survival time.The immune-virologic failure of the study participants was high. This may be due to late presentation and low baseline CD4 cell count; therefore health workers need more efforts for immediate initiation of the therapy prior to depletion of baseline CD4 count.

The median survival time of patients who stayed on their first line ART was higher and the overall failure cumulative probability is significant. The overall failure cumulative probability with different types of second line ART regimen is high with p-value of 0.027, this may be due to late presentation or drug toxicity, and thereforein maturing HIV treatment program in Ethiopia, prompt initiation and maintaining patients on first line treatment to identify those who are more likely to develop immune-virologic failure is highly crucial.

In conclusion, the present findings confirm the previous studies that the degree of CD4 depletion prior to ART initiation is the most consistent determinant of subsequent immune reconstitution and viral depletion. Shift in ART regimen also showed significant contribution for immune-virologic failure which also attributed to drug toxicity, therefore therapies better be individualized.

7.2. Recommendation

- Clinicians should encourage patients to start therapy and exert their effort to maintain patients on their initial regimen for as long aspossible duration with appropriate care and close follow-up. Among the different markers of immune-virologic failure the level of peak CD4 cell count achieved during ART should be monitoredclosely.
- To enhance the evidence in this regard, research on trends of CD4 counts and viral load has to be studied. Further research is required to understand the risk factors and pathogenesis and clinical management associated with the discordant treatment responses despite its relative frequency.

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9 Annex's: Data extraction tool

Part-I: Data on Socio-Demographic Factors								
S.No	Patient Reg.No	Age(in year)	Sex	Residence	Religion	Marital status	Educational status	Occupation
101								
102								
103								
104								
105								
106								
107								
108								
109								
110								

1. Male	1. Urban	1. Orthodox	1. Single	1. Illiterate	1. Employee
2. Female	2. Rural	2. Muslim	2. Married	2. Primary	2. Unemployed
		3. Protestant	3. Divorce	3. Secondary	
		4. Catholic	4. Widowed	4. Tertiary	
		5. Other			

Part-II: Data on Baseline Clinical Factors								
S.No	Last follow-up Date	CD4 cells count	viral load	Weight	Height	WHOstage	Hemoglobin e	ART regimen
201								
202								
203								
204								
205								
206								
207								
208								
209								
210								

CD4 cells count	iral load	Weight (kg)	ART regimen	
1. < 100	**1.** ≤ 400	1. <40	1. d4t(30)-3TC-NVP	5. TDF-3TC-EFV
2. ≥ 100	**2.** > 400	2. 40-60	2. d4t(30)-3TC-EFV	6. TDF-3TC-NVP
		3. >60	3. AZT-3TC-NVP	7. ABC-3TC- EFV
			4. AZT-3TC-EFV	8. ABC-3TC-NVP

Part-III: Data on Follow-up Clinical Factors								
S.No	Last follow-up Date	CD4 cells count	viral load	Weight(kg)	Height (cm)	WHO stage	Hemoglobine	ART regimen
301								
302								
303								
304								
305								
306								
307								
308								
309								
310								

CD4 cells count	viral load	Weight (kg)	ART regimen	
1. < 100	**1.**≤ 400	1. <40	1. d4t(30)-3TC-NVP	5. TDF-3TC-EFV
2. ≥ 100	**2.** > 400	2. 40-60	2. d4t(30)-3TC-EFV	6. TDF-3TC-NVP
		3. >60	3. AZT-3TC-NVP	7. ABC-3TC- EFV
			4. AZT-3TC-EFV	8. ABC-3TC-NVP

Part-IV: Data on other Clinical Factors					
S.No	Other opportunistic infections	Functional status	TB infection	Shift ART Regimen	Reasons for shift
401					
402					
403					
404					
405					
406					
407					
408					
409					
410					

Other opportunistic infections	Functional status	TB infection	Shift ART Regimen	Reasons for shift	
1. Yes	1. Work	1. Yes	1. Yes	1. Toxicity/side effect	5. New drug available
2. No	2. Ambulatory	2. No	2. No	2. Pregnancy	6. Drug out of stock
	3. Bedridden			3. Risk of pregnancy	7. Others specify
				4. Due to new Tb	

DECLARATION

I the under declared that this is my original work, has never been presented in this or any other university, and that all the resources and materials used for the research, have been fully acknowledged.

Name of the student: Tezera Kefelegn

Date_____ Signature: _____

Approval of the advisor (s)

Principal Adviser

Name	Signature	Date
1. Mr.Getachew Hailu (Asst.Prof. In Epidemiology)	_____	_____

Co-advisor:

2. Mr. Abebayehu Bitew (MPH, In Biostatistics)	_____	_____

Approval of Internal Examiner

3. Dr. Muluken Azage	_____	_____