COLLEGE OF MEDICINE AND HEALTH SCIENCES

PUBLIC HEALTH ACADAMIC AND SERVICE DIRECTORATE

ANTI-RETROVIRAL REGIMEN CHANGE AND ITS PREDICTORS AMONG PEOPLE LIVING WITH HIV AT HAWASSA UNIVERSITY COMPREHENSIVE SPECIALIZED HOSPITAL, SOUTHERN ETHIOPIA

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MAY, 2024

HAWASSA, ETHIOPIA

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THESIS SUBMITTED TO PUBLIC HEALTH ACADAMIC AND SERVICE DIRECTORATE, HAWASSA UNIVERSITY COLLEGE OF MEDICINE AND HEALTH SCIENCES FOR PARTIAL FULFILLMENT OF MPH IN FIELD EPIDEMIOLOGY

MAY, 2024

HAWASSA, ETHIOPIA

DECLARATION

I hereby declare that this thesis is my original work and has not been presented in any other university, and all sources of material used for this thesis have been duly acknowledged.

Name _____

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This thesis work has been submitted for examination with my approval.

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ACKNOWLEDGEMENT

First of all, I would like to acknowledge Hawassa University College of Medicine and Health Sciences, and the Ethiopian Field Epidemiology Training Program for providing this learning opportunity.

Next, special thanks go to my advisor, Dr. Endrias Markos (PhD), and Mr Derese Legese (MPH) for their unreserved supervisory support and guidance during data analysis and writing results to accomplish this task as part of my MPH requirement.

I would also like to extend my thanks to HUCSH, ART clinic workers, data collectors, and coordinators for their indispensable cooperation throughout my work.

ACRONYMS AND ABBREVIATIONS

3TC	Lamivudine
ABC	Abacavir
AHR	Adjusted hazard ratio
AIDS	Acquired Immunodeficiency syndrome
ART	Antiretroviral therapy
ARV	Antiretroviral
ATV/r	Atazanavir/ritonavir
AZT	Zidovudin
CD4	A cluster of differentiations between four
CHR	Crude hazard ratio
COPD	Chronic obstructive pulmonary diseases
CPT	Cotrimoxazole prophylaxis therapy
d4T	Stavudine
DTG	Dolutegravir
EFV	Efavirenz
HAART	Highly active Antiretroviral Therapy
HDL	High-density lipoprotein
HIV	Human immune deficiency virus
HUCSH	Hawassa University Comprehensive Specialized Hospital
INSTI	Integrase strand transfer inhibitor
NCD	Non-communicable diseases
NH	Isoniazid
NNRTI	Non-nucleotide reverse transcriptase inhibitors
NRTI	Nucleoside Reverse Transcriptase Inhibitors
NVP	Nevirapine
SPSS	Statistical packages for social sciences
TAF	Tenofovir alafenamide
TB	Tuberculosis
TDF	Tenofovir
WHO	Word Heath Organization

ABSTRACT

Background: Anti-retroviral regimen change is among the major challenges for the success of treatment among people living with human immunodeficiency virus (PLHIV), affecting its sustainability and outcome among ART patients. Yet, the evidence on the incidence and predictors of regimen change is unknown in this setting and the region.

Objective: The aim of this study was to determine the incidence of antiretroviral regimen change and its predictors among PLHIV at Hawassa University Comprehensive Specialized Hospital in 2024

Methods: An institutional-based retrospective cohort study was conducted among PLHIV who started ART from January 1, 2006, to December 31, 2023. Regimen change was defined as changing the ART regimen due to adverse events. Records were reviewed and standard data extraction form was used to collect data on a kobo tool kit. A Kaplan-Meier plot with a log-rank test at $p<0.05$ was used to estimate the median follow-up time and compare survival between the covariates. Bi-variable cox-regression analysis was done and variables with $p\leq0.25$ were entered into the multivariable cox-regression model. Predictors with p-values<0.05 reported with their adjusted hazard ratios and the 95% confidence intervals.

Results: A total of 3856 patients were followed for 39,350 person-years of observation with the median follow-up period of 11.2 years. The incidence rate of anti-retroviral regimen change was 12.1 (95% confidence interval (CI): 11.5–12.7) per 100 person-years. Female gender (Adjusted hazard ratio (AHR) = 2.9, 95%CI = 2.6–3.4), occurrence of TB (AHR = 4.6, 95%CI = 2.9–7.4), occurrence of side effects (AHR = 3.4, 95%CI = 2.9–3.8), baseline CD4 count below 100 cells/mm^3 (AHR = 1.3, 95%CI = 1.1–1.6) and availability of social support (AHR = 0.47, 95%CI = 0.38–0.58) were the predictors of regimen change among PLHIV receiving anti-retroviral therapy.

Conclusion and recommendation: The incidence of regimen change in this study was comparable to other findings. A number of variables predicted regimen change and female gender, occurrence of drug side effects, occurrence of TB, CD4 below 100cells/mm^3 and availability of social support were predictors of incidence of regimen change. Clinicians are recommended to early assess the adverse effects, TB, immunologic failure and strengthen social support to reduce the risk of regimen change among PLIHV.

Keywords: Regimen change, ART, HIV positive, HUCSH

1. INTRODUCTION

1.1 Background

HIV remains a significant global public health issue, and affected 39 million people globally (1). Advances in prevention and treatment have improved clinical management and outcomes of HIV infection. About 29.8 million people receiving antiretroviral therapy in 2022 (1–3). However, significant proportion of PLHIV changes their ART regimen due to various reasons.

The initial anti-retroviral treatment regimen for PLHIV generally consists of two nucleoside reverse transcriptase inhibitors, usually Tenofovir-alafenamide or Tenofovir disoproxil fumarate plus lamivudine or Emtricitabine (TDF/3TC(or FTC) or either Zidovudin plus lamivudine or Emtricitabine (AZT/3TC(or FTC) or Abacavir plus Lamivudine or Emtricitabine (ABC/3TC (or FTC), plus a drug from one of the three drug classes: an integrase inhibitor (INSTI), or non-nucleoside reverse transcriptase inhibitor (NNRTI), or a boosted protease inhibitor (4).

According to the WHO 2018 interim guideline, TDF+3TC+DTG was recommended as the preferred first-line for adult men, children at least 30kg and breast feeding women with access to effective contraception because of its known safety and efficacy (5,6), and TDF+3TC+EFV as an alternative regimen (3). Ethiopia has also adopted the TDF+3TC+DTG fixed-dose combination regimen as the preferred first-line treatment for adults, adolescents, pregnant and breastfeeding women, and adults with TB co-infection. The alternative first-line regimens are AZT+3TC+DTG, TDF+3TC+EFV, and AZT+3TC+EFV (7).

Ethiopia has increased accessibility to care and treatment, reducing AIDS deaths from 117.7/100,000 in 2001 to 11.73/100,000 in 2019 (8,9). Free ART services have started since 2005, with WHO recommending rapid initiation for those without contraindications (9). Anti-retroviral drugs have been successful in lowering mortality and morbidity rates among ART users; nevertheless, maintaining the regimens throughout the course of time is becoming difficult because of several factors that can lead to regimen changing (10).

Changing regimens may also help control viral load, boost immunity, and reduce the progression and consequences of disease (10), resulting in reduced mortality in HIV patients (11). Nevertheless, such changes may potentially result in new adverse effects, increase drug interactions, impede the availability of alternative medications, and increase drug expenses (12,13). Hence, the strategy to make such changes is determined by the patient's related reasons, the availability of treatment alternatives (14,15), and the durability and safety of the starting regimens (16).

1.2 Statement of the problem

Since 2010, HIV-related mortality has dropped by more than half in the WHO African region, and an estimated 20.9 million people are receiving antiretroviral therapy (17,18). Ethiopia has also made good progress in HIV treatment (8) through the utilization of highly active antiretroviral therapies at various levels of the health system (19). About more than half a million HIV patients received ART in 2023 (20).

Changing of ART regimens is a major challenge to the successful continuation of HIV treatment programs (21), which may result in new side effects and a rise in drug interactions (22). Conversely, it might be an appropriate option for managing toxicities and reducing the likelihood of treatment failure; however, it should be done by bearing the possibility of losing future therapeutic options (23). Besides, failure to alter the regimen when necessary has been challenging to keep patients on regimens (10).

In fact, the rate of frequent changes and interruption in the regimen increased now a day as a result of many factors (23,24). Some of these probable factors that could be attributed to regimen change might include socio-demographic, treatment failures (virologic, immunologic, clinical), drug toxicity, drug interactions due to co-admiration, occurrence of opportunistic infections and other patient-related factors (25–29).

As a developing country, treatment options and resources are limited in Ethiopia. This seeks a evidence-based recommendations through research to enhance effective use of the limited drug options available (8). Thus, determining the predictors of regimen changes at Hawassa Comprehensive Specialized Hospital will be imperative as it offers comprehensive healthcare services to a variety of demographic groups, which can impact the utilization and the choices of treatment regimens (9).

Moreover, previously conducted studies in southern Ethiopia focused on older or previous regimen types and did not consider changes associated with recently added regimens like Dolutegravir (12,30). Besides, there was limited evidence in the Sidama region regarding antiretroviral regimens and their predictors that has not been studied among people living with HIV patients in the past five years. Thus, this study was aimed at determining the incidence of anti-retroviral regimen changes and predictors among people living with HIV at Hawassa University Comprehensive Specialized Hospital.

1.3 Significance of the study

Knowledge of the magnitude and predictors of regimen changes is essential in developing countries like Ethiopia, where limited options are available. It will help clinicians ensure patient safety, monitor patient outcomes, improve adherence, and make cost-effective decisions guiding healthcare policy and resource allocation in clinical healthcare settings.

Antiretroviral regimen changes have several causes. However, it has not been studied and is not well understood in the Sidama region. Therefore, determining the possible causes of regimen change will help to provide evidence and guide policymakers in creating suitable strategies to extend regimen durations while protecting future treatment alternatives.

Moreover, the study will also contribute a lot to providing evidence-based recommendations for safe regimen selection and framing patient follow-up strategies for effective management of HIV infection that will enhance patient outcomes by improving their quality of life.

2. LITERATURE REVIEW

2.1 Overview

The use of antiretroviral therapy (ART) has revolutionized the treatment of HIV/AIDS, significantly improving the quality of life and survival rates of individuals living with the virus (31–33). However, the need for antiretroviral regimen change can arise due to various factors, such as treatment failure (27), drug toxicities (26), drug interactions, and patient preferences (28). This literature review aims to explore the overview of existing evidence and current understanding regarding antiretroviral regimen changes, with a focus on the factors influencing the decision, the outcomes of such changes, and strategies for successful regimen switching in clinical settings.

2.2 The incidence of anti-retroviral regimen change

A study from Latin America showed that 16% and 28% had estimated probabilities of changing within three months and one year of antiretroviral drug initiation (34), whereas similar study in Turkey indicated that treatment changes were made in 23.2% of studied cases (28). According to various retrospective studies conducted in different African corners, the incidences of regimen change rates revealed were 11.1 per 100 person-years in Kenya (35), 11.4 per 1000 person-years in Asmara, Eritrea (36), and 14.6/100 person-years in Cameroon (37).

Different retrospective follow-up studies conducted among HIV patients in Ethiopia revealed varying levels of incidences of anti-retroviral regimen changes that ranged from 10.1 per 100 person-years in Gondar (38), 11.36 per 100 person-years in Arbaminch (30) to 22.2 per 100 person-years of observation in Bahir Dar city (39). Multi-centered follow-up study in southwest Ethiopia showed that 41.2% of people on antiretroviral treatment changed their treatment for various reasons (26), 29.9% switched their ART regimen after three years of regimen commencement in Oromia region (40).

According to systematic review and meta-analysis in Ethiopia, one-third of HIV patients on ART changed their original regimen to other lines of regimens (29), 34.4% of patients changed once and 6.69% changed more than once in Jimma (26), about 15% of patients switched to second-line ART in Dire Dawa (41). According to a retrospective study in northwest Ethiopia, the median time to switch to second-line ART following 1st-line virologic failure is about 162 days (24). Some other retrospective studies in Wolaita Sodo town and

West wollega of Oromia region reported commonly used ART regimens as TDF + 3TC + EFV and d4T + 3TC+ NVP respectively (42,43). Similar study in Addis Ababa showed that majority of ATR patients changed their regimen from d4T + 3TC+ NVP to other forms of therapy (14). According to a study among regional hospitals in Eastern Ethiopia, two-thirds (66.4%) of the patients' initial regimen was changed to tenofovir disproxil fumarate–based alternatives with average of 22(±11.28) changes per year (23).

2.3 Predictors of anti-retroviral regimen changes

Many factors could be attributed to regimen change might include socio-demographic, treatment failure (virologic, immunologic, clinical failure), drug toxicity, and other patient-related factors (25). According to recommendations of the international anti-retroviral society, dosing frequency, pill burden, and comorbidities should be taken into consideration during regimen change (44).

2.3.1 Socio-demographic predictors

According to a study in the Tigray region, the male gender showed 1.7 times higher discordance to immunological and virological response to anti-retroviral regimens (45). A retrospective study among ART patients indicated that being male also has been associated with ART failure which mandates patients to change their regimens (46). Contrarily, a retrospective cohort study among adult HIV positive patients in 2020 showed that females were at increased risk of experiencing adverse drug reactions (ADRs) compared to males and predictor of regimen change in Arba Minch town public hospitals (47).

Another retrospective study conducted in Tigray region showed that HIV patients with no formal education had greater risk of adverse drug reactions urging to regimen modification (48). In contrast to this, multi-centered follow-up study in Amhara region indicated that the rate of regimen change was decreased for patients with formal education (49). Regarding residence, a retrospective cross-sectional study among HIV infected patients showed that urban residents had a lower risk of regimen change compared to their counterparts (50).

Evidences found that patients who perceived lower levels of social support were at higher risk for seeking ART care and medication as reported in a study from USA (51). In Contrast, having social support from family, peers and relatives facilitates staying on regimens in Cameroon (52). A retrospective study from Northeast Ethiopia showed that HIV patients who had better social support had increased likelihood of staying on their initial regimens (53).

2.3.2 Clinical predictors

According to a multi-centered retrospective follow-up study, the regimen change was decreased for clinical stage-III patients, and WHO clinical stage-IV in Amhara region (38). In contrast to this, advanced WHO clinical stages had an increased risk of regimen changes among studied patients due to treatment failures according to systematic reviews in Ethiopia (54). However, adverse drug reaction reported to be high among advanced WHO clinical stages of ART patients in southern Ethiopia (47).

According to follow up study in northwest Ethiopia, the rate of regimen change was increased for patients who were switched to second-line treatment due to treatment failure (27). Similarly, patients on TDF+3TC+LPV/r and AZT+3TC+LPV/r second-line regimens were at a higher likelihood of changing their regimens as a result of treatment failure than those on Abacavir + Didanosine + Lopinavir/ritonavir regimens (55).

2.3.3 Drug-related predictors

In some patients, ART-associated adverse events can range from acute and potentially life-threatening events that require the immediate discontinuation and re-initiation of an alternative regimen (21). According to nested case-control studies in Brazil, adverse events drove 25.7% of regimen changes that occurred in the first year of ART (6). A prospective study in India came up with a final statement on the need for timely switching of ART to prevent metabolic complications in patients taking long-term protease inhibitors (56).

According to a prospective cohort study done in Johannesburg, South Africa, despite its efficacy, patients receiving Dolutegravir containing regimen were found to gain more weight and were at higher risk of hypertension after switching from efavirenz to Dolutegravir than those remaining on efavirenz (57). A study conducted to assess lipid profiles and glucose levels among HIV patients revealed that, raised HDL-c concentration was observed in the Nevirapine group when compared with the Efavirenz group implying that reduced cardiovascular disease risk among the Nevirapine group (58). However, the hazard for regimen change was lowest among Efavirenz-based regimens, except in pregnancy-related cases in southern Ethiopia (12).

According to a systematic review and meta-analysis findings in Ethiopia, toxicity of the drugs, TB co-morbidity, positive baseline TB symptoms, treatment failure, and pregnancy were the main causes for the change of the first-line regimen among HIV patients on antiretroviral therapy (29). Some other retrospective literature provided similar supportive

evidence with specific types of toxicities observed were peripheral neuropathy (36.52%), rash (17.83%), anemia (17.39%), (12,50) as well as hepatotoxicity to the extent that resulted in regimen switch and discontinuation (59). A Few early (2014) conducted prospective study conducted in Hawassa among ART patients indicated that the shift from Stavudine to Zidovudin could minimize the risk of hepatotoxicity, even with periodic monitoring (60).

2.3.4 Virological and immunological predictors

Different comparative and follow up studies in Ethiopia public hospitals at Jimma, Arba Minch and Gondar showed that a baseline CD4 cell count below 100 cells/mm^3 and CD4 count below 200 cells/µl (30,46,47) and drug side effects among HAART naïve patients (61), were the predictors prompting for regimen change. Another retrospective follow-up study conducted in Northwest Ethiopia showed that the risk of switching is higher among HIV-infected adults with viral RNA of 60,000 copies/mL or more at treatment failure (24).

2.3.5 Presence of comorbidity

A follow-up study conducted in Cape town, South Africa found that 32% of patients with HIV had to change their first antiretroviral therapy (ART) regimen due to serious cutaneous adverse effects linked with tuberculosis (62). A systematic review and meta-analysis conducted in Ethiopia also reported that 12% of antiretroviral regimen adjustments in various clinical settings were due to co-morbidity with tuberculosis (29). A study conducted in Tigray Ayder Hospital indicated that the presence of tuberculosis and hepatitis B co-infections was associated with the discordance of immunological and virological response to anti-retroviral regimens (45). A similar follow-up study conducted in Eastern Ethiopia, found that patients who had been taking tuberculosis treatment along with antiretroviral therapy were more likely to get their regimen changed compared to those who were not infected with tuberculosis (23).

A retrospective follow-up research conducted in the Amhara region revealed that patients who received cotrimoxazole prophylactic treatment (CPT) had a higher rate of regimen change compared to other patients (49). A further cross-sectional study conducted in Gondar, Northern Ethiopia, found that the likelihood of changing treatment regimens among HIV patients was ten times greater when they also had other opportunistic illnesses (63).

2.4 Conceptual framework

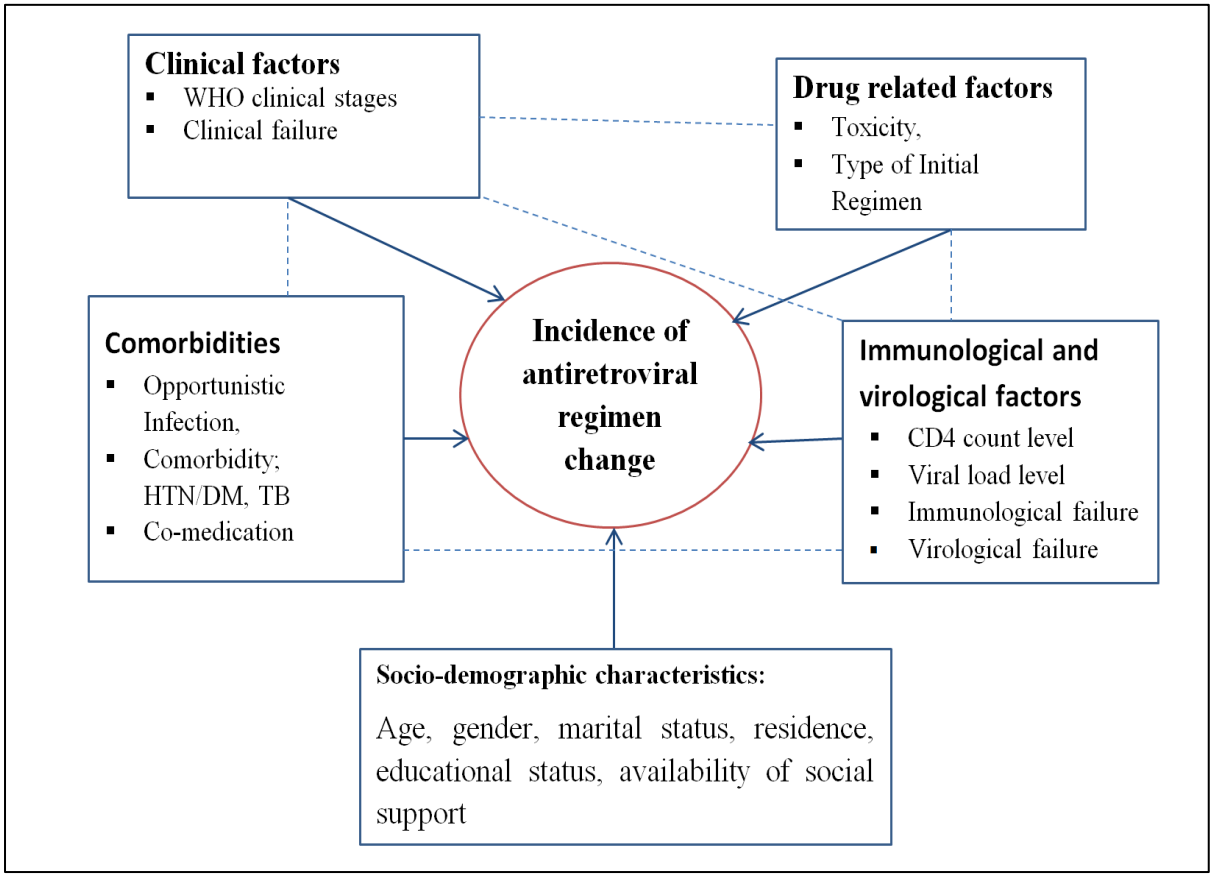

Figure 1 Relationship between regimen change and predictors among PLHIV in HUCSH, 2024(Adapted (12,38,45,47,49,54,63)

3. OBJECTIVES OF THE STUDY

3.1. General Objective

- To assess the incidence of anti-retroviral regimen change and its predictors among people living with HIV at Hawassa University Comprehensive Specialized Hospital in 2024

3.2. Specific objectives

- To determine the incidence of anti-retroviral regimen change among people living with HIV at Hawassa University Comprehensive Specialized Hospital in 2024
- To assess the predictors of anti-retroviral regimen change among people living with HIV at Hawassa University Comprehensive Specialized Hospital in 2024

4. METHODS AND MATERIALS

4.1 Study setting

A retrospective cohort study was done at Hawassa University Comprehensive Specialized Hospital (HUCSH) in Hawassa City, the capital of the Sidama regional state. Hawassa is located at 273 kilometers to the South of Addis Ababa. It's bounded by Lake Hawassa in the West, Oromia in the North, Wondogenet district in the east, and Hawela district in the South.

As of July 2023, according to Ethiopian central statistics agency forecasts, the population of Hawassa is predicted to be 441,536, out of whom 218,317 (49.4%) are men and 223,219 (50.6%) are females. The population rise in Hawassa has been the result of internal migration to seek better urban life and jobs and the expansion of educational and other amenities (64).

Although the HUCSH was built to serve 3.5–5 million people, it presently provides services to over 20 million people from the whole Sidama, Oromia, and the southern parts of the nation. It is a tertiary hospital with more than 20 departments that provide both clinical and academic services. According to the ART clinic report, there are more than 7,900 records of people living with HIV since the beginning of ART service in the Hospital (65).

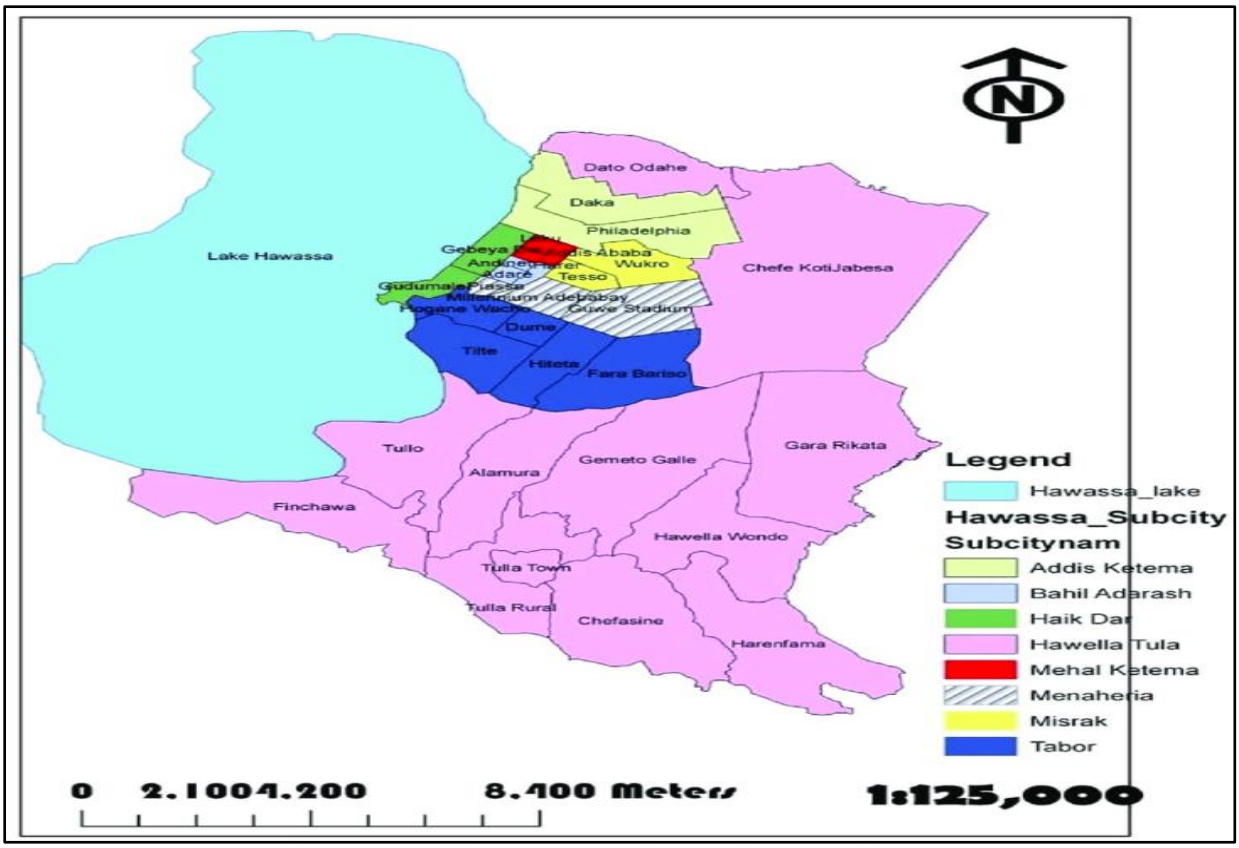

Figure 2 Map of Hawassa city (Source: Development data collection and dissemination process, finance and economic development department, Hawassa city administration)

4.2 Study design and period

An institutional-based retrospective cohort study was conducted from March to April, 2024.

4.3 Populations

4.3.1 Source population

The source populations were all people living with HIV who were on anti-retroviral therapy at Hawassa University's comprehensive specialized hospital ART clinic from January 1, 2006, to December 31, 2023.

4.3.2 Study population

All selected HIV-infected patients who started ART at Hawassa University comprehensive specialized hospital from January 1, 2006 to December 31, 2023 were included in the study.

4.4 Eligibility criteria

4.4.1 Inclusion criteria

All people living with HIV (PLHIV) who started antiretroviral therapy at Hawassa University comprehensive specialized hospital from January 1, 2006 to December 31, 2023

4.4.2 Exclusion criteria

Patients with incomplete chart information (If starting regimen, changed regimen, reasons for change and date of change is unknown), transferred-in from other health facilities and period beyond study period were excluded.

4.5 Sample size determination

The sample size was calculated by using double population proportion formula on Epi-Info 7.2 StatCalc program by the assumption of 95 % level of confidence, power of 80%, adjusted hazard ratio from various literatures and other parameters as shown in table 1 below

Table 1 Sample size determination by different predictors, 2024

Statistical significant predictors	AHR	Power	Sample size	References
Baseline CD4 level < 200 cells/mm^3	2.18	80	378	(30)
History of regimen change	1.38	80	1316*	(41)
Presence of opportunistic infections	1.96	80	326	(47)
Presence of baseline TB symptom	1.63	80	404	(50)

Based on the above calculation using Epi info 7.2 for cohort study, different statically significant predictors of regimen change were checked to determine sample size. Hence, a large sample size of 1316 was obtained from a history of regimen change with an adjusted hazard ratio of 1.38, percent of outcome in exposed (P_1) =16%, percent of outcome in unexposed (P_2) =23.9%, confidence level of 95%, and 80% power. By considering 10% lost to follow-up and incomplete records, the final sample was 1448. However, a total of 3,856 complete data which was jointly collected with Hawassa University data planning and management were included as final sample size in this study.

4.5 Sampling technique and procedures

Hawassa University Comprehensive Specialized Hospital was purposely selected due to its accessibility to conduct the study and providing comprehensive care for a large number of PLHIV in South Ethiopia. From the beginning of ART services in the hospital, a total of 7,967 patient records were enumerated. Out of these, 2,902 were excluded due to dismissed folders and time beyond the study period. A total of 5,065 records were screened as eligible for data collection. One thousand fifty (1,050) PLHIV were excluded due to missed elements, and due to transfer-in from other health facilities with one follow-up. After data collection, we exported a total of 4,015 filled-in data elements from the kobo tool. The data were then cleaned using SPSS 26, and 159 records were excluded due to missing main variables (starting regimen unknown, changed regimen unknown, ART started and changed date unknown, reasons for change unknown and being in pre-ART etc.), and some cases were excluded due to incomplete information as they were transferred from other health facilities. At the end, we left with a completed final sample size of 3,856 patient records that were taken as a total study sample. Figure 1 shows a schematic presentation of the sampling procedure.

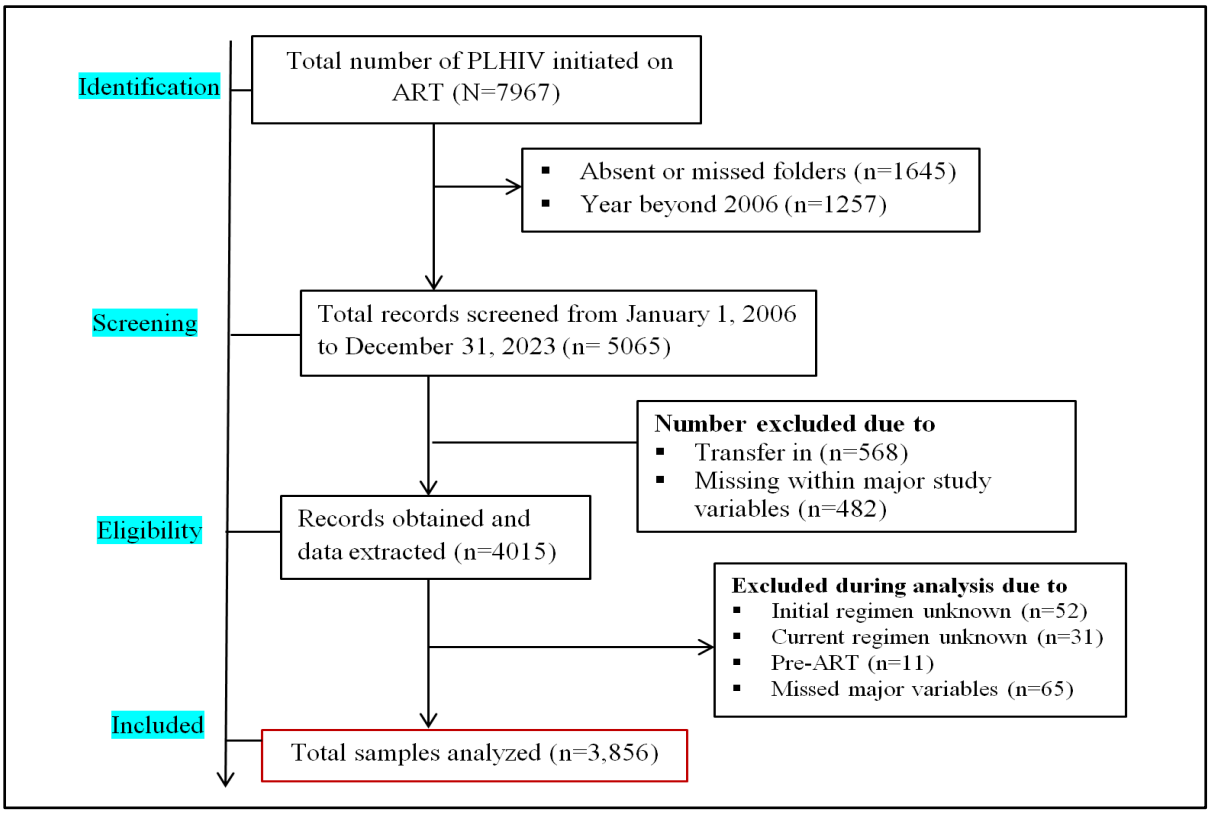

Figure 3 Schematic presentation of sampling techniques of PLHIV at Hawassa University Comprehensive Specialized Hospital, 2024

4.6 Study Variables

4.6.1 Dependent variable

The outcome variable was time-to-anti-retroviral regimen change. Whereas, event was regimen change coded “1” for yes (failure) and “0” for no (censored).

4.6.2 Independent variables

Socio-demographic characteristics such as age, sex of the patient, marital status, occupation, residence, educational status, availability of social support;

Clinical factors like WHO clinical stages;

Immunological and virological variables like baseline CD4 count, baseline viral load, immunologic failure, and virologic failure;

Treatment-related variables like types of an initial regimens, drug toxicity, and treatment failure;

The presence of comorbidities including TB, diabetes, hypertension, co-medication of cotrimoxazole preventive therapy (CPT), and TB treatment were other independent variables.

4.7 Data collection tool and procedures

A standard data abstraction form was developed based on various sources and the current ART patient chart, which included socio-demographic, immunologic, virologic, and clinical, as well as treatment-related factors, to extract from the records of the patients. Then, the tool was developed in the kobo tool and filled with the kobo mobile app v2023.2.4 by eight health professionals working at the ART service point who have the experience in ART services and documentation. The charts were retrieved using the patient registration numbers. Then, data elements of selected PLHIV charts were filled out in the kobo mobile app and sent via a web-based system. Then, data were downloaded following standard procedures in Excel and SPSS formats to run on SPSS for cleaning and analysis.

4.8 Data quality control

Training was given to data collectors on kobo mobile app using, record selection, and data extraction techniques. Regular monitoring and supervision were done during data collection by the principal investigator and supervisor. Regular data completeness was checked regularly by supervisor and principal investigator on the server daily basis to solve problems encountered. Feedbacks were given to the data collectors.

4.9 Data analysis procedures

The data were exported from the kobo tool to the SPSS 26 version for cleaning and further analysis procedures. The variables were labeled and grouped depending on the need for analysis and interpretation. The event was a regimen change, and it was coded as '1' of failure and those censored were coded as '0' which included died, transferred out, lost to follow-up during the follow-up period and those currently in the follow-up. The event was the first ART regimen change, described as either substitution of at least one drug from the original regimen or complete switch of the entire regimen. Censored cases were patients with the first date of loss to follow up, transferred out, death before the end of the follow-up period, and completing the follow-up period without developing the event.

An exploratory analysis was conducted to check the distribution of numerical variables and missing values. Person-time of follow-up was calculated by subtracting the date of ART regimen initiation from the date of the event that occurred or censored. Incidence rate was calculated by dividing the number of events by their person-years contributed during the follow-up periods. The 95% confidence interval of incidence rate was calculated by open Epi. Then, descriptive statistics such frequency, percentages, mean, median and standard deviations were calculated to describe the characteristics of the cohort depending on their distribution.

Survival analysis was carried out to calculate the incidence of regimen change. Kaplan-Meier was used to estimate the median follow-up time with the log-rank test to check the significant difference observed across the levels of categorical variables (groups). Bi-variable and multi-variable cox-regression analysis was done to identify the predictors of the regimen change. Variables with values $p \leq 0.25$ during bi-variable analysis were entered into multivariable cox regression model. The variables with p-values<0.05 were considered statistically significant predictors of regimen change. The strength of the association was measured and presented as an adjusted hazard ratio (AHR) and the 95% confidence intervals (CIs).

4.10 Operational definition

Regimen change: changing the entire first ART regimen or substituting at least one drug from the ART regimen due to drug toxicity, treatment failure (clinical, immunological or virological) and, co-infections and other related reasons.

Side effects: defined as the occurrence of drug toxicity either hepatic, central nervous, hematologic or renal and lipodystrophy, metabolic disturbances, or any other related to antiretroviral therapy reported during follow-up (8,38).

Clinical failure: new or recurrent clinical event indicating severe immunodeficiency (WHO clinical stage IV condition and certain WHO clinical stage III conditions or occurrence of pulmonary TB after six months of effective treatment (8).

Immunologic failure: CD4 count at or below 250 cells/mm3 following clinical failure or persistent CD4 levels <100 cells/mm3 (8).

Virologic failure: viral load above 1000 copies/ml based on viral load measurements in three months following the first viral load test (8).

4.11 Ethical consideration

Written ethical clearance was obtained from institutional review board (IRB/136/16) of the Hawassa University College of Medicine and Health Sciences. Then, Public health academic and service directorate provided us a written support letter (SPH/219/16) to HUCSH to facilitate the data collection process based on standard rules and procedures. Confidentiality of the data before and after data collection was strictly followed. (Annex-III)

5. RESULTS

5.1 Socio-demographic characteristics of participants

Out of the 4015 patient records, 3856(96%) complete records were analyzed and the rest had missing elements and thus excluded. The mean (±standard deviation (SD) age of participants at the initiation of ART was 34±10 years, and 1576(40.9%) of them were in the age group between 25 and 34 years. The majority of participants, 2042(53.0%), were married, with 595 (18.4%) being divorced. Female participants accounted for 2324(60.3%) of the total. In terms of education level, 1564(40.6%) of the participants completed secondary education.

Over two-third, 2617(67.9%) of the participants had history of HIV infection in their family, 2307(59.8%) disclosed their HIV status to their family members or other relatives, whereas 821(21.3%) had social support during their ART follow-up. (Table 2)

Table 2 Socio-demographic characteristics of PLHIV on ART at Hawassa University comprehensive Specialized Hospital, 2024

Characteristics	**Categories**	**Frequency**	**%**
Total participants		3856	100
Sex	Female	2324	60.3
	Male	1532	39.7
Age at initiation (years)	<15	90	2.3
	15-24	380	9.9
	25-34	1576	40.9
	35-44	1236	32.1
	≥45	574	14.9
Education at initiation	No Formal Education	400	10.4
	Primary level	1440	37.3
	Secondary level	1564	40.6
	College and above	452	11.7
Marital status at initiation	Married	2042	53.0
	Divorced	633	16.4
	Widowed	594	15.4
	Single	587	15.2
Occupation at initiation	Unemployed	2126	55.2
	Employed	1722	44.8
Disclosure status	Yes	2307	59.8
	No	1549	40.2
Social support available	Yes	821	21.3
	No	3035	78.7

The mean (±SD) weight of the participants at the start of ART and at the end of the follow-up period was 54.6±12.9 kg and 62.6±14.2 kg, respectively. The majority of them, 2117(54.9%), had a corresponding normal body mass index of 18.5-24.9 kg/m^2 at the initiation of treatment. The majority of 1186(30.8%) had a baseline CD4 level of 200–349 cells/mm^3, with a corresponding median baseline CD4 level of 213 cells/mm^3 (IQR = 107–322). The mean (±SD) hemoglobin level at the initiation of ART and at the end of follow-up was 12.6±1.9 g/dl and 14.2±1.6 g/dl, respectively. About 1703(44.2%) were in WHO stage III at the start of

treatment, whereas the vast majority, 3296(85.5%), were in WHO stage I at the end of follow-up. (Table 3)

Table 3 Physical, clinical and immunological characteristics of PLHIV at Hawassa University comprehensive Specialized Hospital, 2024

Characteristics	**Categories**	**Frequency**	**%**
Baseline WHO stages	Stage I	877	22.7
	Stage II	836	21.7
	Stage III	1703	44.2
	Stage IV	440	11.4
Baseline hemoglobin level (Mean=12.6±1.9g/dl)	<7g/dl	48	1.2
	7-9.9g/dl	144	3.7
	10-12.9g/dl	1933	50.2
	≥13g/dl	1729	44.9
Baseline CD4 (cells/mm^3) (Median=213, IQR=107-322cells/mm^3)	<100	878	22.8
	100-199	942	24.4
	200-349	1186	30.8
	≥350	849	22.0
Baseline Weight (Mean=54.6±12.9kg)	<54.5kg	1975	51.2
	≥54.5kg	1881	48.8
Body mass index at initiation (kg/m^2) (Mean=20.5±4.4)	<18.5	1196	31.0
	18.5-24.9	2117	54.9
	25-29.9	438	11.4
	≥30	105	2.7

About 1844(47.8%) and 129(3.3%) of study participants received other medications and NCD medication over ART, respectively. More than three-fourths (2993, or 77.6%) of participants received cotrimoxazole prophylactic therapy (CPT), whereas, small proportion 103(2.7%) of them received fluconazole prophylactic therapy. Out of 3,782 participants screened for TB, 1095(28.4%, 95%CI = 27–29.8) tested positive and put on anti TB treatment. Nearly 246(6.2%) developed COPD before and after starting anti-retroviral treatment. About 56(1.5%) and 70(1.8%) developed hypertension and diabetes mellitus before the initiation of anti-retroviral therapies. About 1723(44.7%) of the study participants

were diagnosed with opportunistic infections other than tuberculosis before the initiation of ART. (Table 4)

Table 4 Status of comorbidities and opportunistic infections among PLHIV at Hawassa University comprehensive Specialized Hospital, 2024

Characteristics	Categories	Frequency	%
TB status test	Positive	1095	28.4
	Negative	2687	69.7
	Not Done	74	1.9
TB treatment (n=1095)	Yes	1095	100
Opportunistic infections other than TB	Yes	1723	44.7
	No	2133	55.3
Diabetes mellitus at start	Yes	70	1.8
	No	3786	98.2
Hypertension at start	Yes	56	1.5
	No	3800	98.5
Chronic obstructive pulmonary disease (COPD) at start	Yes	245	6.4
	No	3611	93.6

5.2 Incidence of regimen change among people living HIV

The follow-up period ranged from 0.08–17 years, with a median follow-up period of 11.16 years (IQR: 6–14.75). The total sum of overall follow-up time was 39,350 person-years of observation. Regarding participant status, 136(3.5%, 8.25 per 100 person years) died, 428(11.1%, 7.73 per 100 person years) lost to follow-up, 768(19.9%, 7.78 per 100 person years) transferred out, and 1327(34.4%) stayed on their beginning regimen. Out of the antiretroviral regimens initially prescribed, 1735(45%) consisted of a combination of Tenofovir, Lamivudine, and Efavirenz (TDF+3TC+EFV), whereas 631(16.4%) were comprised of Zidovudin, Lamivudine, and Nevirapine (AZT+3TC+NVP)-based regimens. Among the backbones of regimens, 2175 (56.4%) were put on tenofovir (TDF)-based regimens. Regarding current regimen, Dolutegravir (DTG)-based regimens accounted 2488(64.5%) with its incidence rate of 5.27 per 100 person years of observation. (Table 5)

Table 5 Regimen change status and treatment related factors among PLHIV at Hawassa University comprehensive Specialized Hospital, 2024

Characteristics	Categories	Frequency	%
Regimen changed	Yes	1436	37.2
	No	2420	62.8
Regimen at initiation	TDF+3TC+EFV	1735	45.0
	AZT+3TC+NVP	631	16.4
	AZT+3TC+EFV	505	13.1
	d4T+3TC+NVP	310	8.0
	TDF+3TC+DTG	255	6.6
	d4T+3TC+EFV	215	5.6
	Others*	205	5.3
Most recent regimens (anchors)	Dolutegravir-based	2488	64.5
	Efavirenz-based	854	22.1
	Nevirapine-based	319	8.3
	Lopinavir/Atazanavir-based	195	5.1

*Others [TDF+3TC+NVP], [TDF+3TC+ATV/r], [AZT+3TC+LPV/r], [ABC+3TC+LPV/r], [AZT+3TC+EFV]

Over the follow-up period, a total of 2549(66.1%, 95%CI: 64.6-67.6) anti-retroviral regimens were changed, out of which 1113(43.6%, 13.43/100 person years) were due new drug availability. Hence, a total of 1436[37.2%, 95%CI= 35.7–38.8] patients changed their regimens for other reasons than availability of new drugs. Out of these, 1329(34.5%) changed their regimen at least once, and the rest changed more than once. (Table 6)

The overall incidence rate of ART regimen change was 12.1(95% CI: 11.47–12.72) per 100 person-years of observation. Among the common reasons for regimen change, the occurrence of tuberculosis and adverse drug effects were the most common, with corresponding rates of 11.49 and 12.22 per 100 person years, respectively (Figure 5).

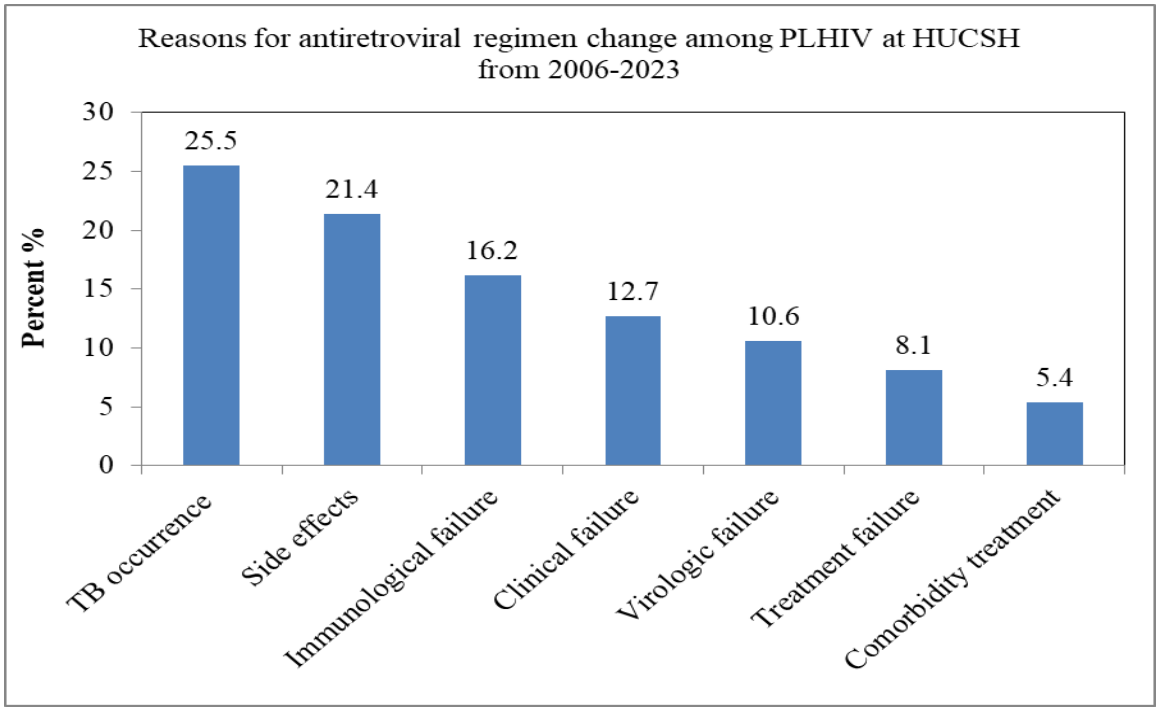

Figure 4 Common reasons for antiretroviral regimen change among PLHIV in Hawassa University comprehensive Specialized Hospital, 2024

Regarding the change of regimen in different follow-up durations, the majority of patients 1070(27.8%) changed their regimens after five years of follow-up. Regarding starting regimens, Stavudine (d4T)-based regimens had higher incidence rates (7.36 per 100 person years) of regimen changes compared to Zidovudin (AZT) and Tenofovir (TDF)-based regimens. (Table 6)

Table 6 The incidence of anti-retroviral regimen change among PLHIV by study variables at HUCSH, 2024

Variables	Character	Survival status		IR/100 PYs	95%CI	
		Censored	Events		Lower	Upper
Sex	Males	1197	335	1.65	1.48	1.83
	Females	1223	1101	5.78	5.44	6.13
Side effects occurred	Yes	5	321	8.83	10.80	13.40
	No	2415	1115	5.48	2.86	3.22
Starting regimen backbone	Tenofovir(TDF)	1567	608	2.75	2.55	2.97
	Stavudine(d4T)	691	373	7.36	6.64	8.13
	Zidovudin(AZT)	152	454	3.77	3.43	4.13
Opportunistic infections	Yes	968	755	4.25	3.95	4.56
	No	1452	681	3.15	2.92	3.39
WHO clinical stages	Stage I	684	193	2.24	1.94	2.57
	Stage II	582	254	3.04	2.68	3.43
	Stage III	917	786	4.44	4.14	4.76
	Stage IV	237	203	4.31	3.75	4.94
TB status test	Positive	104	991	10.29	9.66	10.94
	Negative	2260	427	1.47	1.34	1.62
	Not done	56	18	2.47	1.51	3.82
COPD at start	Yes	66	179	7.97	6.88	9.21
	No	2354	1257	3.39	3.20	3.58

5.3 Survival probability of regimens among ART patients

Cumulative median survival probability of surviving on the regimen at the end of one year was 97%; at the end of five year was 88%; at the end of ten year was 70%; and at the end of follow-up was 42%. The midterm survival probability of females on regimen (49%) was smaller compared to the midterm survival probability of the males (73%), indicating that there was a survival difference across genders.

The overall Kaplan–Meir survival function estimate showed that most of the ART regimen changes occurred and overall regimen survival declined as time gets longer (Figure 5).

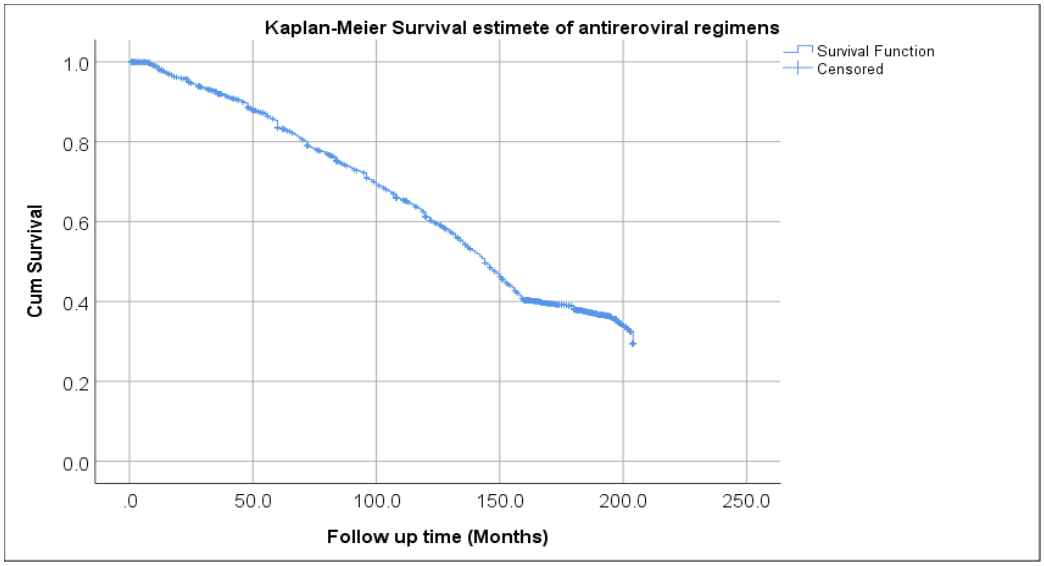

Figure 5 Kaplan-Meir estimate of survival time on antiretroviral regimen among people living with HIV at Hawassa University comprehensive Specialized Hospital, 2024

5.4 Comparison of survival probability among covariates

The Kaplan-Meier curve, together with the log-rank (Mantel-Cox) test, was used to check for the existence of any significant differences in survival probability between different explanatory variables for the incidence of regimen change. The mean survival time on the regimens for the male patients (183.3 months, 95% CI = 181.0–185.6) was higher compared to the female patients (106.3 months, 95% CI = 104.0–108.5), with a significant difference between groups (log-rank x2 = 1810.7, p-value<0.001). (Figure 6)

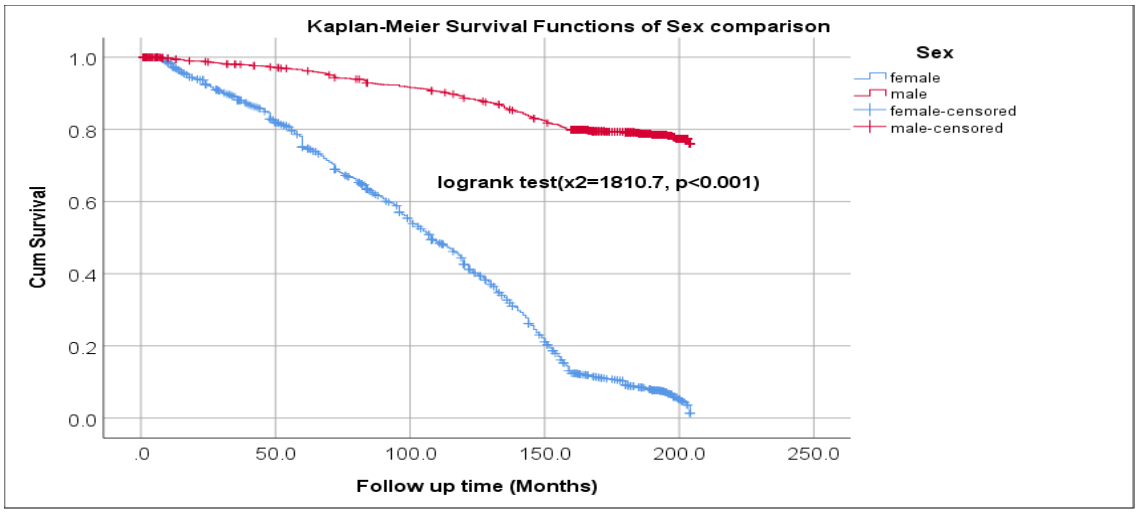

Figure 6 Comparison of survival time by sex on antiretroviral regimen among PLHIV at Hawassa University comprehensive Specialized Hospital, 2024

Similarly, patients who developed tuberculosis during follow-up had a shorter mean survival time of 107.9 months (95% CI = 104.7–111.2) on the regimen compared to tuberculosis-negative patients, 182.6 months (95% CI = 180.7–184.6), with a significant difference between the two groups (log-rank x2 = 1826.1, p-value<0.001). (Figure 7)

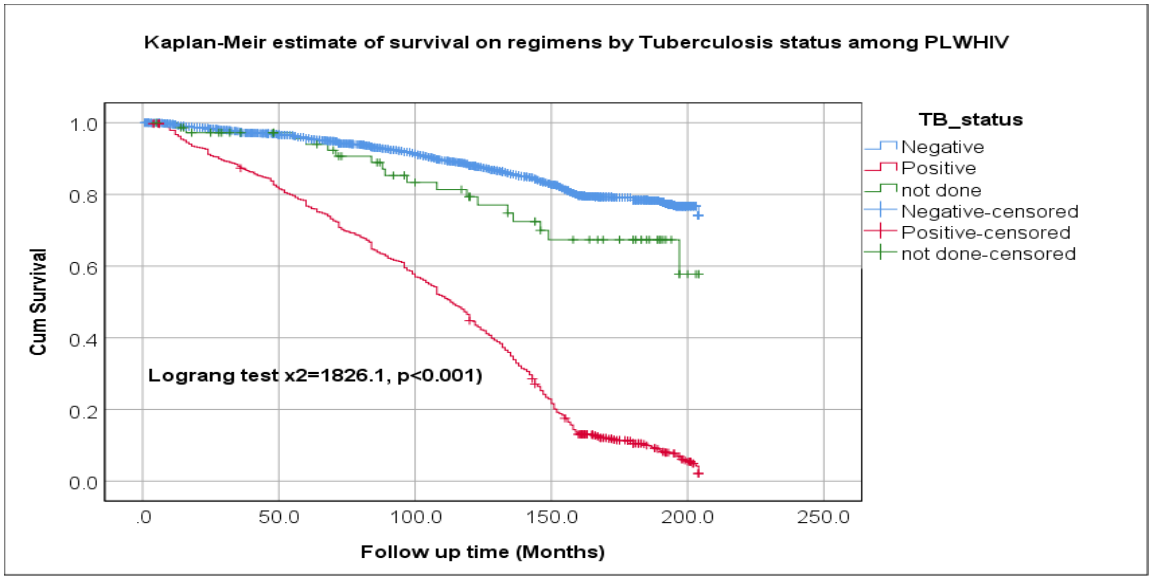

Figure 7 Comparison of survival time by TB on antiretroviral regimen among people living with HIV at Hawassa University comprehensive Specialized Hospital, 2024

Estimated mean survival time on regimens by availability of social support indicated that; PLHIV who did not have social support had a shorter mean survival time on the regimen (146.9 months, 95% CI = 144.6–149.3) compared to PLHIV who had social support from families, relatives or peers (187.7 months, 95% CI = 184.8–190.6), during the follow-up with a significant difference (log-rank, x^2 = 321.2, p<0.001) between the two groups. (Figures 8)

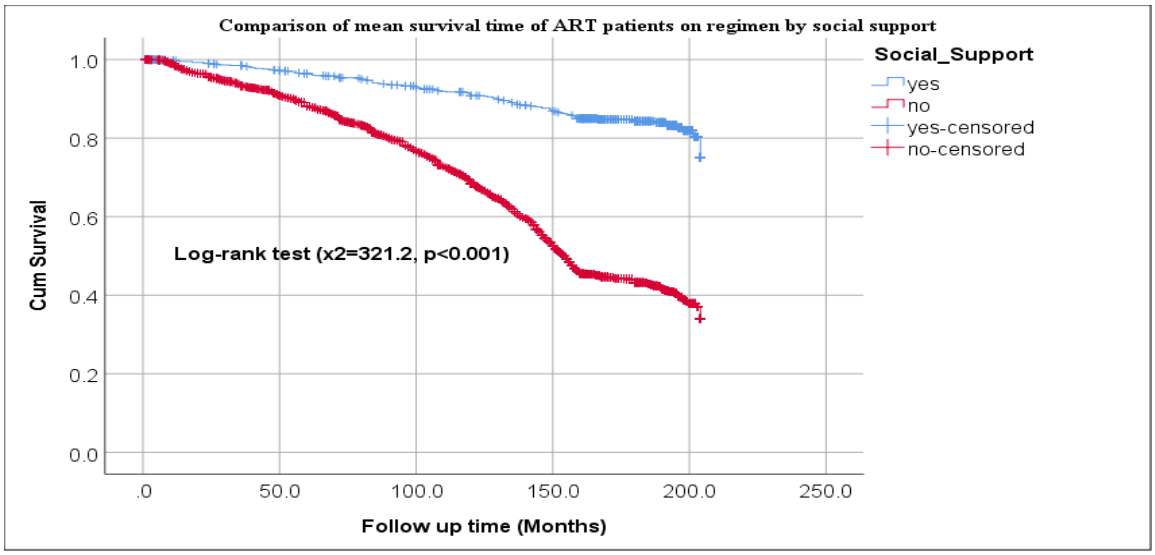

Figure 8 Comparison of mean survival time by social support among PLHIV at Hawassa University comprehensive Specialized Hospital, 2024

5.5 Predictors of anti-retroviral regimen change among people living with HIV

Bi-variable cox-regression analysis was done and sex, the occurrence of side effects, baseline WHO stages, baseline CD4 level, the initial regimen backbone, the occurrence of TB, the presence of social support, disclosure status, opportunistic infections, and NCD medications were predictors with the incidence rate of regimen change. Variables with p≤0.25 were selected for the multi-variable cox-regression model. (Table 7)

Table 7 Bi variable analysis of predictors of antiretroviral regimen change among PLHIV at Hawassa University comprehensive Specialized Hospital, 2024

Characteristics	Category	Survival status		CHR(95%CI)	P-value*
		Censored	Events		
TB status test	Positive	104	991	4.7(2.9-7.4)	0.001
	Negative	2260	427	0.56(0.35-0.9)	0.016
	Not done	56	18	1	Ref
Baseline WHO stages	Stage I	684	193	1	Ref
	Stage II	582	254	1.4(1.2-1.6)	0.001
	Stage III	917	786	2.0(1.7-2.3)	0.001
	Stage IV	237	203	1.8(1.5-2.3)	0.001
Side effect occurred	Yes	5	321	4.7(4.1-5.3)	0.001
	No	2415	1115	1	Ref
Sex	Male	1197	335	1	Ref
	Female	1223	1101	4.9(4.3-5.6)	<0.001
Social support availability	Yes	698	123	0.21(0.18-0.26)	<0.001
	No	1722	1313	1	Ref
NCD medication taken	Yes	30	99	2.1(1.7-2.6)	<0.001
	No	2390	1337	1	Ref
Baseline CD4 (cells/mm^3)	<100	482	397	1.4(1.3-1.7)	<0.001
	100-199	541	401	1.3(1.2-1.6)	<0.001
	200-349	805	381	0.98(0.8-1.2)	0.81
	≥350	592	257	1	Ref
Backbone of starting regimens	TDF based	1567	608	3.4(0.4-24)	0.22
	AZT based	691	454	4.9(0.6-35)	0.11
	d4T based	152	373	10.0(1.4-71)	0.02
	ABC based	10	1	1	Ref.
Opportunistic infections	Yes	968	755	0.73(0.65-0.8)	<0.001
	No	1452	681	1	Ref.

*Significant at p≤0.25

In multivariable cox-regression analysis, female sex, the occurrence of side effects, occurrence of tuberculosis, baseline CD4 level, and social support status remained statistically significant predictors of the incidence rate of regimen change. Accordingly, female patients had a 2.9 times higher risk of regimen change (AHR = 2.9, 95% CI: 2.6-3.4) when compared with male patients. Regarding co-infections, HIV patients on ART who developed tuberculosis had a 4.6-fold increased risk of regimen change when compared to those who did not have tuberculosis (AHR = 4.6, 95% CI: 2.9–7.3). On the other hand, patients who had developed ART drug side effects on their first regimen were 3.4 times more likely to change their regimen as compared to those who had not developed side effects (AHR = 3.4, 95% CI: 2.9–3.8).

Similarly, ART patients whose baseline CD4 level was below 100cells/mm^3 had a 1.3 times increased rate of regimen change when compared to other CD4 levels (AHR = 1.3, 95% CI: 1.2–1.7). On the other hand, HIV patients who had social support during ART initiation, the hazard of regimen change at any time was reduced by 53% compared to those who did not have social support (AHR = 0.47, 95% CI: 0.38–0.58). (Table 8)

Table 8 Multi variable analysis of predictors of antiretroviral regimen change among PLHIV at Hawassa University comprehensive Specialized Hospital, 2024

Characteristics	**Category**	**Survival status**		**CHR(95%CI)**	**AHR(95%CI)**	**P-value**
		Censored	**Events**			
TB status test	Positive	104	991	4.7(2.9-7.4)	4.6(2.9-7.4)	<0.001*
	Negative	2260	427	0.56(0.35-0.9)	0.62(0.4-1.0)	0.06
	Not done	56	18	1	1	Ref.
Side effects occurred	Yes	5	321	4.7(4.1-5.3)	3.4(2.9-3.8)	0.001*
	No	2415	1115	1	1	Ref
Sex	Male	1197	335	1	1	Ref.
	Female	1223	1101	4.9(4.3-5.6)	2.9(2.6-3.4)	<0.001*
Social support	Yes	698	123	0.21(0.18-0.26)	0.47(0.38-0.58)	<0.001*
	No	1722	1313	1	1	Ref.
Baseline CD4 (cells/mm^3)	<100	482	397	1.4(1.3-1.7)	1.3(1.1-1.6)	0.001*
	100-199	541	401	1.3(1.2-1.6)	1.1(0.9-1.3)	0.20
	200-349	805	381	0.98(0.8-1.2)	1.0(0.8-1.2)	0.56
	≥350	592	257	1	1	Ref.

*Significant at p<0.05

6. DISCUSSIONS

The findings of this study showed an incidence of antiretroviral regimen change of 12.1 per 100 person-years, which indicated nearly comparable rate with other findings. The occurrence of tuberculosis and adverse medication effects were the most common reasons for regimen change. Among studied variables, sex, occurrence of tuberculosis, occurrence of medication adverse effects, CD4 level, and availability of social support were statistically significant predictors of regimen change among people living with HIV.

The incidence of regimen change in our study setting is nearly comparable to the reports from Arbaminch (11.36/100 person-years), Gondar (10.1/100 person-years), South Africa (10.0/100 person-years), and Kenya (11.1/100 person-years (30,35,38,66). However, studies done in other settings reported a higher rate than the current study finding (In Bahir-dar it was 22.2/100 person-years (39), in Thailand it was 13.8/100 person-years (67) and in Cameroon it was 14.6/100 person-years (37). The difference in incidence rates might be due to variations in population characteristics and the follow-up time across different study settings.

The current study revealed that Stavudine (d4T)-based regimens had a higher incidence rate of regimen changes (7.4 per 100 person-years) than Zidovudin (AZT) and tenofovir (TDF)-based regimens. This finding is supported by studies from South Africa and Kenya (66,68,69). In south Africa, Stavudine-based regimens had the highest changing rate compared to Zidovudin-based regimens (13.6/100 person-years) (66), whereas Tenofovir (TDF)-based regimens had a lower hazard of drug substitution in Kenya (68,69). The possible reasons studied were that Stavudine-based regimens are associated with a significant level of toxicity (68) and 58.1% of all adverse effects were associated with Stavudine based regimens in this study.

In our cohort, there was a major change from the Efavirenz-based anchor to the Dolutegravir (DTG)-based anchor (integrase strand transfer inhibitor) regimen as a “new drug” during the study period. It was due to a new guideline endorsed by the Federal Ministry of Health Ethiopia in 2019 to use DTG as a preferred anti-retroviral therapy in Ethiopian settings (8), because of its long-term efficacy and safety during treatment of HIV patients (37). However, the occurrence of adverse effects was prominent among the Nevirapine and Efavirenz groups. This may be due to the hepatic toxicities associated with Nevirapine and the persistent unresolved central nervous system toxicity associated with an efavirenz-based regimen that may limit patients taking the drugs appropriately. Therefore, clinical decisions for changing

subsequent regimens should be made based on the studied reasons for ART drugs rather than the availability of new drugs.

HIV patients on ART who had experienced adverse effects on the first regimen had three times the increased hazard of changing their regimen at any time as compared to their counterparts. This finding is supported by studies done in Thailand, South Africa, Eretria (36,66,67) and other studies from Ethiopia (12,70). The occurrence of adverse effects may affect quality of life and result in the death of patients, particularly if patients face grade III and IV toxicity. To prevent these consequences, it is important to consider changing regimens with cautious follow-up of the patients' condition when a regimen change is needed (13). On the contrary, delaying regimen change when there are severe adverse drug effects may affect patients, leading to drug resistance and treatment failure (8).

The occurrence of TB influences the beginning regimen to alter in order to avoid drug-drug interaction and urges evaluation for treatment failure (68). As evidenced in our study, those who developed TB on the initiation of ARV drugs had nearly five times the increased hazards of regimen change compared to those who had not tested for TB. According to findings obtained from studies conducted in other settings, 32% and 12% antiretroviral regimen changes were associated with TB comorbidity and adverse reactions in South Africa and Ethiopian clinical settings, respectively (29,62). TB-co-infected HIV patients had higher odds of treatment failure than others in Gondar (46). A study from eastern Ethiopia found that those who used anti-TB and antiretroviral drugs concurrently were more likely to change their regimen than those who were not infected with tuberculosis (23). The possible reason for this may be the enzyme-inducing nature of TB drugs, especially Rifampicin, which induces cytochrome-450 enzymes that facilitate the metabolic activity of the liver, which makes the therapeutic level of ART drugs low, particularly Nevirapine, which results in viral resistance (8). The pill burden may also affect medication, and common toxicities occurring with ART drugs result in the need for a regimen change (71).

Patients whose baseline CD4 counts were less than 100cells/mm^3 were 1.3 times more likely to change their regimen at any time as compared to those whose baseline CD4 count was at least 350cells/mm^3. Studies done in Kenya, Gondar, Jimma, and Arba Minch supported the current study findings (30,46,47,68). The possible reasons might be that those patients who started ART treatment at the advanced stage are sicker and are more likely to have side effects and more regimen changes, probably due to the interaction of other medications for opportunistic infections they are facing.

In our study, women on anti-retroviral therapy had a nearly three-fold increased risk of regimen changes compared to men. This finding is supported by study reports from Thailand in which female gender was associated with an increased risk of developing lipodystrophy (67). Females were 2.4 times at higher risk of experiencing adverse drug reactions (ADRs) compared to males in a report by Sherfa A. and et al (47). In contrast to this, being male has been associated with increased likelihood of ART failure, which makes patients change their regimens, according to a study from Gondar (46). This variation is due to sex differences, in which women had lower lean body mass, reduced hepatic clearance, differences in the activity of enzymes (cytochrome P450), and drug metabolism at different rates compared with men (72,73).

Evidence found that social support from family, peers, and relatives was a regimen adherence facilitator in Cameroon (52). Contrarily, people living with HIV who perceive lower levels of social support are at higher risk for poor engagement in ART care and medication, as reported in a study from the USA (51). Our study indicated that people living with HIV who had social support during ART initiation had a 53% reduced hazard of regimen change compared to their counterparts. A study from Northeast Ethiopia showed that people living with HIV who had better social support had an increased likelihood of staying on initial regimens (53). Therefore, promoting psychosocial support for ART patients should be given emphasis to protect them against the negative consequences of stress, which worsen drug adverse effects, and urge them to make a regimen change (74,75).

Strength and limitations

Due to the retrospective nature of the study, factors like viral load that were found to have significant association with regimen change in earlier research were missed. Also other characteristics that were overlooked, but may have been predictive include cancer screening, toxicity grading, and the presence of mental disease. Selection bias was also probably present in the case of participant selection. The strength of this study is that, it is based on large sample size and long-term data, which have not been taken into account in other reports.

Conclusion and recommendations

The current study revealed that the incidence of regimen change was nearly comparable to other findings and female gender, occurrence of drug side effects, occurrence of TB after starting ART, CD4 below 100 cells/mm^3, and availability of social support were statistically significant predictors of regimen change.

Therefore, clinicians should give attention to patients who are more at risk of changing their regimens, particularly females and patients with advanced diseases who have had immunologic failure, by strengthening careful immunologic follow-up. Moreover, early assessment of adverse effects and the occurrence of tuberculosis during treatment are important to prolong the duration of regimens. Additionally, promoting psychosocial support should be emphasized to protect HIV patients against the negative consequences of stress that push patients to change their regimens. The future study should rely on prospective cohort to determine the true incidence and the role of predictors.

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ANNEX I: INFORMATION SHEET

My name is _____. I am a Field Epidemiology master's student at Hawassa University and I plan conduct a study on “Incidence of anti-retroviral regimen change and its predictors among people living with HIV at Hawassa University comprehensive specialized hospital in 2024”. The purpose of the research is to improve the clinical care of HIV patients. This will assist in coming up with effective recommendations. The information collected from your patients will be confidential. I swear not to disclose any of your patient's personal information to others. Thank you for your cooperation!

Principal investigator: _____

Advisors: Dr. Endrias Markos

Questionnaire Number: _____

Name of data collector _____sign_____ date _____

Checked by_____ sign _____date _____

ANNEX-II DATA COLLECTION TOOL

Part I: Data from ART follow-up chart

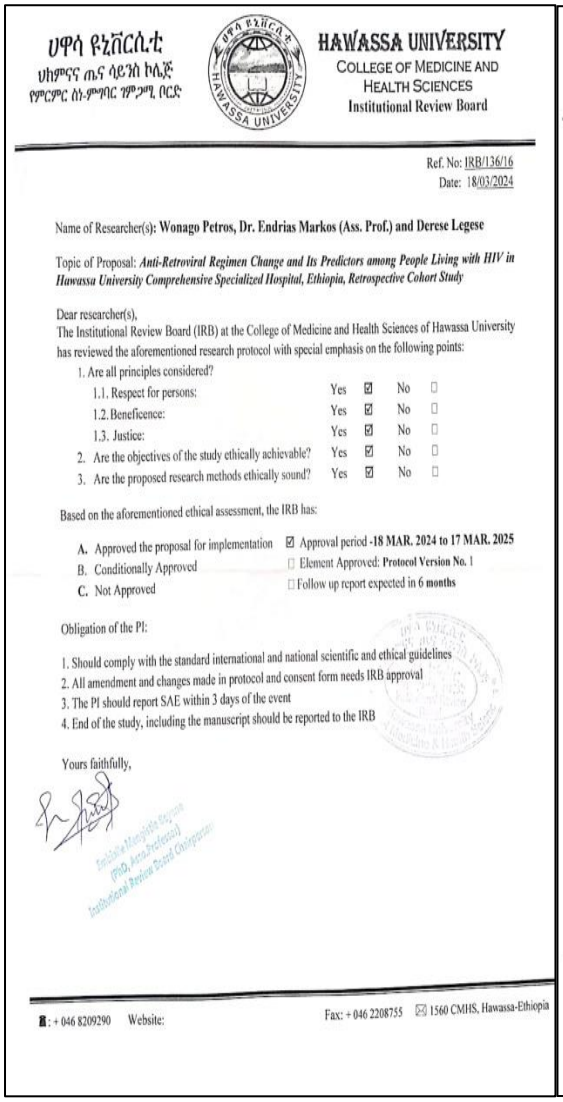
1.1 Health Facility _____
1.2 Card n^{o} _____ ART n^{o} _____
1.3 Address: Region _____ District _____ Kebele _____
1.4 Age at start _____ 1.4 Age now _____
1.5 Sex: 1. Male 2. Female
1.6 Date of HIV Diagnosis _____
1.7 Date ART start _____
1.8 Type of HIV test: 1. Rapid HIV tests 2. DNA/PCR 3. Other specify _____
1.9 Client readiness date _____
1.10 Height in cm _____
1.11 Occupation at diagnosis _____
1.12 Current occupation _____
1.13 Education at the start (highest achieved) _____
1.14 Current education _____
1.15 Marital status 1. Single 2. Married 3. Divorced 4. Widowed 5. Other specify _____
1.15 Family size _____
1.16 Family history of HIV test _____
1.17 PLHIV in the family 1. Yes, 2. No
1.18 Status disclosure to family 1. Yes, 2. No
1.19 Social support availability 1. Yes, 2. No

1.20 Follow-up start date _____
1.21 Months on follow-up_____
1.22 Months on ART _____
1.23 Current status _____
1.24 Weight in kg at the start (date) _____ 1.25 Recent weight (date) _____ 1.26 BMI at the start (date) _____ 1.27 BMI recent (date) _____
1.28 WHO stage at start of follow-up _____ 1.29 Recent WHO stage of follow-up _____
1.30 TB screen 1. Positive 2. Negative (date) _____
1.31 If positive, TB treatment during the cohort 1. Finished 2. On treatment 3. other specify _____
1.32 Other OIs or HIV-related cancers during the follow-up 1. Yes, 2. No Specify the OIs _____ date identified OIs _____
1.33 Diagnosed & managed for pain during the follow-up _____
1.34 First CD4/mm3 (date) _____ Most recent CD4 values (date) _____
1.35 Viral load at start, copies per ml (date) _____ Most recent viral load, (date)_____
1.36 Hgb at start _____ Date _____ Hgb most recent _____ Date _____
1.37 ALT at start _____ Date _____ ALT most recent _____ Date _____
1.38 AST at start _____ Date _____ AST most recent _____ Date _____
1.39 Cr at start _____ Date _____ Cr most recent _____ Date _____

1.40 Cotrimoxazole prevention therapy during the follow-up 1. No 2. Yes
1.41 Fluconazole prevention therapy FPT during the follow-up 1. No 2. Yes
1.42 Other medications during the cohort 1. No 2. Yes
1.43 NCD medications taken during cohort 1. No 2. Yes, specify it _____ Date started medications for NCDs _____
1.44 ART adherence (Good, Fair, Poor) 1. Good 2. Fair 3. poor
1.45 Why fair or poor 1. Side effect 2. Share with others 3. Forgot 4. Felt better 5. Too ill 6. Stigma 7. Drug stock out 8. Other specify _____
1.46 ARV side effects reported 1. Yes, 2. No specify the side effects _____
1.47 ARVs at start _____ ARVs recent _____
1.48 Change of ARVs and from _____ to _____ date of change _____
1.49 Reasons for change of ARVs 1. Side effects 2. New TB 3. New drug available 4. Drug stock out 5. Clinical failure 6. Immunologic failure 7. Virology failure 8. other specify _____
1.50 Client status at data collection 1. In the cohort 2. Died 3. LTFU 4. Other specify ____
1.51 For died or Lost to follow up specify the date _____
Part II: Data from patients' medical records
2.1 Did the client have hypertension at the start of the cohort (B/P record above 130/90 mmHg)? 1. Yes 2. No
2.2 Did the client have hypertension now (B/P record above 130/90 mmHg)? 1. Yes 2. No If yes, diagnosis date _____
2.3 Did the client have DM at the start of the cohort? 1. Yes 2. No
2.4 Did the client have DM now? 1. Yes 2. No If yes, diagnosis date _____
2.5 Did the client have any COPD at the start of the cohort? 1. Yes 2. No
2.6 Did the client have any of the COPDs now? 1. Yes 2. No, If yes, diagnosis date _____

Specify the COPD he or she developed _____
2.7 Did the client have cancer of any organ at the start of the cohort? 1. Yes 2. No
2.8 Did the client have cancer now or at any time during the cohort? 1. Yes 2. No Specify the type/organ involved in cancer he or she developed _____
2.9 Type of cancer 1. Benign 2. Malignant 3. Specify the type ____ Date diagnosed the cancer/s? _____
2.10 Did the client have Cardio Vascular Diseases before starting the cohort? 1. Yes 2. No
2.11 Did the client have cardio vascular diseases now or at any time during the cohort? 1. Yes 2. No
2.12 If yes, Specify the type of Cardio Vascular Diseases _____
2.13 Date diagnosed CVD _____
2.14 Did the client have TB at the start of the cohort? 1. Yes, 2. No
2.15 Did the client have TB now? 1. Yes 2. No
2.16 Date diagnosed the TB? _____

Annex-III: IRB and support letters



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HAWASSA UNIVERSITY
COLLEGE OF MEDICINE AND HEALTH SCIENCES
Institutional Review Board

Ref. No: IRB/136/16
Date: 18/03/2024

Name of Researcher(s): **Wonago Petros, Dr. Endrias Markos (Ass. Prof.) and Derese Legese**

Topic of Proposal: ***Anti-Retroviral Regimen Change and Its Predictors among People Living with HIV in Hawassa University Comprehensive Specialized Hospital, Ethiopia, Retrospective Cohort Study***

Dear researcher(s),
The Institutional Review Board (IRB) at the College of Medicine and Health Sciences of Hawassa University has reviewed the aforementioned research protocol with special emphasis on the following points:

1. Are all principles considered?
   - 1.1. Respect for persons: Yes ☑ No ☐
   - 1.2. Beneficence: Yes ☑ No ☐
   - 1.3. Justice: Yes ☑ No ☐
2. Are the objectives of the study ethically achievable? Yes ☑ No ☐
3. Are the proposed research methods ethically sound? Yes ☑ No ☐

Based on the aforementioned ethical assessment, the IRB has:

A. Approved the proposal for implementation ☑ Approval period **-18 MAR. 2024 to 17 MAR. 2025**
B. Conditionally Approved ☐ Element Approved: **Protocol Version No. 1**
C. Not Approved ☐ Follow up report expected in **6 months**

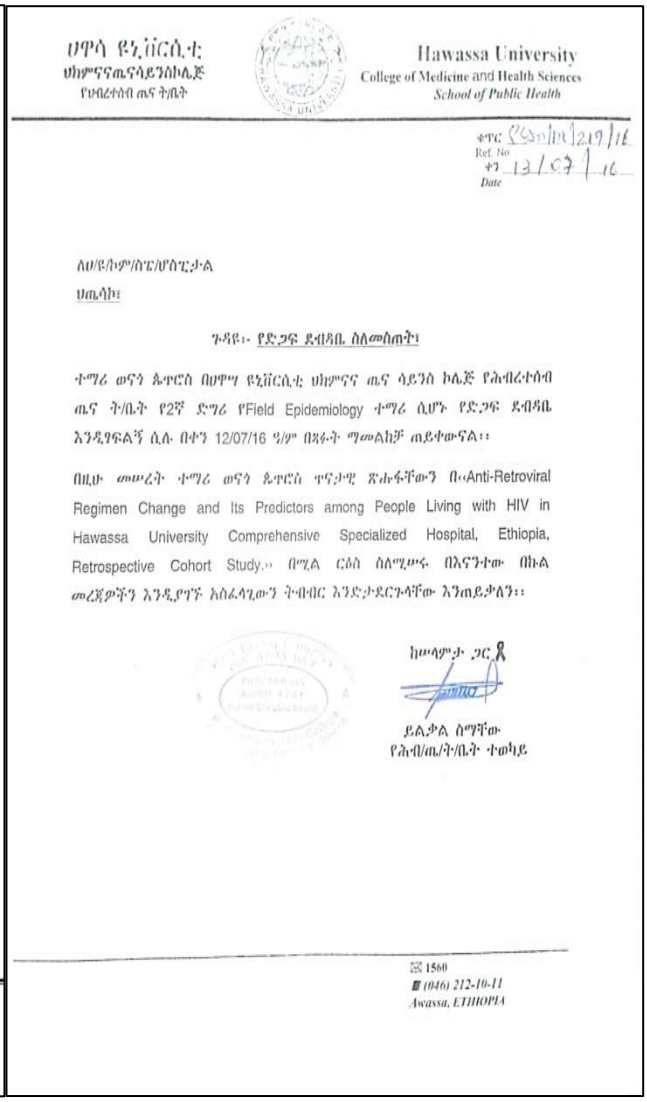
Obligation of the PI:

1. Should comply with the standard international and national scientific and ethical guidelines
2. All amendment and changes made in protocol and consent form needs IRB approval
3. The PI should report SAE within 3 days of the event
4. End of the study, including the manuscript should be reported to the IRB

Yours faithfully,

Institutional Review Board Chairperson

☎: + 046 8209290 Website: Fax: + 046 2208755 ✉ 1560 CMHS, Hawassa-Ethiopia



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Hawassa University
College of Medicine and Health Sciences
School of Public Health

ቁጥር Ref. No ህጉ 13/07/16
Date

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ሀጢሳ፣

ጉዳዩ፡- የድጋፍ ደብዳቤ ስለመስጠት፣

ተማሪ ወናጎ ጴጥሮስ በሀዋሣ ዩኒቨርሲቲ ህክምናና ጤና ሳይንስ ኮሌጅ የሕብረተሰብ ጤና ት/ቤት የ2ኛ ድግሪ የField Epidemiology ተማሪ ሲሆኑ የድጋፍ ደብዳቤ እንዲያፍልኝ ሲሉ በተን 12/07/16 ዓ/ም በጻፉት ማመልከቻ ጠይቀውናል፡፡

በዚሁ መሠረት ተማሪ ወናጎ ጴጥሮስ ጥናታዊ ጽሑፋቸውን በ‹‹Anti-Retroviral Regimen Change and Its Predictors among People Living with HIV in Hawassa University Comprehensive Specialized Hospital, Ethiopia, Retrospective Cohort Study.›› በሚል ርዕስ ስለሚሠሩ በእናንተው በኩል መረጃዎችን እንዲሰጎ አስፈላጊውን ትብብር እንድታደርጉላቸው እንጠይቃለን፡፡

ከሠላምታ ጋር

ይልቃል ስማቸው
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