VIROLOGICAL FAILURE AMONG HIV-INFECTED ADULT PATIENTS TAKING SECOND LINE ANTIRETROVIRAL TREATMENT IN ADDIS ABABA, ETHIOPIA

BY

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D E D I C A T I ON

This milestone is dedicated to my dearest husband, Abay Sisay (Dr), who’s love and patience have been my constant companions on this academic journey. Thank you for being my rock.

D E C L A R A T I ON

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VIROLOGICAL FAILURE AMONG HIV-INFECTED ADULT PATIENTS TAKING SECOND LINE ANTIRETROVIRAL THERAPY IN ADDIS ABABA, ETHIOPIA

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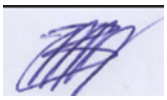
Signature: 

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VIROLOGICAL FAILURE AMONG HIV-INFECTED ADULT PATIENTS TAKING SECOND LINE ANTIRETROVIRAL THERAPY IN ADDIS ABABA, ETHIOPIA

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A B S T R AC T

HIV virological failure presents significant challenges, including drug resistance, increased transmission of HIV, morbidity, and mortality. The study aimed to assess the magnitude and risk factors of virological failure among HIV-infected adult patients taking second line Anti-Retroviral Therapy (ART) in selected hospitals in Addis Ababa, Ethiopia.

A concurrent mixed-methods study was conducted among adults living with HIV on second-line ART in Addis Ababa, Ethiopia, enrolled between 2018 and 2022. The study underwent rigorous ethical review and received approval. The research period spanned from August 20 to November 25, 2024, and involved retrospective and prospective data, including records, FGDs, and KIIs. Quantitative analysis was conducted using SPSS 28, STATA 18, and R; qualitative data were thematically analyzed with Atlas.ti 24.

A total of 369 study participants were enrolled in this study. Of these, 191 (52%) were male, with a median age of 44. The study found a magnitude of 14.9% virological failure (VF). Risk factors influencing VF included clients transferred from other facilities [AOR 2.726 (95% CI: 1.235, 6.016, P-value: 0.013)] and a greater risk of VF among those lost to follow-up (LTFU), with an AOR of 6.007 (95% CI: 2.778, 12.990, P-value < 0.001), as well as those with poor adherence, with an AOR of 6.641 (95% CI: 1.077, 40.95, P-value: 0.041). Patients not changing their regimen were less likely to experience VF, with an AOR 0.475 (95% CI: 0.250, 0.902), P-value: 0.023.

The study revealed an incidence density of 27.2 per 10,000 person-months. Cumulative probabilities of failure were 4.5% at 24 months, 80.7% at 60 months, and 92% at 72 months. The qualitative result identified effective strategies for enhancing ART adherence, including Enhanced Adherence Counseling (EAC). Guidelines for managing virological failure were developed, along with policy recommendations for improving the quality of life.

The findings provided valuable insights for HIV program managers and policymakers to strengthen the monitoring and management of second line ART programs and highly recommend the implementation of DSD modalities, strengthening EAC, and active follow-up using technology to capture LTFU clients, drug resistance testing, and timely switching to the next level appropriate regimen.

Keywords: Adherence, Antiretroviral Therapy, Disclosure, Enhanced Adherence Counseling, Ethiopia, HIV/AIDS, Lost to follow-up, Second line ART, Viral suppression, Virological failure.

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ABBREVIATIONS AND LIST OF ACRONYMS

AACAHB	Addis Ababa City Administrative Health Bureau
AIDS	Acquired Immune Deficiency Syndrome
ART	Antiretroviral Therapy
CDC	Centers for Disease Control and Prevention,
DRM	Drug Resistance Mutation
EAC	Enhanced Adherence Counseling
EPHI	Ethiopian Public Health Institute
FHAPCO	Federal HIV Aids Prevention and Control Office
FMOH	Federal Ministry of Health
FGD	Focused Group Discussion
HBM	Health Belief Model
HF	Health Facility
HIV	Human Immune Deficiency Virus
IRB	Institutional Review Board
KII	Key Informant Interview
MOH	Ministry of Health
NNRTI	Non-Nucleotide Reverse Transcriptase Inhibitor
NRTI	Nucleotide Reverse Transcriptase Inhibitor
OI	Opportunistic Infections
PLHIV	People Living With HIV
PIs	Protease Inhibitors
PPS	Population Proportion Sampling Technique
PST	Proportion Sampling Technique
RHB	Regional Health Bureau
RNA	Ribonucleic Acid
SPSS	Statistical Package for the Social Sciences
TB	Tuberculosis
UNAID	United Nations Program on HIV/AIDS
UNISA	University of South Africa
VF	Virological Failure
VL	Viral Load
WHO	World Health Organization

CHAPTER 1

ORIENTATION TO THE STUDY

1.1. INTRODUCTION

In people living with HIV (PLHIV), who are taking second line Antiretroviral Therapy (ART), Virological Failure (VF) refers to two consecutive viral load test results exceeding 1,000 copies/mL after six months of treatment (WHO 2014:58). This occurs when second line ART fails to effectively control the replication of HIV in PLHIV. This means that second line ART does not lower the amount of virus (HIV RNA) in the blood to undetectable level, which is against the main objective of ART.

Second line ART is used to treat PLHIV who experience failure to first-line ART based on the World Health Organization (WHO) criteria (FMOH 2018:74). The WHO ART failure criteria can be either clinical when new or recurrent clinical events indicate severe immunodeficiency with WHO clinical stage 4 and certain WHO clinical stage 3 conditions after six months of optimal adherence level to the appropriate ART regimen, immunological failure where CD4 count at 250 cells / mm^3 or below following, clinical failure or persistent CD4 count below 100 cells /mm^3 in adults and/or Virological when the Viral Load (VL) test are greater than 1000 copies/ml determined by two consecutive viral load assessments taken three months apart with enhanced adherence support (EAS), following the first high VL test (FHAPCO, 2018; Lailulo, Kitenge, Jaffer, Aluko and Nyasulu 2020:2; WHO 2021:153; MOH-Ethiopia 2022:81).

PLHIV on ART can present a challenge. They may appear clinically stable, despite experiencing virological failure, meaning the virus is replicating and not suppressed by ART. Conversely, some PLHIV might show signs of clinical failure with a low viral load. This can lead to misdiagnosis and unnecessary treatment switching and can have a significant impact on individuals, public health, and the programme (Lailulo et al. 2020:7).

Second line virological failure is defined as a viral load test result greater than 1,000 copies/mL of blood sample in two consecutive measurements after 6 months of second line treatment (WHO 2016:177).

Virological failure poses a public health problem that increases the risk of HIV transmission, leads to ART drug resistance, raises the likelihood of opportunistic infections, and intensifies treatment challenges (FMOH 2018). A study conducted in resource limited countries, indicated that the second line

Virological Failure in adult patients were 21.8%, 23.1%, 26.7% and 38.0% at 6, 12, 24, and 36 months of ART, respectively (Ajosea, Mookerjeeb, Millsc, Boulled and Ford 2012:5). Despite the high rate of second line VF, in resource-limited settings, second line ART failure was mostly assessed using clinical and immunological criteria until recent time. These are inadequate for detecting early virological failure, potentially leading to delayed switching to next-level ART and poorer health outcomes for PLHIV (Zakaria, Raru, Hassen, Ayana, Merga, Debele, Kiflemariam, Kebede and Ayele 2022:6)

1.2. BACKGROUND OF THE STUDY

A research problem is a specific and focused question within a broader area of concern by researchers with the objective to answer it or to contribute to its solution (Brink, Walt, and Rensburg, GV 2018:13).

1.2.1 The source of the research problem

The source of information for the development of the research problem were from the body of recent literature and national HIV consolidated guidelines which showed that, while viral load (VL) testing is the gold standard for detecting second line ART failure, its routine implementation in Ethiopia began in 2018 (FMOH Ethiopia 2018:79). This lack of widespread VL testing prior to 2018 creates a significant gap in understanding the true burden of second line ART VF in the country. Previous studies in Ethiopia have primarily relied on less accurate clinical and immunological criteria to assess second line ART failure. For example, study carried out in Ethiopia indicated that 35.8% and 16.4% of second line ART failure were assessed using immunological and clinical criteria, respectively (Alene, Awoke, Yenit and Tsegaye 2016:5). Studies in the Amhara region and northwest Ethiopia also showed that 9.86 per 100 person-year and 61.7 per 1000 person-year of second line ART failure were assessed using clinical and immunological criteria (Tsegaye, Wubshet, Awoke and Alene 2016:5; Assemie, Alene, Ketema and Mulatu 2019:4). The reliance on less accurate immunological and clinical criteria for diagnosing second line ART failure likely led to an underestimation of its true prevalence in Ethiopia. Consequently, this restricted the scope of

research on the burden of second line virological failure in the country.The limited information on the burden and causes of second line ART VF in Ethiopia inspired the researcher to investigate its prevalence and the associated risk factors of second line VF in this study.

1.2.2 Background of the Research Problem

Ethiopia, a country in Sub-Saharan Africa, is the 10th most populous nation globally and ranks the second most populous nation in Africa, next to Nigeria, with an estimated population exceeding 132 million people (Worldo Meter: 2025). The health system of the country is headed by the Ministry of Health (MOH) in Ethiopia at the national level, along with twelve regional state health bureaus (RHBs) and two city administration health bureaus (Addis Ababa and Dire Dawa) at the regional level.

In 2023, there were an estimated 39.9 (36.1- 44.6) million PLHIV worldwide. Of these, 38.6 million were adults aged 18 years or older. Approximately 1.3 million people were newly infected with HIV, with adults accounting for 1.2 million of these cases (UNAIDS 2023:1,4). In 2022, globally 86% (69–>98%) of PLHIV knew their HIV status, among those who knew their HIV status, 77% (61–89%) were on treatment, and 72% (65–80%) of those on treatment had achieved viral suppression (UNAIDS, 2023:4). In Eastern and Southern Africa, around 20.6 million people were living with HIV. The Ethiopian Public Health Institute (EPHI) estimates that approximately 610,350 people are living with HIV in Ethiopia. Of these, 573,538 were adults, and the overall prevalence of HIV was 0.91% (EPHI 2022:5).

UNAIDS has established a target of 95-95-95 aimed at ending the AIDS epidemic by the year 2030. This goal includes ensuring that 95% of people living with HIV (PLHIV) are aware of their HIV status, 95% of those who know their status are receiving treatment, and 95% of those receiving treatment achieve a suppressed viral load. Compared to this ambitious target, 87.4%, 74.7%, and 91.2% of PLHIV knew their HIV status, accessed ART, and were virally suppressed in Ethiopia (UNAIDS 2020:4; EPHI 2020:8,19).

Antiretroviral treatment aims to block viral replication and suppress the virus to undetectable levels in the blood. It prevents HIV-related diseases, prevents AIDS-related death, and prevents new HIV infections. The first single ART, Zidovudine (AZT), was approved in 1987 and the first triple combination ART regimen was developed in 1991 (Vellaa,

Schwartla¨nderb, Sowc, Eholied and Murphy, RL 2012:5). Since 1996, WHO recommended ART for all PLHIV, worldwide, ART prevented approximately 21 million deaths between 1996 and 2022 (UNAIDS 2023:22).

The expansion of ART services has positively influenced the quality of life of PLHIV by reducing Acquired Immune Deficiency Syndrome (AIDS) related diseases and deaths. Before 2016 there were immunological and WHO clinical stages criteria to initiate ART for PLHIV, but in 2016 the WHO revised the ART guideline to start ART for all HIV-tested positive individuals without any preconditions except a few clinical conditions like PLHIV with Tuberculosis (TB) and few advanced stage 4 clinical conditions (WHO 2015:24).

The 2018 WHO guideline came with a better recommendation, which is same-day ART initiation based on the readiness of the PLHIV (WHO 2018:47). By 2021, globally 28.7 million people were accessing ART (WHO 2022:1). Accordingly, PLHIVs in Eastern and Southern African countries, 78% of them accessed ART. In response to the HIV/AIDS epidemic, Ethiopia initiated a fee-based ART service in 2003, followed by a free ART service in 2005 (FMOH 2014:23). As of 2020/21, there were 441,464 PLHIV in Ethiopia who were receiving antiretroviral therapy (ART). Of these, 426,967 were adults (MOH 2020/21:52).

Even though PLHIV have gained significant advantages from ART, there is increasing apprehension regarding treatment failures, the development of drug resistance, and the delayed toxic effects linked to the prolonged use of ART. Antiretroviral therapy failure can be categorized into immunological, clinical, and virological. In real-world treatment failure, virological failure occurs first, followed by immunological and clinical failure. As the number of PLHIV that start antiretroviral therapy (ART) increases, so does the number of PLHIV that need to switch to a second line regimen due to failure of their first-line ART (Seid, Cherie and Ahmed 2020:2).

There are several reasons why PLHIV may need to switch from their first-line ART regimen to a second line ART regimen. These include immunologic failure, virological failure, clinical failure, and drug toxicity, and the combination of two or three to first-line ART (Tsegaye et al 2016:5). In the same study, the proportion of second line ART failure accounted for 35.8% and 16.4% were immunological and clinical failures, respectively. Another study in Sweden indicated that 28.8% and 14.2% of PLHIV switched to second line ART due to VF without

drug resistance mutation (DRM) and VF with DRM, respectively (Ha¨ggblom, Santacatterina, Neogi, Gisslen, Hejdeman, Flamholc and So¨nnerborg 2017:5).

Second line ART regimens are used to treat PLHIV who have experienced failure to first-line ART and the decision to switch to second line ART is based on the WHO clinical stage, CD4 cell count, and viral load (FMOH 2018:74). These regimens are more complex and expensive than the first-line ART regimen and more likely to cause side effect. However, second line ART regimens can be more effective in suppressing HIV and disease progression than the first line. As more PLHIV taking first-line ART are being switched to a second line regimen, second line ART failure is becoming increasing likely (Edessa, Sisay and Asefa 2019:10). In Ethiopia, second line ART services were started in secondary-level hospitals in 2007 and expanded to the health centers level by 2018, making the service more accessible to PLHIV (FMOH 2014:23; FMOH 2018:101-102). It is important to understand the causes and monitor the effectiveness of second line ART regimens to prevent and treat virological failure. However, there is currently limited documentation on its effects. Studying second line ART virological failure can provide valuable insights into the challenges and help develop and design new interventions to improve the care of PLHIV.

Second line VF is defined as a viral load test result > 1,000 copies/mL in two consecutive measurements after six months of second line treatment. HIV VL testing is the most ideal indicator of disease progression and response to ART and the preferred ART monitoring approach to detect early ART failure and help reduce the accumulation of drug-resistant mutations and improve clinical outcomes promptly. Although the use of VL test is highly recommended for ART monitoring and detecting ART failure worldwide, most resource-limited countries are still using clinical and immunological criteria (WHO 2014:58; WHO 2016:177).

Failure to promptly detect ART failure can result in increased drug toxicity, the development of drug resistance, higher morbidity and mortality rates, and also high risk of HIV transmission (Seid et al 2020:2). PLHIV may appear clinically stable while virological failing, or they may appear with signs of clinical deterioration with a low CD4 T cell count, with a suppressed viral load. This can lead to misdiagnosis and unnecessary treatment switching and can have a significant impact on individuals, public health, and programs.

In developing countries, including Ethiopia, the outcome of ART was being monitored and predicted primarily using a clinical assessment that is used to assess side effects, toxicities, and other complications and immunological (CD4 count) to monitor the progression of HIV disease and to assess the response to ART for a long period. However, clinical and immunological criteria are not the most preferred measurement to detect early ART failure. Studies conducted in the Amhara region and the northwest part of Ethiopia indicated that the overall prevalence of second line ART failure that was assessed using immunological and clinical criteria was 9.86 per 100 person-year and 61.7 per 1000 person-year, respectively (Tsegaye et al 2016:5; Alene *et al* 2019:4).

Various risk factors can lead to second line ART failure including, late switching to second line ART as indicated in a study conducted in Sub Sahara Africa (Sigaloff, Hamers, Wallis, Kityo, Siwale, Ive, Botes, Mandaliya, Wellington, Osibogun, Stevens, Vugt, and Wit 2012:5). CD4 count below 100 cells / mm^3, WHO clinical stage 4 at the beginning of second line ART, experienced drug side effects, and opportunistic infections increase the risk of developing ART failure (Masaba, Woelk, Siamba, Ndimbii, Ouma, Khaoya, Kipchirchir, Ochanda and Okomo 2023:9).

PLHIV who developed virological failure in their first-line ART were also at risk of developing second line ART failure. A study in Tanzania showed that, among PLHIV with VF of first-line ART, 60% of them developed subsequent second line ART failure (Pettersen, Brox, Naman, Bruun and Dyrhol-Riise 2015:5). Along with these factors, the degree of adherence among PLHIV, which is defined as ‘the act of following the provider's instructions regarding the timing, dosage, and frequency of medication intake’ is a significant reason for the failure of ART, (Cramer, Roy, Burrell, Fairchild, Fuldeore, Ollendorf and Wong 2008:3).

The minimum WHO treatment adherence rate recommendation to achieve viral load suppression for PLHIV who are taking ART is 95%. This means that PLHIV takes its ART medications at least 95% of the time as prescribed by healthcare professionals. An adherence rate below 95% may lead to incomplete viral suppression and end up with ART failure (FMOH 2018:231). Therefore, PLHIV should follow the prescribed ART regimen as closely as possible and take their medications as ordered by healthcare professionals (Mohammed, Abeje, Kebede and Mohammed 2023:18). A study in South Africa stated that

non-adherence to ART is the most identified cause for second line ART failure (Levison, Orrell, Gallien, Kuritzkes, Fu, Losina, Freedberg, and Wood 2012:5).

Studies in different parts of Ethiopia also illustrated that the adherence rate of PLHIV taking ART was between 51.8%, and 73.1% (AbadigaI, Hasen, Mosisa and Abdisa 2020:4; Mengistie Tariku, Worede and Belete 2022:6). According to a study conducted in Dessie Public Health Facilities (Amhara region, Ethiopia), the adherence rate of PLHIV taking second line ART was 66.8%, which is far from the WHO adherence rate recommendation (Mohammed et al 2023:18).

Studies showed that different factors such as; being young (18-24 yr), widowed PLHIV, socially stigmatised PLHIV, presence of opportunistic infections (OIs) (Tariku, Worede, and Belete 2022:4), poor family and social support, knowledge about HIV and its treatment, developed adverse drug reaction, nondisclosure to the family members are associated with poor adherence (Abadiga et al 2020:10). Good first-line ART adherence track record, active participants with adherence support, and absence of substance use were the most identified factors associated with good second line ART adherence (Mohammed et a*l* 2023:19).

Although third-line ART is very expensive and complex, it is a treatment option for PLHIV that failed or are intolerant to first and second line ART, and it is very effective in suppressing the virus and preventing HIV-related complications. A study conducted in India indicated that among PLHIV who switched to third-line ART, 83% and 93% achieved virological suppression at 6 and 12 months, respectively **(**Gill, Bergh, Kyaw, Laxmeshwar, Das, Rastogi, Galindo, Mansoor, Kalon and Isaakidis 2019:5)**.**

A study in Ethiopia indicated that the initiation of third-line ART lowered the viral load to an undetectable level (Ketema, Taye, Shibeshi, Tagesse, Hirigo, Woubishet, Gutema, Eifa and Toma 2021:3). A study in South Africa found that the median time to switch to third-line ART after failing second line ART was 500 days. The main reasons for the delay were the time it took to request a drug resistance test after confirmed virological failure, review the test results, and make a decision about third-line ART by clinicians **(**Majova, Variava and Martinson 2022:3)**.**

Due to the limited availability of viral load testing services, most studies conducted in Ethiopia to assess second line ART (antiretroviral therapy) failure relied on WHO clinical and

immunological criteria. While viral load tests can identify treatment failure earlier than immunological and clinical markers, the latter two criteria are not the most accurate methods for timely detecting second line ART failure (WHO 2021:93). As a result, virological-failed individuals living with HIV (PLHIV) may not be identified and managed as promptly as necessary. Furthermore, despite the high sensitivity and superior positive predictive value of viral load tests for early detection of second line ART failure compared to immunological and clinical criteria, this approach has not been extensively studied in Ethiopia. Although routine viral load testing was not widely available or recommended for ART monitoring in Ethiopia before 2018, there is still very limited information on this topic (FMOH Ethiopia 2018:99).

The present study provided much-needed information about the true prevalence of second line ART virological failure and associated risk factors in Ethiopia and improved the diagnosis and proportion of this important public health problem.

1.3 RESEARCH PROBLEM

ART has been highly beneficial for PLHIV, but there is growing concern about the failure of treatment associated with its long-term use and The limited availability of third-line ART services, primarily concentrated in urban centers, further exacerbates the challenges faced by PLHIV who experience treatment failure According to previous studies conducted in Ethiopia in Gondar and Addis Ababa, 9.86 second line ART failures per 100 person-years and 12.2% failure rate were reported, respectively (Ayele, Tessema, Amsalu, Ferede, and Yismaw 2018:4; Zakaria et al 2022:5). Due to the limited availability of the viral load test service, most of the studies conducted in Ethiopia to assess second line ART failure used WHO clinical and immunological criteria (Assefa et al 2017:5). However, these two criteria are not the most accurate way to detect second line ART failure promptly, and virological failing PLHIV may not be identified and managed as quickly as they should be. Although viral load testing is the most accurate way to detect second line ART failure, it is not widely studied in Ethiopia, as routine viral load testing was not widely available, even if it was recommended before 2018 for ART monitoring in Ethiopia.

Therefore, the researcher believes that there is insufficient evidence regarding the burden of second line ART virological failure and its associated risk factors in Ethiopia. Understanding the prevalence and associated factors of second line ART virological failure is essential for the timely development of effective public health interventions to improve the lives of PLHIV.

It can help policymakers to allocate resources to ensure access to second line and third-line ART and quality care for PLHIV, help healthcare professionals to better identify PLHIV who are at risk of failure earlier for appropriate intervention, either switching to different second line regimen options or switching to third-line regimen. Furthermore, it motivates researchers to conduct ART drug resistance research and might be used as a baseline reference for fellow researchers.

Consequently, these issues and causes have inspired the researcher to assess the prevalence and predictors of VF among PLHIV taking second line ART in Ethiopia. In addition to these, the investigator incorporate the experience of ART providers and program managers regarding monitoring and prevention of second line VF to develop best practice guidelines to address the challenges and improve treatment outcomes for PLHIV in Ethiopia.

1.4 AIM AND OBJECTIVES OF THE STUDY

1.4.1 Research aim

The research purpose is the “why” of the study. It is the reason why the researcher is interested in investigating the topic. It helps to ensure that the study is focused and well-designed and helps to communicate the significance of the study to policymakers, the public, and other researchers. Thus, the research purpose is a statement that sets the major idea of the study by explaining what the researchers hope to achieve with their research. It should be written in a way that is easy to understand and is specific enough to provide a clear direction for the study (Creswell 2013:168).

Accordingly, the study aimed to assess the prevalence and risk factors influencing virological failure among adults aged 18 years and older who switched to second line antiretroviral therapy (ART) in Addis Ababa, Ethiopia, 2018-2022.

1.4.2 Research objectives

The research objectives were:

1. To determine the prevalence of second line ART virological failure in PLHIV taking second line ART aged 18 years and older between 2018-2022 in Addis Ababa, Ethiopia.

2. To identify contributing risk factors for unfavourable treatment outcomes among PLHIV in second line ART aged 18 years and older between 2018-2022 in Addis Ababa, Ethiopia.
3. To assess the time to switch to third-line ART among PLHIV aged 18 years and older between 2018-2022 in Addis Ababa, Ethiopia.
4. To explore the factors that affect the adherence of PLHIV aged 18 years and older taking second line ART b/n 2018-2022 in Addis Ababa, Ethiopia.
5. To develop guidelines for health care professionals for the timely management of second line ART virological failure among PLHIV aged 18 years and older in Ethiopia.

1.4.3 Research Question

The research question is the “what” of the study. It is a specific question that the researcher wants to answer through the research. It helps to guide the design and implementation of the study. Thus, it is the central part of the study that contains the types of information the researcher is looking for, identifies the specific area the researcher is interested in studying, and identifies the group of people the researcher is going to be studying, as well as the variables the researcher is interested in (Burn & Grove's 2018:432).

Hence, from the background and problem statement, the following research question is formulated:

- What is the prevalence and risk factors influencing the virological failure among HIV-infected adults taking second line ART in Addis Ababa, Ethiopia?

1.5 SIGNIFICANCE OF THE STUDY

Despite significant progress in HIV treatment and care in Ethiopia, second line ART virological failure remains a pressing public health concern. The limited availability of third-line ART services, primarily concentrated in urban centers, further exacerbates the challenges faced by PLHIV who experience treatment failure.

This study aims to address this critical gap by investigating the prevalence, predictors, and risk factors associated with virological failure in patients on 2nd line ART in Ethiopia. These factors can vary significantly based on context and geographical location. By understanding the extent of VF among PLHIV on second line ART and identifying the associated risk

factors, this research will inform the development of evidence-based guidelines to optimize HIV care and treatment.

These guidelines will provide practical recommendations for healthcare providers, helping them proactively identify and manage PLHIV at risk of virological failure. In addition, it will improve treatment adherence and facilitate timely transitions to more effective treatment regimens. Ultimately, the findings from this study will enhance the quality of HIV care, improve health outcomes for PLHIV, and support the expansion of third-line ART services by informing policy makers. Additionally, the results of this study could serve as a valuable reference and baseline for fellow researchers.

1.6 DEFINITION OF KEY TERMS

- **Human Immune Deficiency Virus (HIV):** is a virus that attacks the body's defense system, making it hard to fight off infections and diseases. Long-term HIV infection can lead to AIDS, a serious condition that weakens the immune system even further (Iloaids 2014:14).

- **Antiretroviral Therapy (ART):** is a combination of medicines that helps fight off HIV in the body. It is not a cure for HIV, but it can significantly slow down the disease and improve overall health and longevity for people living with HIV (WHO 2015:7).

- **Adherence**: In this research, adherence means taking HIV medicines as directed by a healthcare provider. It's important to take them consistently to keep the level of HIV in the blood (FMOH 2017:163).

    - **Good** if >95% of doses are taken by or less than three doses are missed.
    - **Fair adherence**: if 85-94% of dosages are taken or three to nine doses are missed
    - **Poor adherence**: if < 85% of doses are taken or more than nine doses are missed.

- **Second line ART**: In this research, second line ART was considered: if the first HIV medicines stop working or fail, a person may need to switch to different HIV medicines called second line ART. Second line ART is usually a combination of different antiretroviral medications (FMOH 2018:102).

- **Virological Failure:** This occurs when the level of HIV in the blood rises again even though a person is taking HIV medicines. This can happen if the medicines are not taken consistently or if the HIV develops resistance to the medicines. As a result, the amount of viral load couldn't be suppressed below 1,000 copies/ml (FMOH 2014:75). In this research, Virological failure occurs when the VL test results are above 1000 copies/ml after 6 months on second line ART. It is based on two consecutive VL results three months apart, with Enhanced Adherence Support (EAS) provided after the first high VL result.

THEORETICAL FOUNDATION OF THE STUDY

1.7

1.7.1 Research paradigm

A paradigm is a set of fundamental beliefs and assumptions that guide our understanding of the world and how we interact with it (Wicaksana and Rachman 2018:223)**.** A research paradigm refers to a set of basic beliefs and assumptions that guide the way research is conducted. It provides a framework for understanding the world and for developing research methods and theories. There are different types of research paradigms, some of the most common are positivist researchers typically using quantitative methods, Interpretivist researchers typically using qualitative methods, and pragmatist researchers use mixed method research (Creswell 2013:38-40).

In this research, because of the nature of questions being addressed, the researcher adopts the pragmatism research paradigm**.** The assumptions behind this research paradigm are that both quantitative and qualitative data types can provide valid insights into the study.

1.8 SCOPE OF THE STUDY

This research is in the field of public health. The study evaluates the prevalence and risk factors of virological failure among HIV-infected adults taking second line ART in Addis Ababa, Ethiopia. The research is limited to patients aged 18 years and older who are currently taking second line ART drugs. The study investigated the prevalence of VF within this population, aiming to identify and explore the associated factors for VF. To enrich and supplement the findings, we include health care providers' and program managers' views.

Other populations, such as patients under 18 years of age or those on first-line ART drugs, were not encompassed in the research.

1.9 STRUCTURE OF THE THESIS

The thesis is organized into seven main chapters.

Chapter One: In this section, we present more about the introduction of the study. It provides the background of the study problem, the aim and study objectives, as well as the theoretical foundations and conceptual framework.

Chapter Two: Present the most recent literature review conducted on HIV Virological Failure and factors related to the research topic in terms of sources consulted on the topic and research methods employed.

Chapter Three: This chapter presents and is more focused on the research material and methods, such as the study design, study population, sample size determination, sampling techniques, study variable requirements, quality assurance mechanisms, and ethical considerations were discussed and presented.

Chapter Four: This section presents more about the results and findings, with their interpretation

Chapter Five: In this chapter, the researcher discussed and analyzed the research findings in comparison with existing literature and studies to formulate and convey a refined message to healthcare professionals on the subject matter.

Chapter Six: In this section, the researcher prepares and presents guidelines.

Chapter Seven: Conclusion and the way forward, and evidence-based recommendations is presented in the seventh chapter of this thesis.

1.10 SUMMARY

In this chapter, the study's introduction was presented. It outlined the context of the research problem, along with its purpose and objectives, while also detailing the theoretical foundations and conceptual framework.

Moreover, in the subsequent chapter, the research methods and the literature relevant to the research study were described.

CHAPTER 2

LITERATURE REVIEW

2.1 INTRODUCTION

A literature review provides a comprehensive and critical evaluation of the existing research on a particular topic. It comprises systematically collecting, evaluating, and synthesizing academic information sources such as books, journal articles, reports, and dissertations to understand the current state of knowledge on the subject matter (Creswell, 2014:60).

In this research, the literature review aims to critically examine and synthesize existing research related to the prevalence of virological failure in HIV patients taking second line ART. By exploring relevant studies, theoretical frameworks, and empirical findings. This review highlights key trends, identifies gaps in the current knowledge, and establishes the context for the present study. This comprehensive analysis demonstrates the significance of addressing virological failure in the management of PLHIV in Addis Ababa, Ethiopia.

The purpose of a literature review is to examine and combine existing studies on a specific topic. It highlights current knowledge, identifies research gaps, and suggests areas for future research. It gives a broad understanding of the subject, helps position new research within the existing work, and ensures that the study builds on established knowledge while avoiding redundancy (Hempel 2020:102).

2.2 ANTIRETROVIRAL THERAPY

Antiretroviral therapy (ART) is the cornerstone of HIV treatment, aimed at controlling viral replication, preserving immune function, and preventing the progression to AIDS. It involves the use of combinations of antiretroviral (ARV) drugs that inhibit the replication of HIV, thereby dropping the VL to undetectable levels (FMOH 2018:72). The introduction of ART in the mid-1990s marked a pivotal moment in HIV care, drastically improving the life expectancy and quality of life for PLHIV by reducing HIV replication (Boettiger, Nguyen, Durier, BUI, SIM, Azwa, LAW and Ruxrungtham 2021:16).

There are three primary groups of ARV drugs used in ART regimens: nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs),

and protease inhibitors (WHO 2015:7). The initial treatment regimen for HIV, referred to as first-line ART, typically involves a combination of two NRTIs and one NNRTI or PI. The first-line ART is highly effective in the majority of patients, reducing VL to undetectable levels and maintaining immune function. However, for some patients, first-line ART may fail due to factors such as poor adherence, drug resistance, or drug interactions, leading to virological failure (NIH 2021:56).

Second line ART regimens are used to treat PLHIV who have experienced failure of first-line ART, and the decision to switch to second line ART is based on the WHO clinical stage, CD4 cell count, and viral load (FMOH 2018:74). As more PLHIV taking first-line ART are being switched to a second line regimen, second line ART failure is becoming increasingly more likely (Edessa et al 2019:10).

When first-line ART VL occurs and the viral load becomes detectable despite ART, patients are switched to second line ART. Second line ART typically includes a combination of different drugs, often incorporating protease inhibitors (PIs) with a new set of NRTIs, to combat drug-resistant strains of HIV, and it is designed to target the virus more aggressively when first-line therapy is no longer effective (FMOH 2018:77).

Second line ART refers to the treatment regimen used when first-line ART fails to effectively control HIV replication. Virological failure, indicated by a consistently detectable viral load, is the most common reason for transitioning to second line therapy. The goal of second line ART is to regain viral suppression and reduce the risk of disease progression to AIDS. According to WHO, second line ART regimens typically incorporate different classes of antiretroviral drugs than those used in the first-line regimen, targeting drug-resistant HIV strains more effectively (WHO, 2016:75).

The transition from first-line to second line therapy occurs when the patient experiences clinical, immunological, and virological failure, often caused by factors such as poor adherence to treatment, drug resistance, or drug interactions (Masaba et al 2023:9). The purpose of second line ART is to preserve immune function, prevent disease progression, and reduce the risk of opportunistic infections and mortality among PLHIV.

Globally, transitioning to second line ART guided by VL monitoring, which is considered the most proximal indicator of treatment failure. The WHO recommends that patients with confirmed VF (viral load >1000 copies/ml) despite adherence to first-line therapy should be switched to second line regimens (WHO 2016:101).

However, WHO guidelines stress the importance of individualized treatment plans for patients transitioning to second line ART, taking into consideration factors like previous drug exposure, side effects, and resistance patterns. In many developing settings, access to VL testing is limited, leading to delays in identifying VF and making timely treatment adjustments (UNAIDS, 2021:112). This delay highlights the need for robust monitoring systems and timely intervention to avert the occurrence of drug resistance and keep viral suppression.

Ethiopia, one of the countries most affected by HIV/AIDS, has made significant progress in expanding access to ART, including second line therapies. ART started in 2003 as a paid service, and free ART was subsequently introduced in 2005. The Ethiopian ministry of health, in line with WHO recommendations, has established national guidelines for managing HIV treatment, which include clear protocols for switching patients to second line ART following confirmed virological failure (FMOH Ethiopia, 2018:100). These guidelines commend viral load testing every 6 to 12 months for patients on ART, and if first line treatment failure is detected, a second line regimen is initiated as promptly.

According to the annual report of the Ministry of Health of Ethiopia (MOH) of 2020/21, 573,162 (81%) of PLHIV knew their HIV status. Among those aware, 77% (441,464) were taking the ART. Of those on ART, 96% (426,967) were adults aged 18 years and older. Among those taking ART, viral load testing was performed for 358,109 (81%), and 340,379 (95%) of them were virally suppressed (MOH 2020/21:52, 54-55).

Due to the limited availability and accessibility of the viral load testing service, most of the studies conducted in Ethiopia for assessing second line ART failure used the WHO clinical and immunological criteria. Studies conducted in the Amhara region and the north west part of Ethiopia indicated that the overall magnitude of second line ART failure assessed using immunological and clinical criteria were 9.86 per 100 person-year, and 61.7 per 1000 person-year respectively (Tsegaye et al 2016:5; Alene *et al* 2019:4). However, these two criteria are not the most accurate way to detect second line ART failure in a timely manner, and

virological failing PLHIV may not be identified and managed as quickly as it should be. Although viral load testing is the most accurate way to detect second line ART failure, it is not widely studied in Ethiopia, as the routine viral load test was not widely available and recommended before 2018 for ART monitoring in Ethiopia.

In Ethiopia, second line ART regimens have been mostly managed by adhering to the WHO recommendations. However, the availability of newer ARVs and comprehensive drug resistance testing remains limited (Steegen, Zyl, Claassen, Khan, Pillay, Govender, Bester, Straaten, Kana, Cutler, Kalimashe, Lebelo, Moloi, and Hans 2023:9). To address these challenges, the Ethiopian government has collaborated with international organizations such as the Global Fund to scale up ART services, including the provision of second line therapies and improved diagnostic infrastructure.

2.3 VIROLOGICAL FAILURE IN HIV TREATMENT

The main aim of ART is to reduce HIV replication in the blood to undetectable levels, thus preventing drug resistance emergence, HIV-related illness, averting AIDS-related death, and reducing the risk of new HIV infections. Virological failure in HIV treatment occurs when the amount of HIV RNA in the blood sample, often called viral load, becomes detectable while the patient is taking ART. According to the WHO ART guideline, virological failure is defined as a viral load test result greater than 1,000 copies per mL in at least two consecutive measurements after 6 months of ART initiation, despite appropriate adherence to the prescribed regimen (WHO 2016:104).

Virological failure can be attributed to various factors, including drug resistance, adverse drug reactions, drug interactions, poor adherence to treatment, and underlying health conditions. When virological failure happens, it can lead to several negative consequences, such as elevated risk of HIV-related illnesses, increased risk of HIV transmission, and development of drug resistance (McCluskey, Siedner and Marconi 2019:11).

Studies indicated that, three common causes for virological failure includes patient factors, encompassing poor adherence due to comorbidity, substance use, and psychosocial features; viral factors, including persistence of resistant strain, innate resistance, and higher pretreatment RNA; and treatment factors which involve, suboptimal pharmacokinetics of ART regimen that prevents adequate serum concentration of the drug, suboptimal potency,

low genetic barrier, and medical conditions have been indicated as major factors for virological failure (Cutrell, Jodlowski and Bedimo 2020:3).

In resource-limited settings like Ethiopia, where access to drug resistance testing for PLHIV is limited, patients experiencing virological failure often rely on the WHO guidelines and national treatment guidelines. These guidelines provide a standardized approach to managing HIV treatment, particularly in situations where advanced diagnostic tools may not be readily available (McCluskey et al 2019:11).

2.4 FACTORS INFLUENCING VIROLOGICAL FAILURE IN SECOND LINE ART

Several factors can contribute to virological failure in second line ART. A study conducted in Ethiopia found that poor adherence to ART, not disclosing HIV status or ART use to their parents or close relatives, presence of opportunistic infections (OI), Body Mass Index (BMI) <16kg/m^2, and CD4 count <350 cells/mm3, were determinants for second line virological failure (Seid et al 2020:6). Another study in Ethiopia showed that not using condom, and VL between 150 and 999 Copies/ml during switched to second line ART were among the associated risk factors for second line failure (Ayenew, Agumas, Shibabaw, Getaneh and Getie 2024:8).

A case control study conducted in Tanzania also found that, age less than 30 years was one of the most identified factors in related with second line ART failure (Gunda, Kilonzo, Mtaki, Bernard, Kalluvya and Shao 2019:3). In addition, the development of drug resistance is among the most significant factors. When patients are on first-line ART and do not achieve or maintain viral suppression, the virus can mutate, which leads to resistance to one or more drugs in the regimen. These drug-resistant strains of HIV can limit the effectiveness of second line therapy, for those patient who had a history of poor adherence or prior exposure to suboptimal treatment regimens (WHO 2016:115, South African HIV Clinicians Society 2020:12).

A study in Tanzania found that baseline viral load ≥1000 copies/mL during first-line ART, using of lopinavir (PI) during second line treatment were more related to virological failure. As a receipt of care at lower-level healthcare facilities, being on ART for 13 to 35 months, TB infection during first-line ART, and having CD4 counts <200 cells/mm3 during second

line ART were the identified predictors for second line ART failure, (Mwavika, Kunambi, Masasi, Lema, Kamori and Matee 2024:7).

Likewise, a study conducted in Ethiopia found that older age (>45 years), low CD4 count (<100 cells/mm^3) at the initiation of second line ART, and co-infection with tuberculosis were significant predictors of second line ART failure (Zakaria et al 2022:10). Another study conducted in Rwanda revealed that; age groups 15–29, CD4 cell count ≤500 cells/mm3 WHO clinical stage III & IV at ART programme enrollment, ATV/r based second line regimen and receiving care at a health center relative to the regional hospital were found to be risk factors for second line ART failure (Nsanzimana, Semakula, Ndahindwa, Remera, Sebuhoro, Uwizihiwe, Ford, Tanner, Kanters, Mills, and Bucher 2019:4).

2.5 PREVALENCE OF SECOND LINE ART VIROLOGICAL FAILURE

Virological failure on second line antiretroviral therapy (ART) remains a significant challenge in the management of HIV infection. While substantial progress has been made in expanding access to ART, understanding the prevalence of second line virological failure is essential for optimizing treatment strategies and improving patient outcomes.

A study conducted in China revealed that individuals with high or low-level viremia and non-suppressed viral loads faced a significantly higher risk of VF compared to those with viral suppression. More specifically, the cumulative rates of virological failure were 18.45% for the high/low-level viremia group and 82.99% for the non-suppressed group, significantly higher than the rate observed in the viral suppression group(Qin, Lai, Zhang, Wei, Lv, Pan, Huang, Lan, Meng, Liang and Ning 2021:4). Similarly, an observational cohort study conducted in Malawi found a substantial prevalence, 32% of participants experienced VF while on second line ART (Gupta-Wright, Fielding, Oosterhout, Alufandika, Grint, Chimbayo, Heaney, Byott, Nastouli, Mwandumba, Corbett, and Gupta 2020:4). In Tanzania, a study reported a 12.18% prevalence of virological failure among patients taking second line ART (Gunda, et al 2019:6).

A study in Ethiopia reported a pooled incidence of 5.98 per 100 person-years of observation (Kassie, Wolda, Woldegeorgis, Gebrekidan, Haile, Meskele and Asgedom 2024:8). This finding highlights the substantial burden of second line ART failure in the country. Individual studies have also reported varying prevalence rates. A study in Amhara region, Ethiopia,

observed a higher incidence of 9.86 per 100 person-years, while another study in the same region reported a lower incidence of 4.03% (Kassie et al 2024:6; Alene et al 2019:4). These disparities may attributed to factors such as differences in study populations, treatment regimens, and adherence rates.

In another study in Ethiopia, the incidence of second line ART failure was reported to be 72.3 per 1000 person-years of observation (Haftu, DestaI, Bezabih, Kahsay, Kidane, Zewdie and Woldearegay 2020:7). Additionally, a study conducted in Addis Ababa, Ethiopia, showed that 12.22% of PLHIV on second line ART experienced virological failure (Zakaria et al 2022:5).

2.6 FACTORS CONTRIBUTING TO UNFAVOURABLE TREATMENT OUTCOMES

Several factors have been identified as contributing to unfavourable treatment outcomes, including virological failure, among adults aged 18 years and older on second line ART. Poor Adherence to ART is a consistent finding across multiple studies; there is a strong association between poor adherence to ART and increased risk of second line VF. A study conducted in Tanzania revealed that poor adherence level is associated with factors for second line virological failure (Mwavika et al 2024:7). Studies in Ethiopia have also shown that individuals with poor adherence are significantly more likely to experience virological failure compared to those with optimal adherence. Patients with poor adherence were six times more likely to develop treatment failure compared to those with good adherence (Ambaw *et al.*, 2024:9,10).

A low CD4 cell count at the initiation of second line ART has been identified as a risk factor for treatment failure. Studies in Ethiopia have shown that individuals with CD4 counts below 100 cells/mm^3 are at higher risk of virological failure compared to those with higher CD4 counts. Additionally, in a study conducted in Ethiopia, participants with CD4+ counts of 500 cells/µL or less were 5 times more likely to experience VF compared to those with higher CD4+ counts (Kassie et al 2024:6).

Co-morbidities, particularly tuberculosis (TB) co-infection, have also been associated to a higher risk of treatment failure. A study from Addis Ababa, Ethiopia, indicated that the risk of virological failure was 2.48 times greater among patients who began second line ART with TB co-morbidity compared to those without TB co-morbidity (Kassie et al 2024:8).

Advanced WHO clinical stage at the initiation of second line ART has been linked to inferior treatment outcomes. According to study in Ethiopia, the pooled risk of second line treatment failure was nearly three times higher among PLWHIV with advanced WHO clinical stage at switch than among those with WHO clinical stage I/II (Endalamaw, Mekonnen, Geremew, Yehualashet, Tesera and Habtewold 2020:10).

A study conducted in China revealed that individuals who underwent ART modifications were 1.728 times more likely to exhibit high viral load than those who maintained their original treatment regimen (Qin et al 2021:6).

2.7 THE TIME TO SWITCH TO THIRD-LINE ART

In accordance with both WHO and national guidelines, a transition to third-line ART is recommended after two consecutive Enhanced Adherence Counseling (EAC) sessions of three months apart, subsequent to the initial detection of a high viral load on second line ART if the viral load persists at a high level despite adherence counseling (FMOH Ethiopia 2018:75 & WHO 2021:150). A retrospective cohort study in South Africa found that the average time to switch to third-line ART after failing second line ART was 500 days, and 66.7% were longer than one year (Majova, Variava and Martinson 2022:3).

In settings with limited access to third-line ART, timely diagnosis of second line ART failure and switching to third-line ART are crucial to prevent the occurrence of drug resistance and worsening health outcomes. A study conducted in Tigray region of Ethiopia revealed that despite the presence of second line ART failure, none of the patients were shifted to 3rd line ART (Gidey, Mache, Hailu, Asgedom, Tassew and Nirayo 2023:8).

A qualitative study conducted in Kenya, Malawi, and Mozambique found that among participants who experienced second line virological failure, the median duration on a second line ART regimen was 12 months. The study also highlighted the negative impact of delayed treatment switches from failing second line to third-line ART. Participants reported experiencing adverse health consequences, such as hospitalization for tuberculosis, due to prolonged exposure to ineffective therapy (Burns, Borges, Blasco, Vandenbulcke, Mukui, Magalasi, Molfino, Manuel, Schramm and Wringe 2019:7).

A research conducted in Asian-Pacific countries, revealed a median follow-up time of 2.8 years post second line ART failure, indicating a small portion of the patients had treatment

modification due to limited accessibility of third line ART and prolonged reliance on second line regimens (Jiamsakul, Azwa, Zhang, Yunihastuti, Ditangco, Ku,arasamy, Ng,Chan, Ly, Choi, Lee,Pujari, Kiertiburanakul, Chaiwarith, Merati, Sangle, Khusuwan, Sim, Avihingsanon, Duy, Tanula, Ross, Law 2020:6).

Though studies have demonstrated that delaying the switch to third-line ART can lead to serious consequences, there remains a lack of definitive evidence specifying the exact timing for switching to third-line ART among PLHIV who have failed the second line ART.

2.8 FACTORS INFLUENCING ADHERENCE TO SECOND LINE ART

Antiretroviral treatment adherence refers to taking ART as prescribed by healthcare providers, comprising the accurate dosage, frequency, and duration upon WHO and national established ART guidelines recommendations (Cramer et al 2008:3). The minimum WHO adherence rate recommendation to achieve viral load suppression for PLHIV who are taking ART is 95%. This means that PLHIV take ART medications at least 95% of the time as appropriately prescribed by healthcare professionals. An adherence rate below 95% may result in non-compliance with viral suppression and end up with ART failure (FMOH 2018:231).

Adherence to ART is essential for optimal treatment outcomes, leading to viral suppression, improved immune function, reduced drug resistance, and enhanced quality of life. However, adherence can be influenced by various factors, including patient-related, treatment-related, healthcare provider-related, and social and cultural factors, as elaborated in the subsequent sections.

2.8.1 Patient-related factors

Factors related to patients that influence adherence to second line ART are the most important and should be explored promptly for effective treatment success. A cross-sectional study in Nepal indicated that patients who do not receive ART medicine from the ART center themselves were less adherent compared to those who receive ART medicine from the ART center themselves (Neupane, Dhungana, and Ghimire, 2019:4).

A study in Ethiopia found that people aged 39-40 were less likely to stick to their HIV treatment compared to younger people, aged 18-27 years. Additionally, people who didn't

read or write were less likely to adhere to treatment compared to those with higher education levels. From the same study, patients with comorbid diseases were 96% less likely to adhere to ART care than those without comorbid diseases. Additionally, the probability of adherence to ART care among WHO clinical stage II patients were 90% times lower than in WHO clinical stage I patients (Angelo and Alemayehu, 2021:6).

A cross-sectional study in Peru revealed that nearly 60% of participants were not adhering to their ART regimen. The primary reasons for non-adherence included forgetfulness, neglect due to other commitments, and illness. Additionally, concurrent tuberculosis infection, default from treatment, and childlessness were identified as risk factors for non-adherence (Leyva-Moral, Loayza-Enriquez, Palmieri, Guevara-Vasquez, Elias-Bravo, Edwards, Feijoo-Cid, Davila-Olano, Rodriguez-Llanos and Leon-Jimenez. 2019:8).

2.8.2 ART related factors

Respondents who experienced ART side effects such as nightmares were more likely to have sub-optimal adherence compared to those who did not experience side effects (Leyva-Moral et al 2019:5; Abadiga et al 2020:7). Complexity of the ART was also found to be an ART drug-related factor (Buh, Deonandan, Gomes, Krentel, Oladimeji and Yaya 2023:16).

ART drug toxicity is a significant contributing and risk factor for ART virological failure. Adverse drug reactions or intolerance may result in non-adherence or discontinuation of ART, ultimately heightening the likelihood of virological failure, particularly in cases involving second line ART failure, it can also be related to the evolution of the occurrence of drug resistance (Nega, Taye, Million, Rodrigo and Eshetie 2020:4-7).

Similarly, changes in ART regimen history and track record could indicate the potential for virological failure. Frequent transitions between ART drugs and pill burden can increase toxicity and negatively impact the overall success rate of the treatment (Musana, Ssensamba, Nakafeero, Mugerwa, Kiweewa, Serwadda and Ssali 2021:8).

2.8.3 Healthcare providers' related factors

Healthcare providers from Sierra Leone reported feeling overwhelmed by the demand for care and support for PLHIV, limiting the time they could spend with each patient. They emphasized the need for additional staff to improve assessment, review, and support services (Lahai, Theobald, Wurie, Lakoh, Erah, Samai and Raven 2022:7).

Patients reported that during ART refill appointments, healthcare providers often conducted superficial adherence assessments, merely inquiring about overall adherence and well-being. Continuous ART adherence education was primarily targeted at patients with declining CD4 cell counts (Bukenya, Mayanj, Nakamanya, Muhumuza and Seeley 2019:6).

A systematic review conducted in South Africa revealed that, despite the availability of a separate ART (Antiretroviral Therapy) room for drug collection, the HIV status of patients became publicly noticeable when they entered this room (Makhado and Mongale, 2019:6). This situation is closely linked to concerns about breaching privacy and the need to maintain client confidentiality. It also poses a potential risk for stigma and discrimination, including perceived stigma among patients.

2.8.4 Social and cultural factors

A study conducted in Ethiopia revealed that PLHIV in rural areas were less likely to stick to their HIV treatment compared to those in urban areas. Additionally, those who had not disclosed their HIV status to others were more likely not to adhere to treatment than those who had (Angelo and Alemayehu 2021:6).

A qualitative study conducted in Sierra Leone revealed that PLHIV faced significant stigma and discrimination from family, friends, and community members as a result of their positive HIV status. Participants described HIV/AIDS as a taboo subject, leading them to believe that their condition should not be discussed or disclosed to others (Lahai et al 2022:5). A study conducted in Uganda similarly exhibited that the fear of stigma related to HIV resulted in individuals avoiding taking their medication in public (Bukenya et al 2019:5).

2.9. THEORETICAL/CONCEPTUAL FRAMEWORK

Second line ART is a crucial treatment for PLHIV who have not responded to first-line ART. However, the outcomes of second line ART can be affected by various factors, including socio-demographic status, social status, risk behaviours, baseline clinical and laboratory conditions, opportunistic infections (OIs), and the ART medication status of PLHIV, where most factors are interconnected.

Health Belief Model (HBM) theory outlines, how people's beliefs regarding health and illness impact their health behaviours, focusing on four key factors: perceived susceptibility (how

likely PLHIV believe they are to experience second line ART failure), perceived severity (how serious PLHIV consider second line ART failure to be), perceived benefits (the extent to which PLHIV believe the advantages of taking second line ART outweigh the costs), and perceived barriers (the obstacles PLHIV feel they may encounter when taking second line ART). Cues to action that motivate PLHIV to adhere to their second line ART are also relevant to the concepts presented in the conceptual framework, which examines the factors influencing second line ART outcomes (Green, Murphy, kristina Gryboski & Kate Sweeny 2020:5). Key concepts and relationships that can determine the second line ART virological failure illustrated in Figure 1.

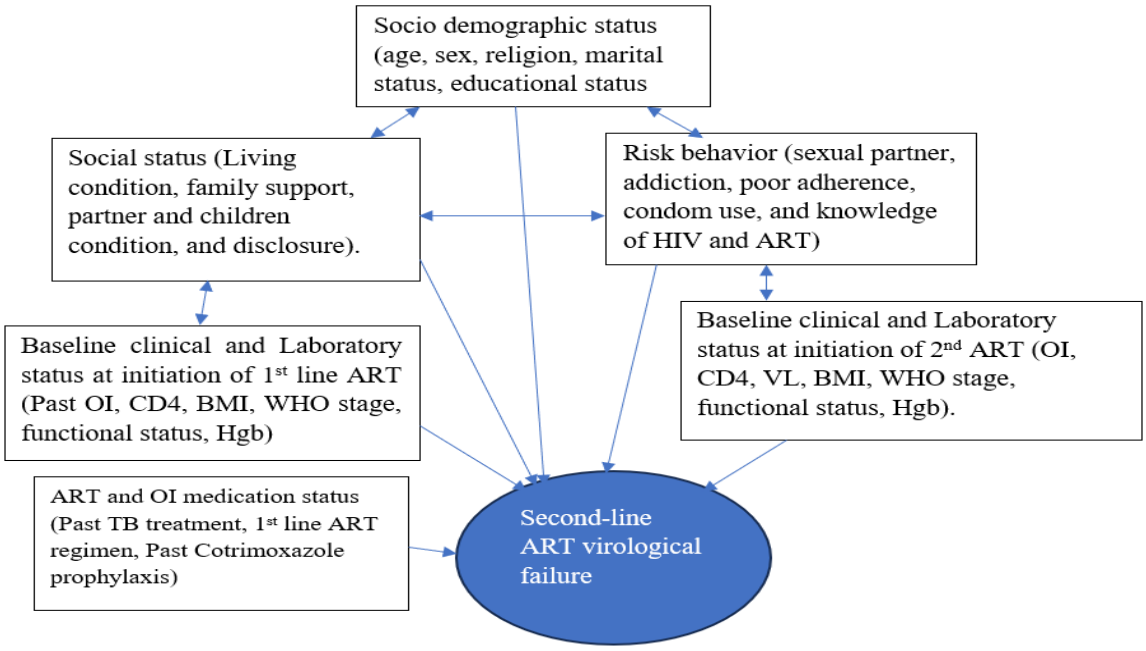


Figure 1. Conceptual framework for the study

These factors can influence a person's decision to take second line ART as prescribed. For example, someone who has a high-perceived susceptibility to second line ART failure and a high-perceived severity of second line ART failure is more likely to take their ART as prescribed than someone who has a low perceived susceptibility and a low perceived severity. In this study, the researcher used the Health Belief Model (HBM) (Shumaker, Ockene and Riekert 2008:54) in qualitative data interpretation to explore the level of perceived stigma and discrimination barrier to adherence to prescribed ART and identify factors that influence PLHIV's perceptions about second line ART outcomes and to develop guidelines that addresses these perceptions, conceptualised in figure 2.

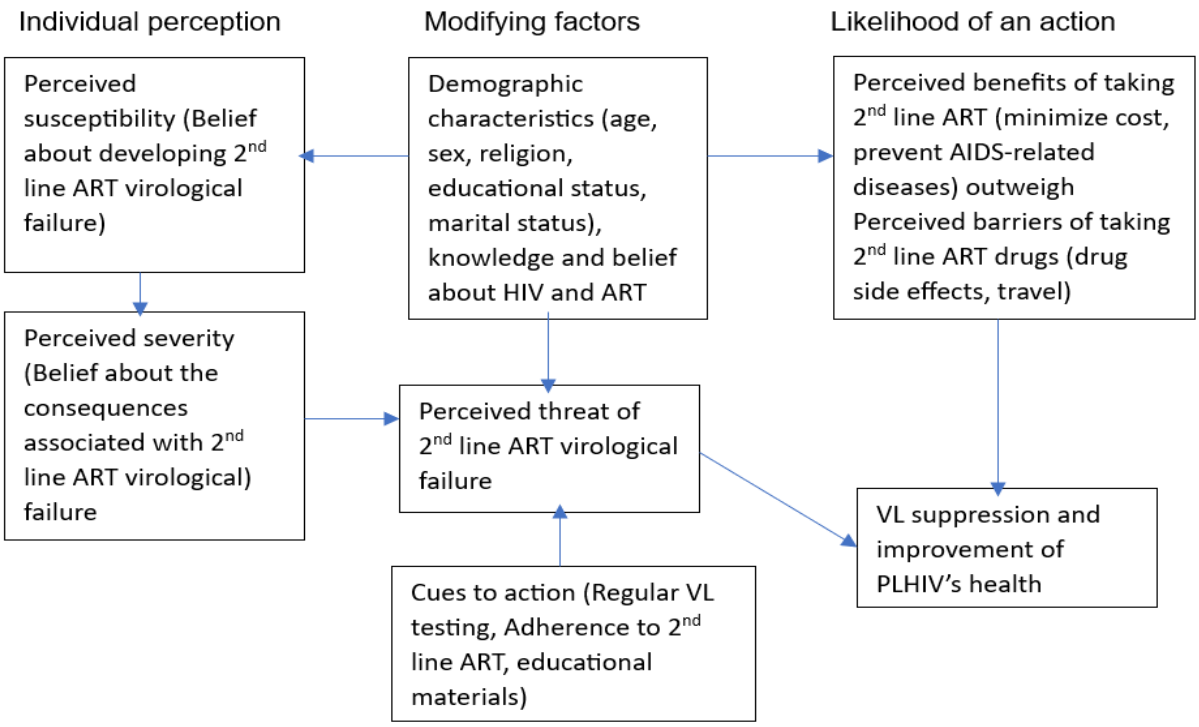


Figure 2. Conceptualizing the health belief model

2.10 SUMMARY

The increasing prevalence of second line ART virological failure, coupled with the emergence of drug resistance and poor patient outcomes, underscores the urgent need for effective viral load monitoring and addressing the adherence level of patients. Adherence to WHO and national HIV guidelines for monitoring PLHIV on second line ART is crucial to preventing further drug resistance and ensuring optimal treatment outcomes.

The following chapter details the research design and methodologies employed to address this pressing issue.

CHAPTER 3

RESEARCH DESIGN AND METHODS

3.1 INTRODUCTION

In the previous chapter, the existing literatures were reviewed to identify the gaps in knowledge pertinent to the study. The purpose of this section is to elucidate the process through which the study's objectives were recognized. The aims outlined in Chapter one have significantly influenced the research design and methodology. Additionally, this chapter provided comprehensive details regarding the study population, sampling methods, data collection tools, processes, data analysis, and ethical considerations.

Furthermore, the measures taken to prove the trustworthiness, validity, and reliability of the findings were also elaborated upon.

3.2. STUDY APPROACH AND DESIGN

3.2.1 Research paradigm

A paradigm is a set of fundamental beliefs and assumptions that guide our understanding of the world and how we interact with it (Wicaksana and Rachman 2018:223). A research paradigm refers to a set of basic assumptions and beliefs that guide the way that research is conducted. It provides a framework for understanding the world and for developing research methods and theories. Textbooks have listed different types of research paradigms, but some of the most common are positivist researchers typically using quantitative methods, Interpretivist researchers typically using qualitative methods, and pragmatist researchers using mixed method research (Creswell 2013:38-40).

Accordingly, in this study, the pragmatism research paradigm was used. The assumptions behind this research paradigm were that both quantitative and qualitative data provide valid insights into the study. Knowledge is constructed through the interaction of data collectors, researchers, supervisors, and participants; in this case, the data, which was collected through both quantitative and qualitative methods, was influenced by the data collectors' own biases and the participants' own experiences. Values are important and should be explicitly acknowledged. This means that the researcher, data collector, and supervisors were aware of their own values and how they might influence the research process. Implementing a

mixed research method approach allowed the collection of quantitative and qualitative data where the best way to understand a research question was to combine quantitative and qualitative methods (Teddlie and Tashakkori 2009:21).

3.2.2 Study Approach

In this research, a concurrent mixed-method approach was employed. The concurrent mixed-methods research approach is typically applied in situations where the research questions require a more comprehensive understanding of the research problem. It is particularly useful when the research aims to explore complex social phenomena, understand the underlying processes, or examine the relationships between variables in a multidimensional context (Creswell 2018:105-107). The reason for selecting this approach in this research is to gain a comprehensive understanding of the risk factors that contribute to virological failure among adults 18 years and older taking second line ART and provide guidelines to address the factors.

The quantitative research approach focuses on collecting and summarising numerical data to examine relationships and test hypotheses for generalizations. It is often used when the research aims to quantify variables, establish causality, or make predictions based on statistical analysis, whereas the qualitative research approach involves collecting and analysing non-numerical data such as interviews, observations, or textual analysis. It is commonly used to explore subjective experiences, understand social processes, and generate in-depth insights into complex phenomena (Patten and Newhart 2023:41).

In this research, by combining the quantitative and qualitative data, the mixed method approach allowed for the triangulation and enriching of the findings to enhance the credibility and validity of the research by verifying results from different data sources (medical records, electronic database, KII, and FGD) and it had the following benefits:

- Complementarity: the mixed method approach enabled researchers to capitalize on the strengths of both quantitative and qualitative methods.
- Enhanced understanding: the mixed method approach facilitated a more comprehensive understanding of complex phenomena in different directions.

This research utilized both quantitative and qualitative research approaches. The quantitative data provided numerical measurements of virological outcomes and their predictors among adults aged 18 years and older who are on second line ART. In contrast, the qualitative data explored the adherence levels of adults living with HIV (PLHIV) taking second line ART, along with other relevant factors. This combination facilitates triangulation, which involves comparing findings from various sources, including medical records, electronic databases, focus group discussions (FGDs) and key informant interviews (KII). The quantitative analysis offered valuable insights into the statistical significance and generalizability of the findings.

Overall, integrating both quantitative and qualitative data in this research allows for a deeper exploration and enhances our understanding of the factors contributing to virological failure, thereby aiding in the development of effective guidelines to address this issue.

3.2.3 Research design

The research design is a blueprint for conducting research systematically and rigorously. It ensures that the study is well-planned, executed and that the research results are valid and reliable (Robert & Brown 2004: 44). To enhance the integrity of the research findings and to obtain full and detail information, this research has used a concurrent mixed method cohort research design in which both qualitative and quantitative data were collected simultaneously, analysed separately over the same period, and interpreted separately (Charles 2009:31). Finally, the findings from both quantitative and qualitative data were combined to draw a more comprehensive conclusion about the study through triangulations of ideas in thematically (Creswell 2011:43; Walliman 2022:101). This approach enabled the researcher to capture a wide range of information using quantitative and qualitative data.

Applying a mixed-methods approach has helped to explore different perspectives, provide a more comprehensive and in-depth understanding, gain a more complete understanding, and provide triangulated findings to the research problem being examined in the study (Nieswiadomy & Bailey 2018:98).

3.3 STUDY SETTING

Study setting represents the actual location and situations in which research data collection were performed (Polit & Beck 2010:568). The study was conducted in a selected health

facility in Addis Ababa, Ethiopia, the capital city of Ethiopia, in the highlands bordering the Great Rift Valley. Founded in the late 19th century by Menelik II. It serves as the country's commercial and cultural hub and is also home to the headquarters of the African Union (AU). Geographically, Addis Ababa is situated at 9º 1' 48" North latitude and 38º 44' 24" East longitude, covering a total area of 527 square kilometers. According to the 2019 population projection, Addis Ababa has an estimated population of 7,823,600. The city operates with three layers of administration: the city administration at the top, 11 sub-city administrations in the middle, and 120 Woredas (Districts) at the bottom. More than 100 functional government-owned health centers are under the Addis Ababa City Administration Health Bureau (Adefris, Damene, and Satyal 2023:4).

Likewise, the city has 13 public hospitals; six are owned under the Addis Ababa Health Bureau (AHB), six under the Ethiopian Federal Ministry of Health (FMO), and two are under the Ministry of Defense and the Federal police commission, providing teaching, specialized, and referral services. According to the list maintained by the Federal Ministry of Health, there are more than 40 privately owned hospitals in Addis Ababa. Out of these, 23 are owned as private general hospitals (https://en.wikipedia.org/wiki/List_of_hospitals_in_Ethiopia).

From these, Zewditu Hospital and Yekatit 12 Hospital Medical College were selected for this study.

Zewditu Memorial General Hospital (Coordinates: 9°1'6"N 38°45'23" E) found in Kirkose Sub City, and Yekatit 12 Medical College Hospital (Coordinates: 9°2'35"N 38°45'35"E), found in Arada Sub City, were selected as the study sites for this research as indicated in Figure 3.

Zewditu Memorial Hospital is located in the central part of Addis Ababa, Ethiopia. It was built and operated by the Seventh-day Adventist Church and was nationalized through the Derg regime around 1976. It is named after Empress Zewditu, who was the cousin and predecessor of Emperor Haile Selassie. It is Ethiopia's leading health facility for treating patients with antiretroviral therapy (ART) and also serves the highest number of HIV patients each month. Zewditu Memorial General Hospital is a tertiary referral hospital and the first hospital that started HIV care and treatment services in Ethiopia in 2003 with the help of the US CDC-Ethiopia. Likewise, Yekatit 12 Hospital Medical College, also known as "Bethsaida" (meaning "house of sick people"), was established in 1923 E.C. It is the second oldest hospital in the country.

These hospitals were selected purposely because both are tertiary referral hospitals with significant experience in HIV/AIDS treatment and programs available in Addis Ababa, Ethiopia. They operate under the City Administration of Addis Ababa Health Bureau (AACAHB), which is part of the federal democratic republic of Ethiopia.

According to the AACAHB HIV program report for June 2023, Zewditu Memorial General Hospital and Yekatit 12 Medical College Hospital had 7,632 and 3,322 PLHIV on ART, respectively. With the same programme-reporting period, 912 and 453 PLHIV were on the second line ART at Zewditu Memorial referral and Yekatit 12 hospital Medical College, respectively.

The study population in research refers to the group of people who are the focus of the study to determine the scope of a particular study and the types of data that can be collected (Christensen, Johnson and Turner, 2015:180-190). The study population for this study were all PLHIV taking second line ART in Addis Ababa, Ethiopia for the quantitative part of the research whereas, hospital-level ART service providers (clinicians, pharmacy professionals, adherence supporters, case managers, and data clerks), MOH and AACAHB level HIV programme managers were encompassed for the qualitative part of the study.

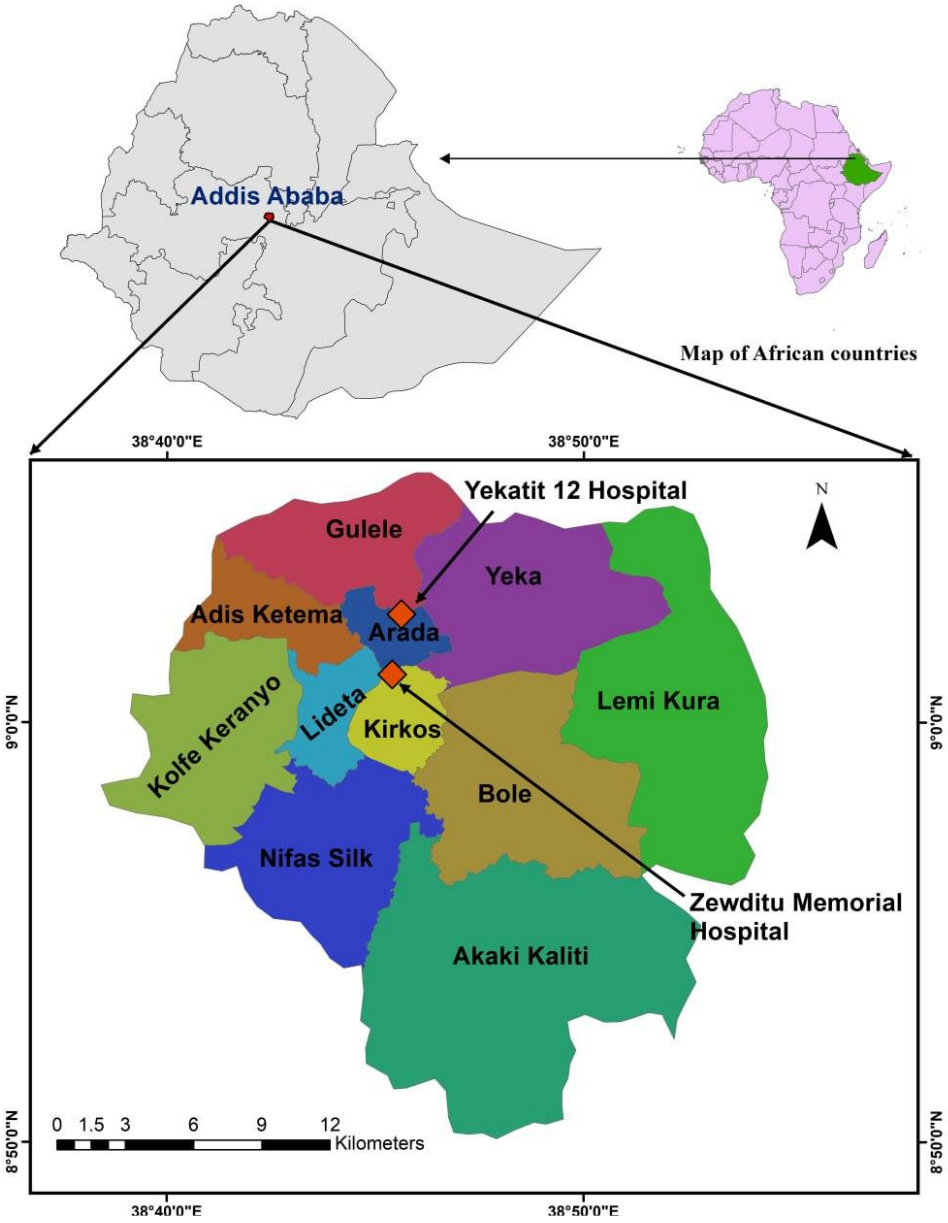


Figure 3. Map of the study site in Addis Ababa, Ethiopia, 2024/2025

3.4 RESEARCH METHODS

Research methods are about the approaches of data collection, summarization, analysis, and interpretation that the study employs for a particular research. The methodology denotes the steps, procedures, and strategies which are used to collect and analyse in a research study (Brink, et al 2018:38). It provides direction on which approaches are more suitable for the type of research being undertaken. In this study, a concurrent mixed methods approach was utilized. In a concurrent mixed methods approach, the researcher has the ability to gather both qualitative and quantitative data simultaneously.

It is particularly useful when the research aims to explore complex social phenomena, understand the underlying processes, or examine the relationships between variables in a multidimensional context (Creswell 2018:105-107). The reason for selecting this approach in this research is to realize a comprehensive understanding of the risk factors that contribute to virological failure among adults 18 years and older taking second line ART and provide guidelines to address the factors. The overall summarized research methods of this study are illustrated in Figure 4.

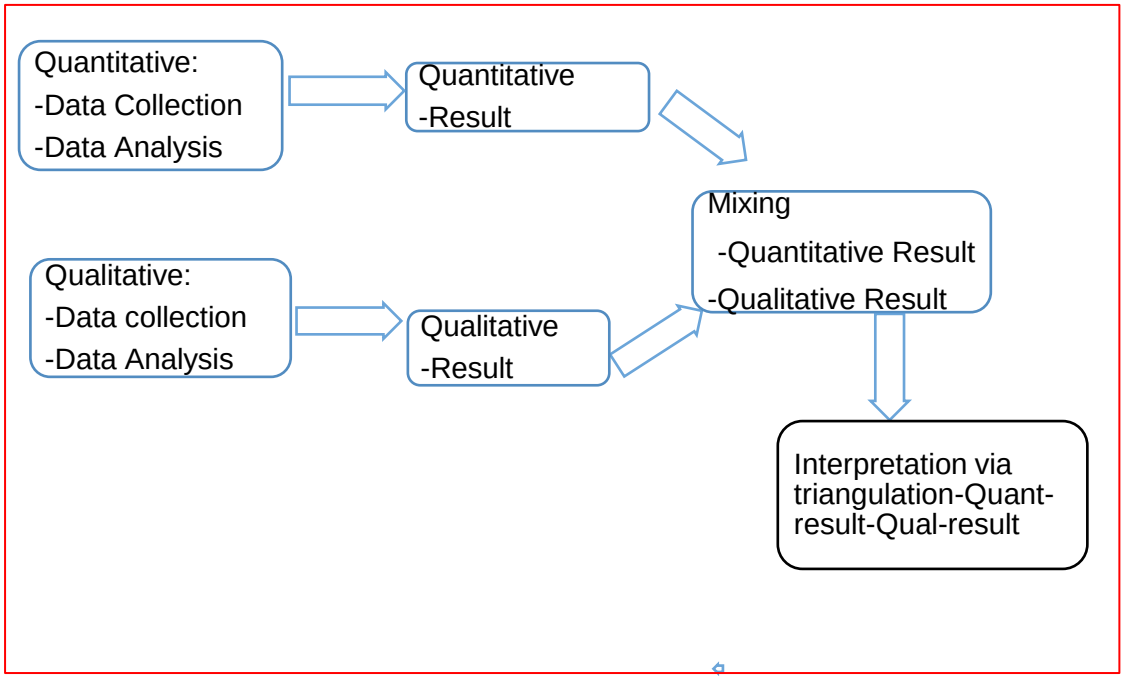


Figure 4. A concurrent mixed method design was used in this study

3.5 Study Population

The study population in research refers to the group of people who are the focus of the study to determine the particular scope of the study and the types of data that can be collected (Christensen, Johnson, and Turner, 2015:180-190). The study population for this research were all PLHIV taking second line ART in Addis Ababa, Ethiopia for the quantitative part of the research study whereas, hospital-level ART service providers (clinicians, ART providers, pharmacy professionals, adherence supporters, case managers and data clerks), AACAHB and sub city level HIV programme managers were sampled for the qualitative part of the study.

The target population was adults aged 18 years and older taking second line ART in Addis Ababa, public hospitals. The accessible population was the group of people that the researcher had reached and recruited to participate in the study (Gliner, Morgan and Leech 2017:162).

Phases in this research

This study comprises of phases: Phase one focuses on quantitative issues and includes three sub-phases: 1a, 1b, and 1c. Phase two is designed for qualitative research and comprises two steps, 2a and 2b, as part of the study methods, which include Focus Group Discussions (FGD) and the Key Informant Interviews (KII)

Phase 1a, 1b and 1c

The sample population for this phase of the study was PLHIV adult's aged 18 years and older taking second line ART in Addis Ababa, Ethiopia. To have a more representative sample and generate a fair distribution, the 369 samples were selected using simple systematic random sampling techniques from the original calculated 371 sample size. Before this, the samples were allocated to the selected hospitals proportionally, based on their respective client loads, as indicated in section 3.6.1.

The researcher used hospital-level PLHIV medical records (ART registration, adherence registration, appointment calendar, and PLHIV chart) and electronic databases. Written permission to access data was obtained from the respective hospital management body as part of the institutional ethical research review approval.

Phase 2a

The sample population for this phase was PLHIV adults aged 18 years and older taking second line ART in Addis Ababa, Ethiopia. In this phase, the participants were selected purposefully.

Phase 2b

The sample population for this phase was hospital-level ART service providers (clinicians, pharmacy professionals, adherence supporters, case managers, and data clerks) and AACAHB and sub-city level HIV programme and adherence managers in Addis Ababa,

Ethiopia. In this phase, the participants were selected purposefully based on their active engagement in the service and invited to participate in the study.

3.5.1 Inclusion and exclusion criteria

In this study, adult PLHIV aged 18 years and older who are receiving second line Antiretroviral ART between 2018 and 2022 for more than six months, undergone at least two follow-up VL tests, and have complete medical records and data in the electronic database at Yekatit 12 Hospital Medical College and Zewditu Memorial General Hospital were included. Added to this, PLHIV willing to participate in KII, ART service providers, adherence supporters, HIV program managers working at the AACAHB and at the sub-city who were volunteer to participate in focus group discussions (FGDs), were also included.

The study excluded PLHIV who are on first-line ART, as well as those who are younger than 18 years old. Individuals with incomplete medical records, unwilling to participate in KII or FGD, and individuals other than ART service providers or program managers working at the AACAHB sub-city were also excluded.

3.6 SAMPLING TECHNIQUES AND SAMPLE SIZE DETERMINATION

The summary of the research sample size determination procedures (plan), sampling techniques and data collection for this study are described in Table 1 using two different phases, which were conducted simultaneously (i.e., Phase one composed of 1a,1b,1c, and Phase two composed of 2a, and 2b).

Table 1. Overview of the study method process

Objective	Phase/stage	Setting, Population	Data collection tool	Sampling Method	Sample Size	Data analysis
Objective 1 (To determine the prevalence of second line ART virological failure)	**Phase 1a**	Record of PLHIV aged 18 years and older who have been taking second line ART at Zewditu Memorial General Hospital and Yekatit 12 Hospital Medical College during the cohort 2018-2022.	Checklist/ Records Review Form, Electronic Data base Kobo Toolbox	Simple Random Sampling (SRS), Purposively	371	Descriptive statistics using SPSS version 28, R, STATA 18
Objective 2 (To identify contributing risk factors for unfavourable treatment outcomes **)**	**Phase 1b**	Record of PLHIV aged 18 years and older, Addis Ababa, Ethiopia				Multivariate analysis using SPSS version 28
Objective 3 (To assess the time to switch to third-line ART **)**	**Phase 1c**	PLHIV aged 18 Years and older, Addis Ababa, Ethiopia				Survival analysis using SPSS version 28
Objective 4 (to explore the factors that affect the adherence**)**	**Phase 2a**	PLHIV age 18 and greater, Addis Ababa	KII guide	Non-probability purposive sampling	20	Thematic analysis using ATLAS.ti. Software
	Phase 2b	ART service providers and HIV programme managers working at the MOH and AACAHB	FGD guide	Non-probability purposive sampling	3	Thematic analysis using ATLAS.ti. Software

For the qualitative component of this study, the non-probability purposive sampling technique utilized to recruit participants based on their active engagement and roles in the HIV program, with their voluntary participation requested. Pertinent information collected from participants using the KII and FGD guide until data saturation was achieved. To safeguard the credibility of the research results, observation and field notes were summarized and utilized. The interviews and FGDs were recorded as this helped the researcher to develop

notes, which assisted during the analysis of codes. The utilized checklists, as well as the interview guides, were pre-tested, and appropriate revisions were made prior to data and information gathering.

3.6.1 Sample size:

Phase 1a.

To determine the sample size, the following assumptions were considered, taking the 12.22% prevalence of second line ART Virological failure from a study conducted in Addis Ababa (Zakaria et al 2022:5), precision (D) 3.5%, and CI of 95%, the sample size for the study after adding 10% contingency using below formula became 371.

$n = \underline{Z^2\alpha/2\ p(1-p)}/d^2$ (Z= 1.96 with 95% CI, P= 12.22%, d= 0.035).

Phase 2a

In qualitative research, determining the sample size until data saturation is reached is a common approach. Data saturation means the point in research data collection and analysis when new data no longer yields significant or novel insights or themes, indicating that theoretical saturation has been achieved (Tracy 2020:196). As there is no similar research conducted in Ethiopia, the researcher used a similar study conducted in Uganda as a reference (Bukenya et al 2019:3). In this study, twenty (20) PLHIV taking second line ART were interviewed using a key informant interview guide.

Participants who complied with the inclusion criteria were selected purely for the KII and assigned to the respective hospitals where the research was conducted. The KII were conducted at Hospital level where the patients are following their HIV care and treatment.

Phase 2b

In addition to the KII, the researcher has conducted three FGDs to address objective four: to explore the factors that affect the adherence of PLHIV aged 18 years and older taking second line ART in Addis Ababa, Ethiopia. In this phase, three FGDs (two with hospital-level ART service providers and one with the HIV programme managers of AACAHB and subcities) composed of five to seven individuals were conducted. Focus group participants were invited to be part of the study based on the inclusion criteria after getting their written consent. The

two FGDs with Hospital level service provider were conducted in their respective Hospitals and the other one FGD with the HIV program manager was conductd centrally.

3.6.2 Sampling techniques

The probability sampling method and systematic random sampling (SRS) techniques were employed. Figure 5 illustrates the probability proportional allocation of the sample for each hospital, where 249 and 122 samples were distributed to Zewditu Memorial Hospital and Yekatit 12 Hospital Medical College, respectively.

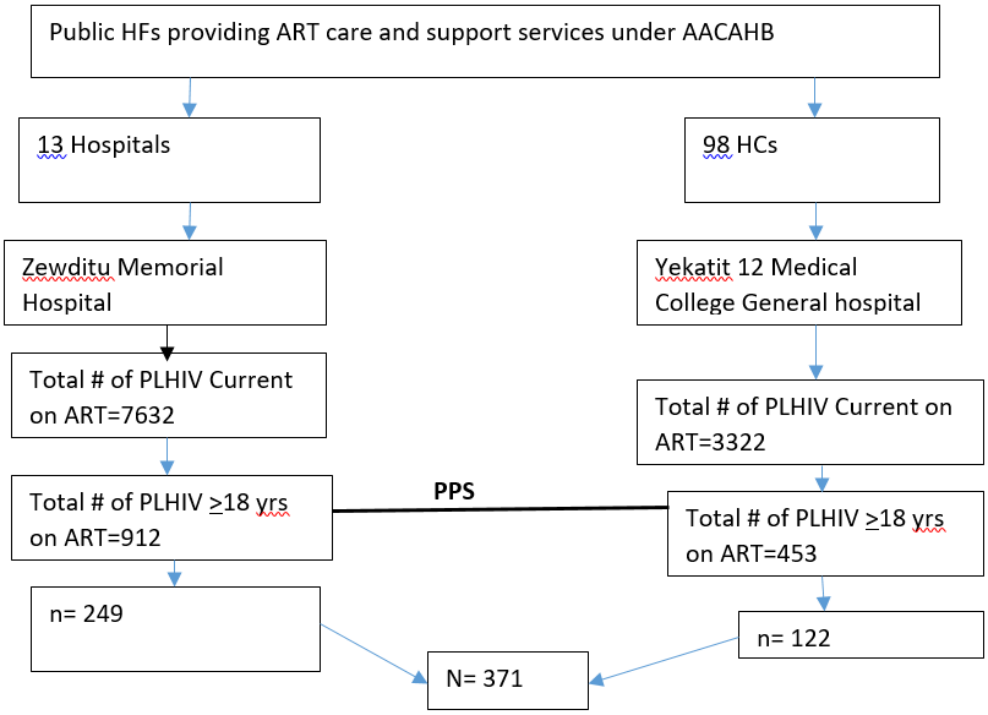


Figure 5. The population proportion sampling technique used in this study

3.7 DATA COLLECTION METHOD AND PROCEDURES

Data collection is the systematic process of gathering and measuring information on specific variables in a structured way (Locharoenrat 2004:108). For this research, no data has been collected before obtaining ethical approval from UNISA and the City Administration of Addis Ababa Health Bureau (AACAHB) Institutional Review Board/IRB committee. This research

involved numerical and non-numerical data collection using quantitative and qualitative methods.

Phases 1a, 1b, & 1c

The data were collected using a structured checklist (Appendix 7), which lasted from August 20, 2024, to November 25, 2024. It contained all the list of objective 1 variables which addressed, and the data sources were the completed PLHIV medical record and the electronic database; encompasses, the patient follow up card, ART intake form, ART follow up form for patients with high viral load, High Viral load form, and EAC observation checklist. The checklist had been pretested using 5 % of the total data, and the pretested data were not included in the final analysis. The researcher simply used this for the necessary revision and improvement of the final used data collection tool and to ensure that no necessary data was missed. To ease the data collection process and for data quality monitoring purposes, the researcher converted the questionnaires into the Kobo toolbox app, a free cloud-based data collection tool for real-time research data. Accordingly, we collected our quantitative research data using the Kobo toolbox.

In each hospital, one supervisor and two data collectors were recruited for the task, and the selection was based on their work experience and educational background. They are senior public health professionals and have recent training on HIV ART consolidated guidelines and are actively working on the program. A one-day orientation was given to the supervisors and the data collectors about the data collection process and procedure by the researcher. All supervisors and data collectors who engaged in this research had signed a confidentiality agreement. The role of the researcher in this phase was provide training for the data collector and supervisors, follow the data collection conducted as planned and confirm the methodological compliance, ensure adherence to ethical protocol, and the daily data quality.

Phase 2a

The information was collected through the KII guide (Appendix 3). The key informants were PLHIV adults aged 18 Years and older taking second line ART from 2018 to 2022. The KII guides were prepared in English, which was then translated into the Amharic language to get full information, which was transcribed back into English (Bloomfield and Fisher

2019:11). Written informed consent was also sought from the key informant participants, who participated voluntarily.

In each hospital, one supervisor and one interviewer were recruited for the task. The supervisors and interviewers were selected based on their work experience and educational background. The interview guide provided them with a one-day orientation to ensure a similar understanding and data quality. All supervisors and data collectors who were engaged in this research had to sign a confidentiality agreement.

KIIs sample selection

In qualitative research, determining the sample size until data saturation reached is a common approach. Data saturation refers to the point in data collection and analysis when new data no longer yields significant or novel insights or themes, indicating that theoretical saturation has been achieved (Tracy 2020:196). As there is no similar research conducted in Ethiopia, the researcher used a similar study conducted in Uganda as a reference (Bukenya et al 2019:3). Patients who meet the inclusion criteria has been recruited for the study during their regular Hospital follow up visit.

In this study, the plan was to conduct interviews with twenty (20) PLHIV taking second line ART. However, data saturation was achieved with 15 (75%) interviews completed, using a key informant interview guide. Participants who met the inclusion criteria were selected voluntarily. Then, purely for the KII, and assigned to the hospitals where the research was conducted.

FGD sample selection

In addition to the KII, the researcher has conducted FGD to address objective four. In this phase, three FGDs (two with hospital-level ART service providers and one with the HIV programme managers of AACAHB and sub-cities), composed of five to seven individuals, were conducted.Focus group participants were invited to be part of the study based on the inclusion criteria and their active engagement in the HIV program. Also, they signed a written consent to be part of it.

Phase 2b

The data were collected through the FGD guide (Appendix 6). The focus groups included health facility-level ART service providers and AACAHB and sub-city programme managers. The FGD guides were prepared in English and then translated into the Amharic language to get full information, which was then transcribed back into English ((Bloomfield and Fisher 2019:11). Informed consent was also obtained from the focus group. In each hospital, one supervisor and one interviewer were recruited for the task. The supervisors and interviewers were selected based on their work experience and educational background. A one-day orientation was given to supervisors and interviewers on the interview guide. All supervisors and data collectors who were engaged in this research had signed a confidentiality agreement.

3.8 DATA ANALYSIS

A research data analysis is a very critical part of the research process, as it allows researchers to make sense of the data they have collected and to draw meaningful conclusions from it. There are many different types of data analysis methods, and the most appropriate method varies depending on the research question and the type of data being analysed **(**Brink et al 2018:176-177).

Quantitative data analysis (Phase 1)

Phase 1a, 1b, & 1c

This phase aimed to address research objective 1. The data collected were entered and analysed by SPSS version 28 and STATA version 18. Descriptive type of research statistics, comprising counts, means, medians, percentages, ranges, standard deviation, proportions, and confidence intervals, were calculated to estimate the proportion of second line ART virological failure in the study population.

Phase 1b

This phase aimed to address research objective 2. The data collected were entered and analysed by SPSS version 28 and STATA version 18. For the second objective, which states the contributing factors for unfavourable treatment outcomes among PLHIV in second line ART aged 18 Years and older. Multivariate analyses, such as logistic regression and Cox

regression with an adjusted model, were fitted to control for potential confounding factors and to identify independent predictors of unfavourable treatment outcomes. A survival analysis, and Kaplan-Meier graph, and a life table analysis have been done using STATA to determine the probability of virological failure at different intervals of time.

Phase 1c

This phase aimed to address research objective 3. The data collected were entered and analysed by SPSS version 28 and STATA version 18. Survival analysis was done to analyse the time from initiation of third-line ART to second line ART Virological failure using the Kaplan-Meier estimator. It's a powerful programming language used for statistical calculation and data analysis.

Qualitative data analysis (Phase 2)

This phase has mainly been designed and address the research objectives 4. The information was analysed using the Atlas.ti software (Creswell 2013:245). Data was collected through interviews using semi-structured KII guides. The transcribed data was imported into Atlas.ti software, labelled to categorise the patterns and themes in the research data that help develop a deep understanding of factors that affect the adherence of adults with PLHIV who are taking second line ART, and visualisation of data to display and interpret that data accordingly.

In a summary

A continuous research variables were expressed as medians with interquartile ranges (IQR) as the data were non-normally distributed. Categorical variables were compared with second line ART virological failure outcomes using Chi-square or Fisher's exact tests, as appropriate, and were reported using frequencies and percentages. The chi-square test was performed to assess the population distribution associated with virological failure among categorical variables and to compare the medians of continuous variables with the P-values provided.

A Cox regression, also known as proportional hazards regression, was used to predict the likelihood of an event (virological failure) occurring within a specific time frame for survival

analysis. Additionally, a multiple logistic regression and cox-regression model was employed to assess significant associations between demographics, clinical factors, laboratory variables, and virological treatment failure.

Risk factors associated with virological failure at a P-value < 0.20 in crude bivariate regression were fitted in a final multivariate model to identify predictor variables associated with failure. Adjusted hazard ratios (HR) and odds ratios (OR), along with their 95% confidence intervals (CIs), served as measures of association. Factors associated with virological failure at a two-sided P-value < 0.05 were considered statistically significant.

Our recent study examined the survival estimation probability of virological failure using a statistically validated visual method. To achieve this, we fitted a graphical illustration using Kaplan-Meier survival estimates, and Log-Rank tests to compare survival differences among various categories of different variables. This approach constructs a survival curve that illustrates the proportion of individuals experiencing virological failure who survive at different time points after enrollment in second line ART treatment. Each time interval represents the survival probability, calculated as the number of subjects surviving divided by the number at risk of virological failure.

A multivariate Cox regression model was employed to measure the risk of virological failure and to identify significant risk predictors. The researcher consider variables with a P-value < 0.05 as statistically significant predictors of virological failure.

All statistical analyses, including data entry and cleaning, were performed using STATA (V.18, STATA Corp, College Station, Texas, USA), SPSS version 28, and R for Windows for quantitative data, while Atlas.ti version 24 software was used for the analysis of qualitative data.

In our study, we used hazard ratios (HR) and odds ratios (OR) as measures in statistical analysis: the HR compares the rate of events occurring at any point in time in two different groups, indicating how quickly two survival curves diverge, focuses on the timing of events; used in survival analysis involving time-to-event data. In contrast, OR was employed to quantify the odds of an event occurring in one group of the study compared to another without accounting for time.

In summary, in the study, the hazard ratio (HR) was employed in the Cox regression analysis, survival analysis, and Kaplan-Meier curve, while the odds ratio (OR) was employed in the logistic regression model.

3.9 DATA ANALYSIS INTEGRATION

After analysing the quantitative and qualitative data separately, the findings from both analyses have been integrated and triangulated to draw a more comprehensive conclusion and develop more effective recommendations.

3.10 ENSURING RIGOUR

Validity and reliability are the important research concepts that refer to the accuracy and consistency of the research methods used to collect and analyse data. Validity of the study refers to the extent to which a particular research study measures what it is intended to measure. It is about whether the results of a study are truthful and reflect the real world. At the same time, reliability refers to the consistency of the results of a research study in which the results of a study would be the same if the study were conducted again (Bagozzi, Youjae and Phillips 2017:12,15). In this study, the validity and reliability of the data were ensured by using existing PLHIV data from individual charts, registrations, and electronic databases. The study also used an adequate sample size, pre-tested the checklist, and obtained strong inclusion and exclusion criteria. These measures have helped to prevent selection bias.

According to Polit and Beck (2010:122), reliability refers to the degree to which data can be trusted to be accurate and consistent. To ensure the reliability of quantitative data, data collectors and supervisors receive a one-day training to familiarize themselves with data collection tools. In addition to training, the data collection tools were pre-tested to incorporate any missing variables. In addition, regular data quality checks were being conducted.

According to Polit and Beck ‘Qualitative reliability refers to consistency between the study and researcher”. In this study, the trustworthiness of the qualitative research data was ensured by carefully documenting the data, checking the accuracy of the transcription, regularly communicating with data collectors and supervisors, and checking and cross-checking the coding of variables. Also, we used a real-time data collection tool, such as Kobo Toolbox. To ensure the credibility of the data, the supervisors and the researcher have spent

more time for close follow-up during the data collection process. To ensure the dependability of the data, the data collection tools were reviewed, pre-tested, and commented on by the area experts. Moreover, the data collectors & supervisors were also trained on the data collection tool.

3.11 ETHICAL CONSIDERATION

In research, the ethical considerations are the very most important aspects because they protect the rights and welfare of research participants. These can comprise informed consent, confidentiality, no harm, benefits, and justice (Burn and Grove 2004:327).

The process of obtaining the ethical approval specific to this research has been illustrated in Figure 6.

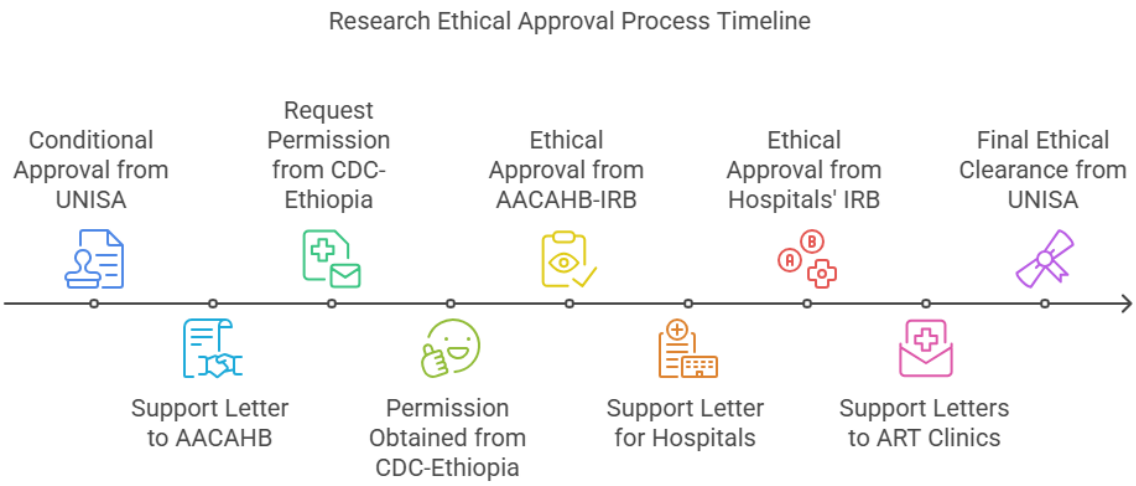


Figure 6. Illustration of the process to obtain the research ethics approval

As indicated in Figure 6, this research went through a series of rigorous ethical approval processes. Accordingly, we got approval from UNISA: CREC Reference #: 20265433_CREC_CHS_2024. Then a support letter to AACAHB received from UNISA Ethiopia coordination office (with reference #: UNISA-ET/KA/ST/29/23-02-2024). Following, this, we secure ethical clearance from Addis Ababa Health bureau Ethical clearance committee (with reference #: A/A/14641/227) and also from the two study selected hospitals of the institutional ethics and review boards, Zewditu memorial referral hospital and Yekatit

12 hospital medical college research ethics committee (with reference #:439/24). Also, the research applied the following basic research ethical protocols through the research process:

Permission: once we had the research ethics, the researcher was granted permission by the ART clinic focal person of the study sites before delving into conducting the study. The researcher assured the ART focal persons of the study sites of ensuring the confidentiality and anonymity of the study participants and clearly explained the objectives of the study, including its aims, benefits, and significance to the participants.

Research study participants were made aware that their involvement in the study was completely voluntary and that they might stop at any moment. They were told that their treatment and services from the hospitals would not suffer in any way if they chose not to participate in the study.

Moreover, the researcher had been ruled by the ethical principles of autonomy, beneficence, justice, and non-maleficence, which are the very essential principles that offer a framework for researchers to conduct their work responsibly and ethically, as described below:

Autonomy describes people's freedom to choose whether or not to participate in research. This includes the right to know the risks and rewards of the study, the freedom to leave the study at any moment, and the freedom to decline to take part in the study entirely (Schmidt and Brown 2019:219).

In this research, to demonstrate the self-determination of the study participants and respect for human dignity, especially in the qualitative part, the study participants were assured their self-determination and freedom to make their own decisions about their voluntary participation in the research.

Informed Consent: The researcher contacted the study participants and informed them of the purpose of the study. Participants were informed that they participated voluntarily and could refuse to participate or withdraw from the study if they wished. In this research, the participants provided their informed consent. This was accomplished by respecting the participants, giving them comprehensive information about the study, and allowing them the option to withdraw from the study at any point. The data collectors ensured and acquired

signed written informed consent from the participants, which is a document indicating that the participants willingly agreed to take part in the study.

The researcher did not need to obtain permission, and it was not necessary to obtain permission to collect data from medical records and electronic databases from PLHIV as a means of “first mouse of the horses”. This is because, during our data collection time, our recruited study variable of 369 PLHIV and PLHIV did not have a follow-up visit to the hospitals during the data collection period. Instead, the researcher obtained permission from hospital managers on behalf of the clients to collect the data as approval of the Ethical request. On top of these, the researcher ensured that the data were collected and used in a way that protected the privacy and confidentiality of PLHIV.

Beneficence refers to trefers to the duty placed on researchers to advance the welfare of study participants. This entails limiting the research's risks while optimizing its possible advantages. Keeping the participants safe is another aspect of it (Schmidt and Brown 2019:89).

The researchers in this study have been taking precautions to ensure the privacy of the participants' data, both qualitative and quantitative. Employing coding and limiting access to the documents to the researcher and those directly involved in the project, this made sure that no participant's names or other identifying information would appear anywhere on the records. The research-associated documents and materials were also kept locked.

Justice refers to the equitable and fair distribution of research risks and benefits. Accordingly, researchers must choose participants fairly and make sure that the advantages of the study are distributed equally(Schmidt and Brown 2019:89).

Purposive sampling was employed by the researcher for the study's qualitative component. This indicates that the qualified individuals who fulfilled the requirements were specifically chosen. To ensure equal representation of both groups in the study, the researcher in this instance applied the identical qualifying requirements to both males and females. The researcher shows respect to each participant throughout the interviews. The researcher used a k^{th} value of impartial systematic random sampling for the quantitative portion without any potential bias.

Non-maleficence refers to the duty placed on researchers to protect their subjects from harm. This implies that researchers should take all appropriate precautions to reduce research risks and safeguard study participants(Christensen, Johnson, and Turner, 2015:121).

Consequently, this research did not include any form of intervention or manipulation; individuals involved were not subjected to any extra risks as a result of their participation in this study. In addition, the data collected during the study has been stored in a file that does not disclose the names of the study participants, instead using the unique ART identification numbers for quantitative data, while a code number was assigned to each participant for qualitative data.

This information was not disclosed to anyone except for the principal investigator and was securely locked and password-protected. Prior to participating in the research study, participants provided informed consent for the qualitative data collection. This means they were informed about the study's purpose, the potential risks and benefits of participation, and their right to withdraw from the study at any point.

As a result, participants had the chance to ask questions and decide against participating in the research if they wished. The principal investigator ensured that all participants were treated equitably and that no group or individual faced disproportionate burdens from the research.

Furthermore, the study did not involve any invasive procedures.

Risk: In research, there are several hazards associated with research ethics. The following are some of the most frequent risks: participant injury, including psychological and bodily harm; confidentiality breach, which may occur if data are not kept private; and coercion or undue influence, which may occur if the researcher coerces the participant into taking part in the study. Participants who are not adequately informed may not give their informed permission, and researchers who have a financial or personal stake in the study's outcome may have a conflict of interest (Creswell 2013:134).

The data collection started after securing the ethics committee's final approval and clearance from the UNISA and AACAHB IRB. The research participant gave their informed consent

after being fully informed about the study's objectives, assured that the researcher would take precautions to protect the privacy of the data, and told them that they could withdraw from the study at any time and that they could report anything that seemed unethical. Additionally, the researcher also allowed the participant to ask any questions and clarify all the questions raised properly.

Confidentiality: In this research, participant confidentiality was ensured by obtaining informed consent from participants. The participants had a clear understanding of the potential risks and benefits of their participation in the study. Participants' data were collected and stored in a way that maintains anonymity. This was achieved using a unique ART number and pseudo name for participants. Participant electronic data and information were password-protected, and information in the hard copy was kept in a locked cabinet.

On top of these, individuals involved in this research (data collectors and supervisors) signed confidentiality agreements and limited access to research data only to those who were involved in this research. Communication was secured in private room when interacting with participants during interview. When reporting research findings and aggregating data to prevent individual participants from being identified, all members of the research team were trained on the importance of having very secure confidentiality.

3.12 CONCLUSION

Note that this chapter mainly focused on and described the overall research materials and methods used in this recent research study. It covers the research settings, research paradigm, research design, research sample size determinations, sampling techniques, data collections, study variable analysis, data quality assurance methods and research ethical considerations.

CHAPTER 4

RESEARCH RESULTS

4.1 INTRODUCTION

To ensure clarity and coherence in the presentation of information, this thesis includes a subchapter dedicated to summarizing the research findings. The first results section focuses on findings drawn mainly from the quantitative data and is followed by insights gathered from qualitative data sources from focus group discussions and the in-depth interviews with key informants. Then, after the findings from both qualitative and quantitative data have been triangulated to provide a comprehensive overview, allowing for a broader understanding of the overall situation.

4.2 DESCRIPTION OF QUANTITATIVE DATA

In this study, out of the calculated sample size of 371, a total of 369 records of PLHIV who were receiving second line ART were included second line representing a 99.5% response rate of the calculated sample size. Among the summarized records, 191 (52%) were male, and their ages ranged from 20 to 74 years, with a median age of 44 (32–52) years. Additionally, 185 (50%) of the records of PLHIV had never married, while 60 (16%) did not disclose their HIV status to others.

Furthermore, one-third of the records of PLHIV had an education level below primary school, as illustrated in Table 2.

Table 2. Socio-demographic characteristics of records of PLHIV in Addis Ababa, Ethiopia, 2018-2022 (N=369)

Variable	Category	Number	Percent (%)
Age (in range years)	18-29	84	23
	30-39	47	13
	40-49	112	30
	50-50	94	25
	60-74	32	9
Sex	Male	191	52
	Female	178	48
Marital Status	Never Married	185	50
	Married	123	33
	Divorced	25	7
	Separated	6	2
	Widowed	30	8
Educational status	No formal education	31	8
	Primary	107	29
	Secondary	190	52
	Tertiary	41	11
Patient linked from	Intra facility	293	79
	Other facility	76	21
Disclosure status of HIV	Disclosed	309	84
	Not Disclosed	60	16
HIV status of spouse(n=123)	Non-reactive (Negative)	20	16
	Reactive	45	37
	Unknown	58	47
Spouse started ART (n=45)	Yes	44	98
	No	1	2

4.3 BASELINE CLINICAL AND LABORATORY CHARACTERISTICS OF STUDY PARTICIPANTS

This section provides more details about the clinical and laboratory background information of records of PLHIV during the final phase of first-line antiretroviral therapy (ART) before they transitioned to second line ART as part of the study. It provides insight and more clues into the previous management of these cases and how those cases were handled.

Accordingly, more than half of the study records of PLHIV, 206 (55.8%), were classified at the third stage based on the WHO clinical stage. Additionally, 294 (79.2%) had a viral load above 1,000 copies/ml. Meanwhile, viral load assessments were not conducted for 75 (20.3%) of records of PLHIV, who instead met immunological failure criteria, and 137 (37.1%) records of PLHIV had a history of lost follow-up, as detailed in Table 3. Likewise, among the ART drugs dispensed, 1c and 1e were the most frequently prescribed drugs during both the

initial and final first-line regimens prior to switching to the second line, as illustrated in Table 3 and Figure 7.

Table 3. Baseline clinical and Laboratory information of study records of PLHIV before transitioning to second line ART, in Addis Ababa, Ethiopia (N=369).

Variable	Category	Frequency	Percent (%)
WHO clinical stage	I	83	22
	II	33	9
	III	206	56
	IV	47	13
Functional status	Working	96	26
	Ambulatory	83	22
	Bedridden	190	52
CD4 level	<50 cell/mm3	59 (16)	16
	50-100 cell/mm3	109 (29.5)	29
	100-350cell/mm3	176 (47.7)	48
	>350 cell/mm3	25 (6.8)	7
1st line regime before switch to 2nd line	1a (d4T+3Tc+NVP)	0	0
	1b (d4T+3TC+EFV)	0	0
	1c (AZT+3tC+NVP)	87	24
	1d (AZT-TC-EFV)	61	16
	1e (TDF +3TC +EFV)	143	39
	1f (TDF+3TC+NVP)	49	13
	1g (ABC + 3TC +EFV)	8	2
	1i Others	3	1
	1j (TDF+3tC+DTG)	17	5
	1k (AZT+3TC+DTG)	1	0.5
History of Lost to follow up	Yes	137	37
	No	232	63
OI prophylaxis	Yes	335	91
	No	34	9
Type of 1st line ART failure	Virological	294	80
	Immunological	75	20
	Clinical	0	0

The types and frequency of first-line antiretroviral therapy (ART) drugs taken by adult HIV-positive patients in Addis Ababa, Ethiopia, during the final phase of their follow-up before switching to second line treatment were depicted in Figure 7. This data pertains to patients who experienced treatment failure with second line ART of adult HIV-positive patients at selected hospitals in Addis Ababa, Ethiopia, 2018-2022 (n=369).

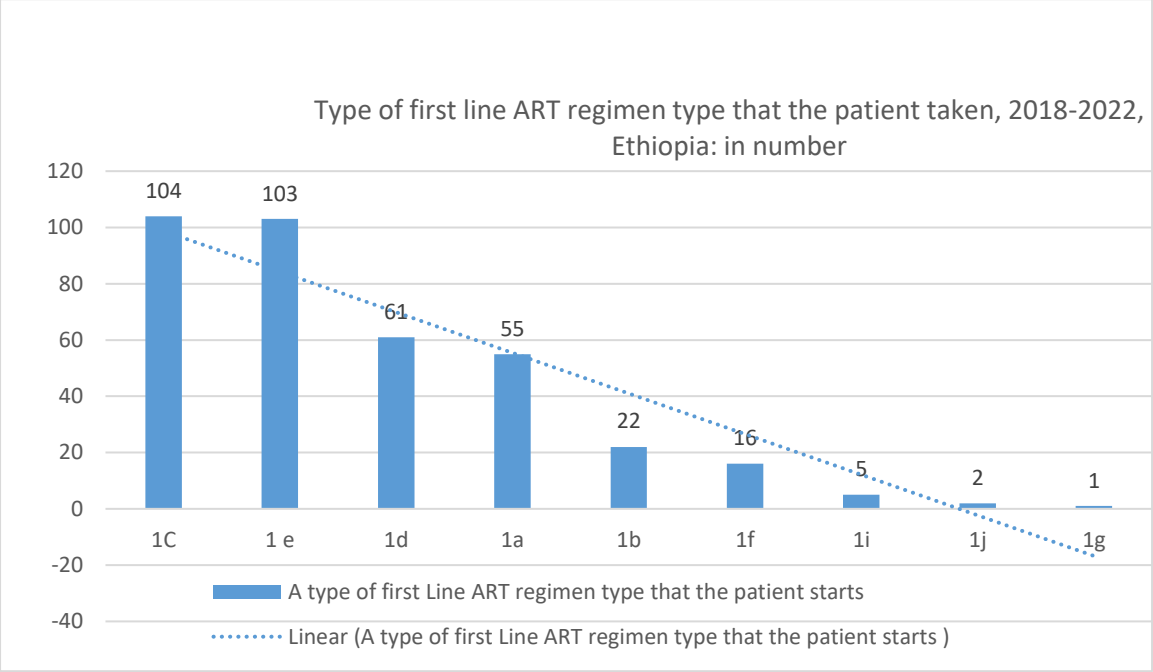


Figure 7. Type of first line ART regimen that the records of PLHIV took.

4.4 FIRST-LINE ART REGIME CHANGE EXPERIENCE IN ADDIS ABABA, ETHIOPIA

As part of this research, we examined the trend and frequency of the regimen changes among enrolled patients who took first-line antiretroviral therapy (ART) in Addis Ababa, Ethiopia, during their follow-up prior to switching to second line treatment, as part of background information to link and there could be a potential contributor for current treatment success. A review of client charts revealed that out of 369 records of PLHIV, 144 had experienced at least one change in their treatment follow-up regimen.

Regimen changes can occur for various reasons, and many clients have undergone such changes to improve the success of their treatment. Table 4 presents the types and frequencies of the first-line regimens that patients initiated upon enrollment in ART care, compared to the regimens in use at the final stage of their follow-up before transitioning to second line ART.

Table 4. First-line ART regimen at initiation and at final visit before switching to second line ART in selected Hospitals in Addis Ababa, Ethiopia (2018-2024, N=369)

	Type of 1st line regimen		
Name of 1st line ART	**at the start or during enrolment (Initiating)**	**At the switch to the 2nd line (Last visit)**	**Remark**
	Frequency (%)	**Frequency (%)**	
1a (d4T+3Tc+NVP)	55(14.9)	0 (0)	Since 2017, it has not been the recommended regimen
1b (d4T+3TC+EFV)	22 (6)	0 (0)	
1c (AZT+3tC+NVP)	104 (28.2)	87 (23.6)	
1d (AZT-TC-EFV)	61 (16.5)	61 (16.5)	
1e (TDF +3TC +EFV)	103 (27.9)	143 (38.8)	
1f (TDF+3TC+NVP)	16 (4.3)	49 (13.3)	
1g (ABC + 3TC +EFV)	1 (0.3)	8 (2.2)	
1i Others	5 (1.4)	3 (0.8)	
1j (TDF+3tC+DTG)	2 (0.5)	17 (4.6)	
1k (AZT+3TC+DTG)	0 (0)	1 (0.3)	

4.5 BASELINE INFORMATION OF THE 2ND LINE ART REGIMEN DISPENSED

Among the prescribed second line ART drugs, 2h and 2f were the most frequently dispensed drugs, as depicted in Table 5, which detailed the types and frequencies of dispensed ART drugs among ART drugs among the records of PLHIV experiencing second line ART regimen failure at the selected hospitals, 2018 to 2022 (n=369), Table 5.

Table 5. Type of second line ART regimen taken among PLHIV in selected Hospitals in Addis Ababa, Ethiopia, 2018-2022 (N=369)

Type of 2nd line regimen	Frequency	Percent
Other adult 2nd line	82	22.2
2e (AZT+ 3TC+LPV/r)	16	4.3
2f (AZT + 3TC + ATV/r)	83	22.5
2g (TDF+3TC+ LPV/r)	33	8.9
2h (TDF+3TC+ ATV/r)	132	35.8
2i (ABC+3TC+LPV/r)	22	6.0
2k (AZT+3TC+DTG)	1	0.3
	369	**100**

4.6 REASONS FOR SECOND LINE ART REGIME CHANGE IN ADDIS ABABA, ETHIOPIA

Among second line ART regimens, changes may occur for various reasons, including treatment failure, adverse drug effects, and inadequate adherence. Additionally, during treatment follow-up, clients may experience regimen changes even without encountering

treatment failure. To optimize treatment effectiveness, the selection of the most preferred second line therapy is often based on the latest clinical progress and the client's previous first-line regimen history. Although not highly recommended, clients may alter their regimen drugs after being admitted to a specific regimen type, which may not be widely available in resource-limited settings, while considering a better quality of life. These regimen changes could involve substitutions or switches.

In the follow-up of HIV treatment, there could be various reasons for changes in the treatment regimen among clients receiving ART. In this study, of the 369 enrolled HIV-positive clients on second line ART, 72 (20%) had well-documented drug regimen changes. The most common reason for these changes was drug toxicity or side effects, 47 (65%), followed by the availability of new drugs at healthcare facilities, 11 (15%), as illustrated in Figures 8 and 9.

The pie chart (Fig. 8) illustrates the extent of regimen changes among second line ART treatment failures in adult HIV-positive patients at selected hospitals in Addis Ababa, Ethiopia, from 2018 to 2022 (n=369).

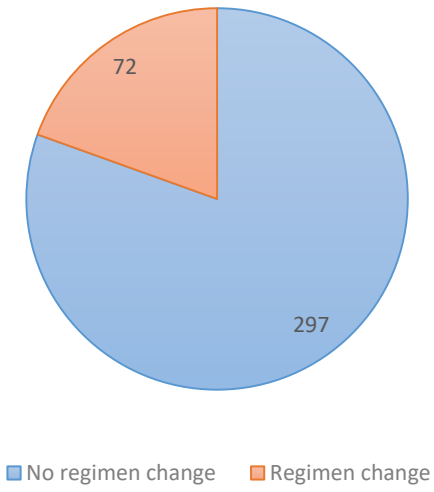


Figure 8 A. Second line ART regimen changed experienced among enrolled patients, in Addis Ababa, Ethiopia

Regimen changes due to toxicity are often quite necessary to enhance adherence, to improve treatment outcomes, and to prevent long-term health impediments. In resource-limited settings, where alternative drugs may not always be readily available, careful clinical

assessment and prioritization of tolerable yet effective treatment options are critical to maintaining viral suppression and preventing ART failure. In this study, ART side effect or drug toxicity is the top reason for second line regimen change, as indicated in Figure 9.

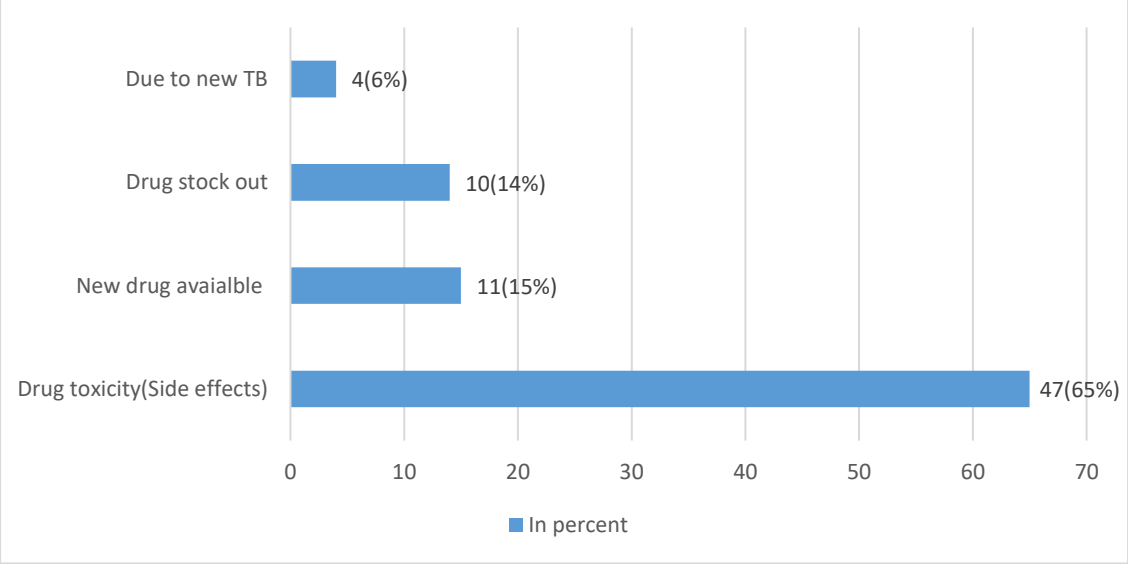


Figure 9. Reason for a second line ART regimen change among PLHIV in Addis Ababa, Ethiopia.

4.7 OPPORTUNISTIC INFECTIONS AMONG SECOND LINE ART

The role of opportunistic infections (OIs) in the progression of HIV and the decline in the quality and effectiveness of treatment is a critical issue that should not be overlooked. Their impact on the success of treatment programs is significant. In this study, we examined the prevalence of OIs among HIV-positive individuals undergoing second line antiretroviral therapy (ART). Out of 369 records of PLHIV, 48 clients developed OIs during their second line treatment. Tuberculosis was the most common, 19 (39%), followed by herpes zoster, as shown in Figure 10.

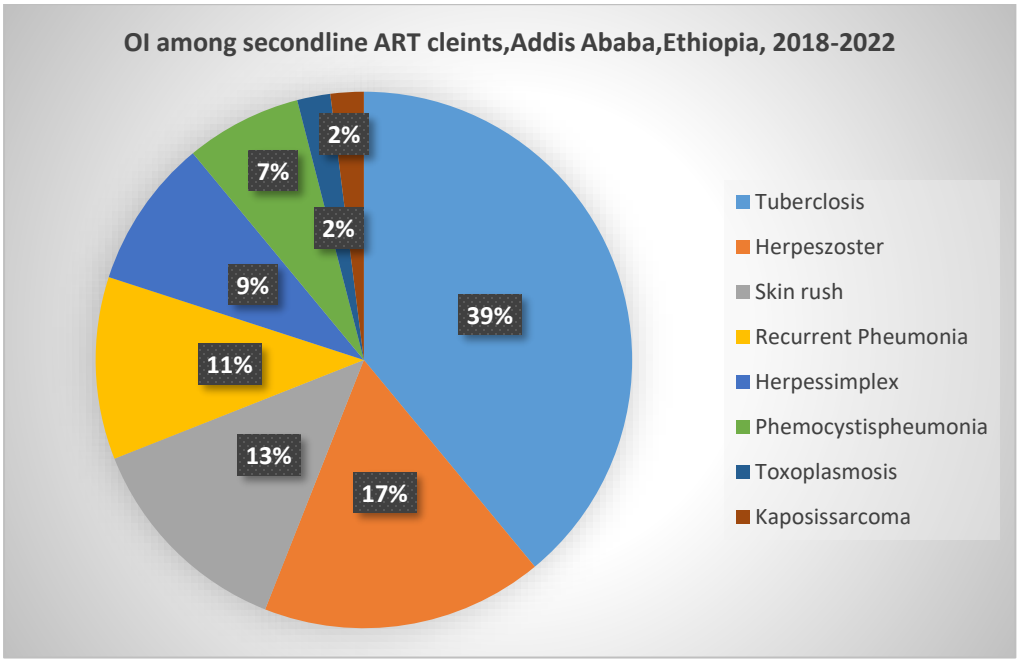


Figure 10. Type of OI developed among PLHIV taking second line ART in selected Hospitals in Addis Ababa, Ethiopia, 2018-2022

4.8 TIME TO OI DEVELOP IN PLHIV TAKING SECOND LINE ART

Recent evidence-based approaches to disease management emphasize the importance of ensuring a high quality of life for HIV patients receiving second line ART, which requires effective management of opportunistic infections throughout their treatment. In this study, the researcher got a chance to evaluate the prevalence and timing of opportunistic infections among the 369 records of PLHIV. Notably, clients in the 24 to 30 month treatment window exhibited the highest incidence of opportunistic infections, as illustrated in Figure 11.

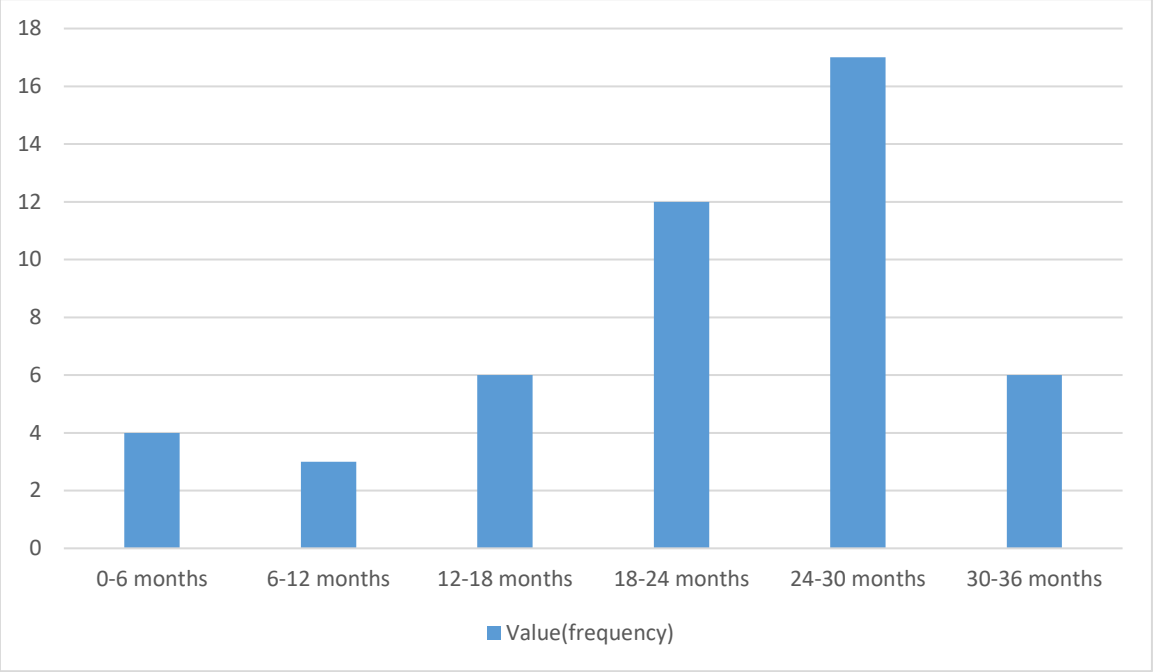


Figure 11. A time range by which the patients developed OI while on second-line ART in Addis Ababa, Ethiopia

4.9 PREVALENCE OF SECOND LINE ART VIROLOGICAL FAILURE IN ADDIS ABABA, ETHIOPIA.

The overall magnitude of VF among PLHIV taking second line ART aged 18 years and older from 2018-2022 in Addis Ababa, Ethiopia, is 14.9 % (55/369) of the total records of PLHIV. The overall median duration of treatment/month is 60 (49-64) months with a range of 20 -74 in months.

Patients linked from other health facilities demonstrated a statistically significant association with virological failure (Chi-square, P-value: 0.040). Similarly, HIV disclosure status (Fisher's exact test, P-value: 0.017) and prior experience of ART regimen change (Chi-square, P-value: 0.021) were significantly associated.

A highly significant relationship was found with loss to follow-up (LTFU) while on second line ART (Chi-square, P-value: <0.001), poor or suboptimal adherence to medication (Chi-square, P-value: <0.001), and the occurrence of opportunistic infections while on second line ART (Chi-square, P-value: 0.023). Statistical analysis revealed significant associations between virological failure and several factors.

Despite females accounting for 31 (17%) of the total second line ART virological failure, this subgroup did not show a statistically significant difference, with a P-value of 0.191. These study variables were tested using a chi-square analysis (Table 6).

Table 6. Socio-demographic and clinical characteristics of second line virological failure in adult HIV-positive patients in Addis Ababa, Ethiopia, 2018-2022, (n=369)

Variable/Characteristics	**Category /level**	**Total** N(%)or Median (Q1-Q3)	**Treatment success status (%) Failure(**event**)** N (%)	**Success (Censored)** **N (%)**	**P-Value, Chi-square (X^2)**
Age/yr, (IQR)		44 (32-52)			
Age in range	<40	137 (37)	21 (15)	116 (85)	0.861
	≥40	232 (63)	34 (15)	198 (85)	
Sex	Male	191 (52)	24 (13)	167 (87)	0.191
	Female	178 (48)	31 (17)	147 (83)	
Marital Status	Never Married	185 (50)	25 (14)	160 (86)	
	Married	123 (33)	22 (18)	101 (82)	0.522
	Others [a]	61 (17)	8 (13)	53 (87)	
Educational status	No formal education	31 (8.4%)	3 (0.8)	28 (7.6%)	0.105
	Primary	107 (29)	23 (6.2)	84 (22.8)	
	Secondary	190 (51.5)	22 (6)	168 (45.5)	
	Tertiary	41 (11.1)	7 (1.9)	34 (9.2)	
Patient linked from	Intra facility	293 (79.4)	255 (69.1)	38 (10.3)	0.040*
	Other facility	76 (20.6)	59 (16)	17 (4.6)	
Disclosure status of HIV	Disclosed	309 (83.7)	52 (14.1)	257 (69.6)	0.017*,@
	Not Disclosed	60 (16.3)	57 (15.4)	3 (0.8)	
Type of 2nd line ART dispensed	2f (AZT + 3TC + ATV/r)	83 (22.5)	73 (19.8)	10 (2.7)	
	2g (TDF+3TC+ LPV/r)	33 (8.9)	28 (7.6)	5 (1.4)	0.623
	2h (TDF+3TC+ ATV/r)	132 (35.8)	113 (30.6)	19 (5.1)	
	other adult 2nd line	22 (22.2)	70 (19)	12 (3.3)	
	Others [b]	39 (10.)	9 (2.4)	30 (8.1)	

Table 6, **Contu'd**

Variable/Characteristics	Category /level	Total N(%)or Median (Q1-Q3)	Treatment success status (%) Failure(event) N (%)	Success (Censored) N (%)	P-Value, Chi-square (X^2)
2nd line ART regimen change experience	Yes	72 (19.5)	17 (4.6)	55 (14.9)	0.021*
	No	297 (80.5)	38 (10.3)	259 (70.2)	
LTFU from HIV care while on 2nd-line ART	Yes	83 (22.5)	28 (7.6)	55 (14.9)	<0.001*
	No	286 (77.5)	27 (7.3)	259 (70.2)	
Second line ART adherence level at 6 months	Good	162 (43.9)	20 (5.4)	142 (38.5)	<0.001*
	Faire	18 (4.9)	9 (2.4)	9 (2.4)	
	Poor	189 (51.2)	26 (7)	163 (44.2)	
developed Opportunistic Infections while on 2nd line ART	Yes	48 (12.5)	12 (3.3)	34 (9.2)	0.023*
	No	329 (87.5)	43 (11.7)	280 (75.9)	
HIV status of spouse(n=123)	NR	20 (16.1)	4 (3.6)	14 (12.5)	0.266
	R	45 (37.5)	4 (3.6)	38 (33.9)	
	Unknown	58 (47)	11 (9.8)	41(36.6)	

*[a] widowed+ Separated+ Divorced,...[b] [2e (AZT+ 3TC+LPV/r+2i (ABC+3TC+LPV/r)+2k (AZT+3TC+DTG) , * significant, @ fisher exact*

Among the adult HIV-positive patients taking the second line antiretroviral therapy (ART) at selected hospitals in Addis Ababa, Ethiopia, between 2018 and 2022 (n=369), it was confirmed that 34 individuals (15%) aged over 40 experienced second line ART VF, as shown in Table 6 and Figure 12.

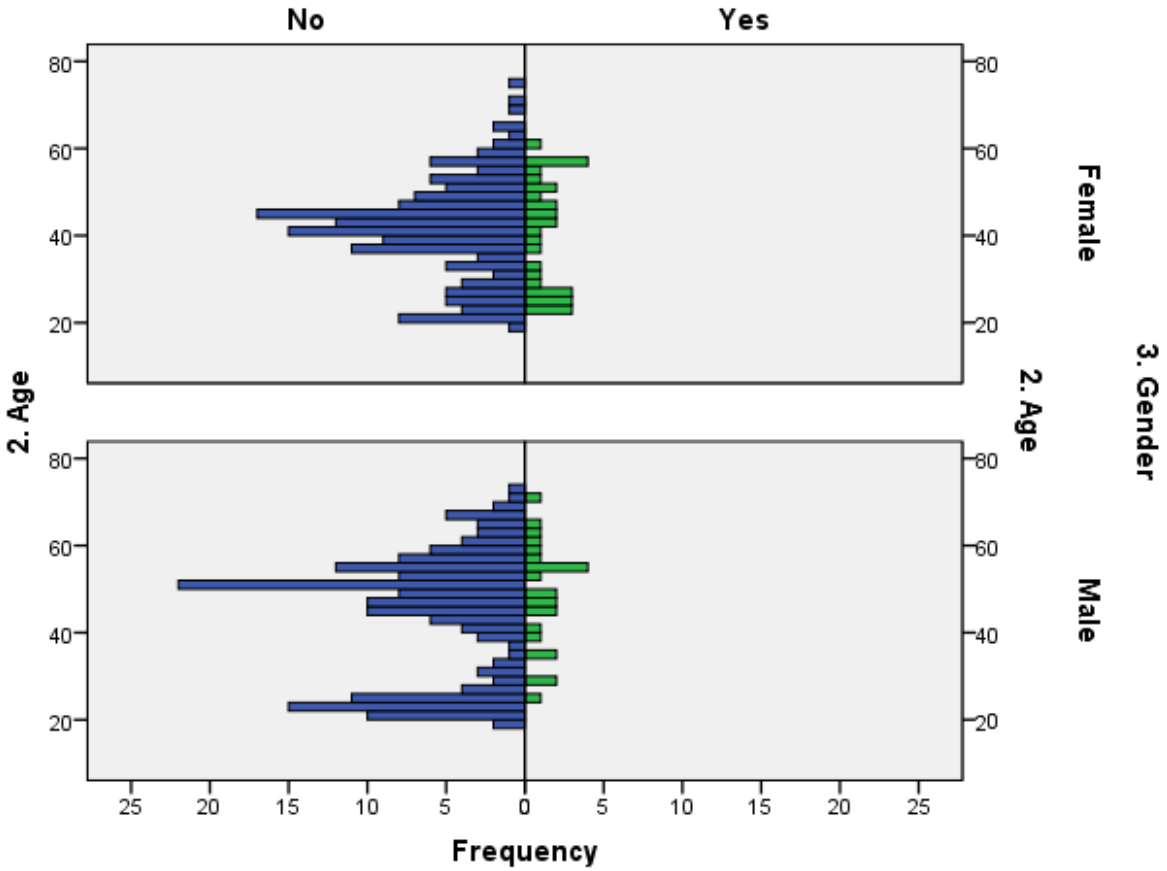


Figure 12. Demographic characteristics with VF of adult HIV-positive patients at selected hospitals in Addis Ababa, Ethiopia, 2018-2022 (n=369)

4.10 FACTORS CONTRIBUTING TO VIROLOGICAL FAILURE IN SECOND LINE ART

Among 369 PLHIV aged 18 and above receiving second line ART in Addis Ababa between 2018 and 2022, the study identified a virological failure prevalence of 14.9%.second line . It raises important questions about the risk factors that contribute to this unfavorable treatment outcome among PLHIV in second line ART and to this level of treatment failure. Thus, this subsection of the study identify the risk factors associated with virological failure in patients receiving second line therapy in Zewdtu Memorial Hospital and Yekatit 12 Medical College referral hospital.

The study revealed that among the 55 patients with confirmed VF, several factors contributed, including poor ART adherence, patients transferred from other health facilities, drug side effects, and LTFU clients.

In this study, patients who transferred from other health facilities are at a higher risk of virological failure, with an AOR of 2.726 (95% CI: 1.235, 6.016; p-value: 0.013). Those who

are lost to follow-up (LTFU) from HIV care while on second line ART have a greater risk, with an AOR of 6.007 (95% CI: 2.778, 12.990, p-value < 0.001). Similarly, clients with poor adherence to ART are a significant risk factor for virological treatment failure, with an AOR of 6.641 (95% CI: 1.077, 40.95, p-value: 0.041), Table 7.

Patients who have not experienced a change in their second line ART regimen during follow-up are less likely to experience treatment failure, with an odds ratio of 0.475 (95% CI: 0.250, 0.902), P-value=0.023. Similarly, clients who have disclosed their HIV status to others are less likely to experience virological failure matched to those who have not disclosed their status [AOR 0.260 (95% CI: 0.078, 0.862, p-value: 0.028], Table 7.

Table 7. Factors associated with virological failure of adult of second line ART at selected hospitals in Addis Ababa, Ethiopia, 2018-2022, (n=369)

Variable	Level	Unadjusted OR (95% CI)	P-value	Adjusted OR (95% CI)	P-value
Age (in years)	>40	0.949 (0.526,1.712)	0.861		
Sex	Female	1.467(0.824, 2.613)	0.193	1.500 (0.490, 4.585)	0.477
Marital Status	Never Married	0.693 (0.289, 1.662)	0.411		
	Married	0.966 (0.411, 2.271)	0.937		
	Others [a]	1			
Educational status	No formal education	0.520 (0.123, 2.201)	0.375		
	Primary	1.330 (0.522, 3.388)	0.550		
	Secondary	0.636 (0.252, 1.607)	0.339		
	Tertiary (Ref)	1			
Patient linked from	Intra facility	1			
	Other facility	0.517 (0.273, 0.979	0.043*	2.726 (1.235, 6.016)	0.013**
Disclosure status of HIV	Disclosed	1			
	Not Disclosed	0.260 (0.078, 0.862)	0.028*	2.091 (0.585, 7.477)	0.257
2nd line ART regimen change experience	Yes	1			
	No	0.475 (0.250,0.902)	0.023*	1.326 (0.595, 2.951)	0.490
HIV status of spouse	Non-reactive (Negative)	1			
	Reactive	0.368 (0.081, 1.677)	0.197		
	Unknown	0.939 (0.257, 3.429)	0.924		
Developed OIs while on 2nd line ART	Yes	0.435 (0.209,).905)	0.026*	0.518 (0.203, 1.327)	0.171
	No	1			
LTFU from HIV care while on 2nd-line ART	Yes	0.205 (0.112, 0.375)	<0.001*	6.007 (2.778, 12.990	<0.001**
	No	1			
Previous history of TB	Yes	1.056 (0.391,2.852)	0.914		
Patient adherence on 2nd line ART @ 6month	Good	1			
	Faire	1.133 (0.606, 2.116)	0.696	0.598 (0.271, 1.319)	0.203
	Poor	0.160 (.058, 0.439)	<0.001*	0.070 (0.020,0.245)	<0.001**
Patient adherence on 2nd line ART @ Last visit [&]	Good	1			
	Faire	14.329 (6.087, 33.729)	<0.001*	10.239 (3.900, 26.88)	<0.001**
	Poor	5.100 (1.113, 23.372)	0.036*	6.641 (1.077, 40.95)	0.041**
WHO stage (@ start of 2ndline ART)	I (Ref)	3.091 (0.274, 34.812)	0.361		
	II	2.250 (0.174, 29.055)	0.534		
	III	1.625 (0.115, 22.981)	0.719		
	IV	1			

* Significance at COR, ** Significance at AOR, [a] widowed+ Separated+ Divorced, [&]last visit means- last date of data collection

4.11 TIME TO TREATMENT FAILURE AMONG SECOND LINE ART PATIENTS

The patients were followed for a minimum of 20 and a maximum of 74 months. Out of 369 study records of PLHIV, a total of 55 (14.9%) PLHIV developed second line virological failure in 20,187 person-months of the total analysis time at risk and under person per month (PM) of observations. The summarized incidence density was 2.72 per 1000 PM with a 95% CI of [2.11, 3.55] or 33 per 1000 person-years (PY) with a 95% CI of [25.0, 42.0].

The overall cumulative survival probability of the sampled client within the cumulative probability of failure at 24 months was 4.9% (95% CI 3.1% to 7.6%). The cumulative survival probability for second line ART within the treatment follow-up duration was found to be decreased, which means, as the time of follow-up goes, the failure rate increases. As depicted in the Kaplan-Meier failure curve, Figures 13 & 14.

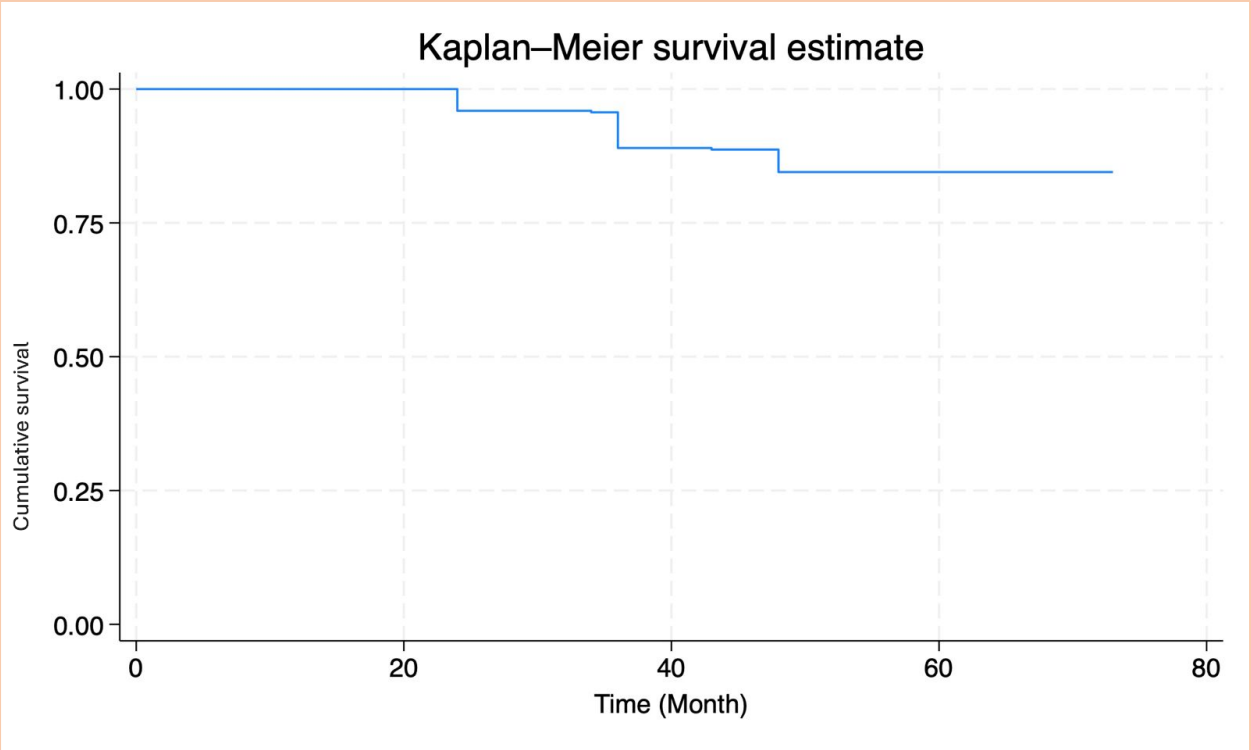


Figure 13. Overall Kaplan-Meier failure curve showing hazard from treatment failure of HIV-positive adults on second line antiretroviral therapy at selected hospitals in Addis Ababa, Ethiopia, 2018-2022, (n=369)

Kaplan-Meier failure curve showing the last time of failure or event was at 48 months of follow-up from treatment failure of HIV-positive adults taking the second line antiretroviral

therapy at selected hospitals in Addis Ababa, Ethiopia, 2018-2022,(n=369) with 95 CI, Figure 14

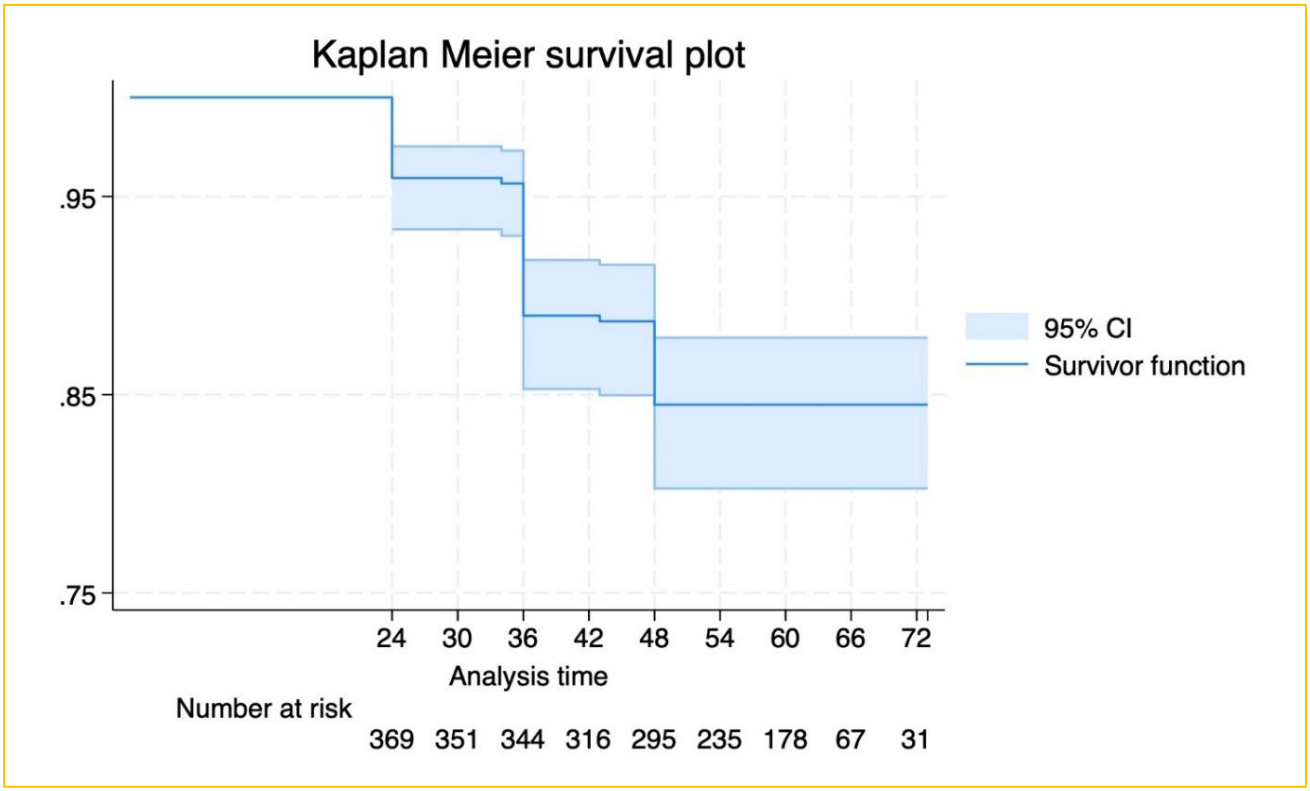


Figure 14 Kaplan-Meier failure curve with 95% CI for treatment failures in HIV-positive adults on second line antiretroviral therapy in Addis Ababa, Ethiopia (2018-2022, n=369)

Likewise, the cumulative proportional hazards regression shows an increasing trend as the follow-up time progresses, as illustrated in Figure 15.

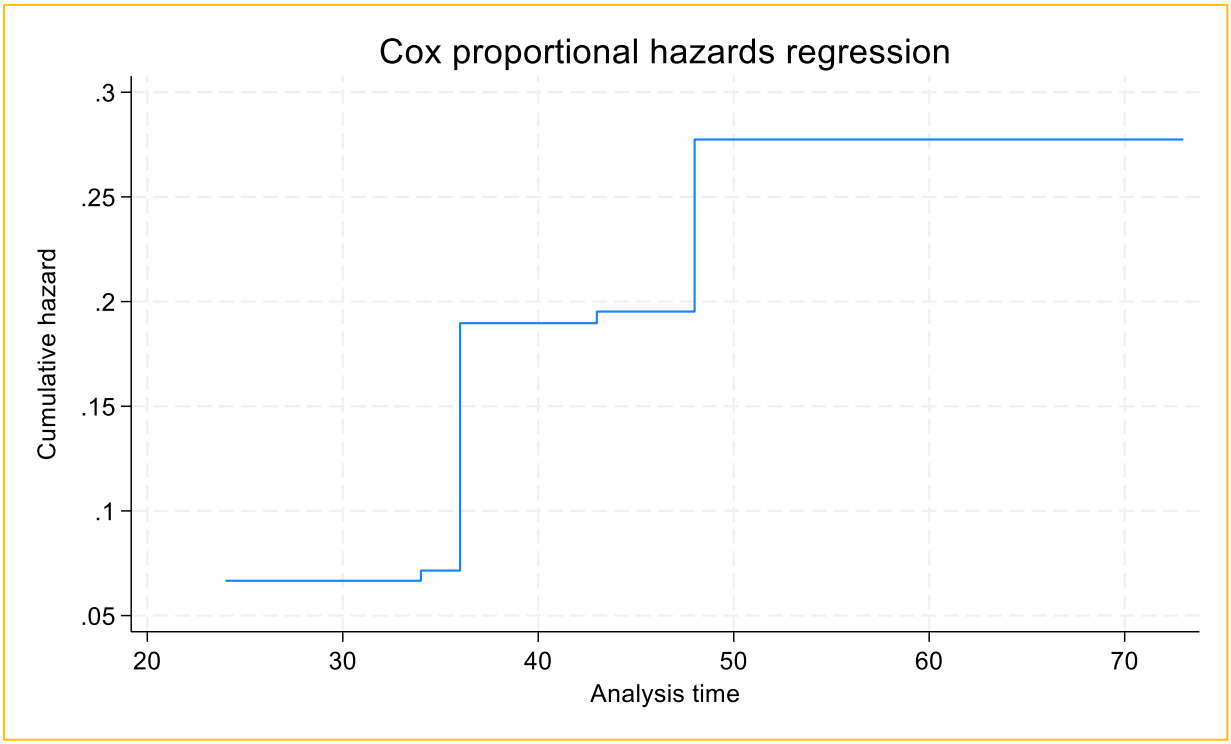


Figure 15. Cumulative proportional hazards regression curve of second line ART failure among adults in Addis Ababa, Ethiopia, from 2018-2022

In another way, considering the combined result, the cumulative probability of VF at 24 months was 4.9% (95% CI 3.1% to 7.6%), at 48 months it was 34.2% (95% CI 29.6% to 39.3%), at 60 months it was 80.7% (95% CI 76.6% to 84.6%), and at 72 months it was 92% (95% CI 88.8% to 94.4%), **Table 8.**

In this study, the occurrence probability of virological failure was detected at 24, 34, 36, 43, and 48 months of treatment follow-up among adults taking second line antiretroviral therapy, with the highest incidence noted at 36 months during the follow-up period. These findings highlight the importance of closely monitoring patients during the earlier stages of follow-up, particularly within the first 48 months. Early and consistent follow-up efforts are critical, as they help to identify and address potential challenges promptly. After this period, patients tend to achieve greater stability in their treatment regimen, which ultimately could lead to better treatment outcomes and improved overall quality of health, **Fig. 14** & **Table 9.**

Table 8. Cumulative probability of failure of adult Patients on second line ART at selected hospitals in Addis Ababa, Ethiopia, 2018-2022

Follow-up time in Months	Cumulative Probability of failure (in percent with 95% CI)
24	4.9 (3.1,7.6)
30	5.2 (3.3,7.9)
36	14.4 (11.2, 18.4)
42	14.6 (11.4, 18.7)
48	34.2 (29.6,39.3)
54	36.9 (32.2, 42.0)
60	80.7 (76.6, 84.6)
66	82.7 (78.6, 86.3)
72	91.9 (88.8, 94.4)

4.12 RISK FACTORS ASSOCIATED WITH VIROLOGICAL FAILURE

In this study, a total of 369 individuals were enrolled, and 55 of them (14.9%) experienced second line ART VF with 20,187 months of time at risk. The risk of virological failure in patients receiving second line ART was found to be higher among those who came from other health facilities, with an adjusted hazard ratio (AHR) of 1.97 (95% confidence interval (CI): [1.07, 3.64], P-value = 0.029). Second line ART regimen change experience was also found to be a predictor of second line ART VF (AHR = 2.05, 95% CI: [1.08, 3.88], P-value = 0.027). The other predictor found in this study was a history of LTFU from ART treatment is 2.5 times more likely to have VF than those retained in care (AHR = 2.52, 95% CI: [1.35, 4.69], P-value = 0.004).

Additionally, poor adherence to ART medication was found to be a significant predictor of second line ART virological failure (CHR = 7.51, 95% CI: [4.19, 13.44], P < 0.001). second line . Nondisclosure of HIV status (CHR = 3.60, 95% CI: [1.12, 11.54], P-value = 0.031) also another identified predictor for second line ART VF in this study. These findings highlight important factors that could contribute to the failure of second line ART treatment, as the details depicted in Table 9.

Table 9. Multivariate Cox regression analysis of predictors of second line ART failure of adult HIV-positive patients at selected hospitals in Addis Ababa, Ethiopia, 2018-2022, (n=369)

Variable	Rx failure		Crude HR (95% CI)	P-value	Adjusted HR (95% CI)	P-value
	Yes N (%)	No N (%)				
Marital Status						
Married	22 (18)	101 (82)	1			
Never married	25 (14)	160 (86)	0.76 (0.43-1.36)	0.364		
Others [a]	8 (13)	53 (87)	0.71 (0.32-1.61	0.424		
Sex						
Male	24 (13)	167 (87)	1			
Female	31 (17)	147 (83)	1.46 (0.85-2.49)	0.164		
2nd line ART regimen change experience						
Yes	17 (4.6)	55 (14.9)	1.92 (1.08-3.41)	0.025*	2.05 (1.08- 3.88)	0.027**
No	38 (10.3)	259 (70.2)	1			
Educational Status						
No formal education	3 (0.8)	28 (7.6%)	1			
Primary	23 (6.2)	84 (22.8)	2.43 (0.73-8.09)	0.148		
Secondary	22 (6)	168 (45.5)	1.25 (0.37-4.17)	0.718		
Tertiary	7 (1.9)	34 (9.2)	1.89 (0.48-7.30)	0.357		
Patient linked from						
Intra facility	255 (69.1)	38 (10.3)	1			
Other facility	59 (16)	17 (4.6)	1.82 (1.027-3.22)	0.040*	1.97 (1.07- 3.64)	0.029**
Weight at start of 2nd line ART						
30-40	4	15	1			
41-50	20	71	0.93 (.31-2.72)	0.897	1.24 (0.41- 3.73)	0.700
50+	31	228	0.48 (0.17-1.38)	0.178	0.75 (0.25- 2.19)	0.59
Disclosure						
Yes	52 (14.1)	257 (69.6)	1			
No	57 (15.4)	3 (0.8)	3.60 (1.12- 11.54)	0.031*		
Previous TB						
yes	5	30	0.98 (0.39-2.46)	0.972		
No	50	284	1			

Cont'd Table 9

T staging at the switch/ at the start of 2nd line ART						
I	313	46	1			
II	6	1	8.65 (3.67-20.37)	<0.001*	4.84 (1.62- 14.41)	0.005 **
III	2	0	8.52 (2.06-35.16)	0.003	24.34 (1.78- 331)	0.017**
IV	1	0	10.65 (1.45-77.95)	0.020	487 (3.64- 65036)	0.013**
Adherence Level at the switch/the start of 2nd line ART						
Good	20	142	1			
Poor	35	172	7.51 (4.19- 13.44)	<0.001*	0.98 (0.52- 1.83)	0.949
Functional Status at the switch/ at the start of 2nd line ART						
Working	47	265				
Ambulatory	3	12	1.28 (0.59- 2.76)	0.535		
Bedridden	5	36	1.41 (0.58- 2.24)	0.699		
Type of 2nd line ART dispensed						
2e (AZT+ 3TC+LPV/r	2 (12)	14 (88)	0.84(0.187-3.74)	0.817		
2f (AZT + 3TC + ATV/r)	10 (12)	73 (88)	0.84(0.36-1.95)	0.688		
2g (TDF+3TC+ LPV/r)	5 (15)	28 (85)	1.01(.35- 2.86)	0.985		
2h (TDF+3TC+ ATV/r)	19 (15)	113 (85)	0.99(0.48- 2.04)	0.984		
other adult 2nd line	12 (15)	70 (85)	2.32 (0.92-5.91)	0.076		
Others [b]	7 (30)	16 (70)		1		
ART drug Side effect						
yes	9 (20)	34 (80)	1.55 (0.76-3.17)	0.227		
No	46 (14)	280 (86)				
Lost Follow Up (LTFU)						
Yes	28 (7.6)	55 (14.9)	3.81 (2.24-6.46)	<0.001*	2.52 (1.35- 4.69)	0.004**
No	27 (7.3)	259 (70.2)	1			
OI Prophylaxis (taking CPT….						
yes	50 (17)	251 (83)	1			
No	5 (7)	63 (93)	0.43 (0.17-1.10)	0.080		

* Significance at CHR, ** Significance at AHR,

4.13 ADHERENCE TO SECOND LINE ART.

Virological failure among PLHIV taking second line ART, becoming an increasing public health concern and poses a significant threat to the control of HIV/AIDS. Numerous risk factors have been identified; among these, suboptimal adherence was the most critical factor. However, there is limited information available on this issue within the context of Ethiopia.

Thus, this study assessed the level of adherence to the prescribed second line ART among individuals enrolled in the study to draw conclusions and for the timely decision and halt an ongoing potential drug resistance and related multidimensional consequences.

A suboptimal level of adherence to second line ART can lead to an increased risk of treatment failure. Adherence to the HIV treatment regimen means taking all the prescribed ART medications at the correct dose, at the right time, and in the right way. An adherence rate of 95% is a standard consideration to achieve for maximal viral suppression. In this study, on average, 60% (43%-86%) of records of PLHIV had achieved good adherence with good progress from time to time. Table 10 and Figure 16.

Table 10. Level of Adherence to second line ART among PLHIV aged 18 years and older at selected hospitals in Addis Ababa, Ethiopia, 2018-2022, (n=369)

Level of Adherence	**Follow up months**							
	6 month, # (%)	12 Months, # (%)	18 months, # (%)	24 months, # (%)	30 months, # (%)	36 months, # (%)	Last months of # (%)	The overall average in percent
Good	162 (44)	160 (43)	171 (46)	167 (45)	260 (70)	314 (85)	318 (86)	60 (43-86)
Fair	18 (5)	25 (7)	44 (12)	137 (37)	85 (23)	36 (10)	27 (7)	14 (7-37)
Poor	189 (51)	184 (50)	154 (42)	65 (18)	24 (7)	19 (5)	24 (7)	26 (5-51)

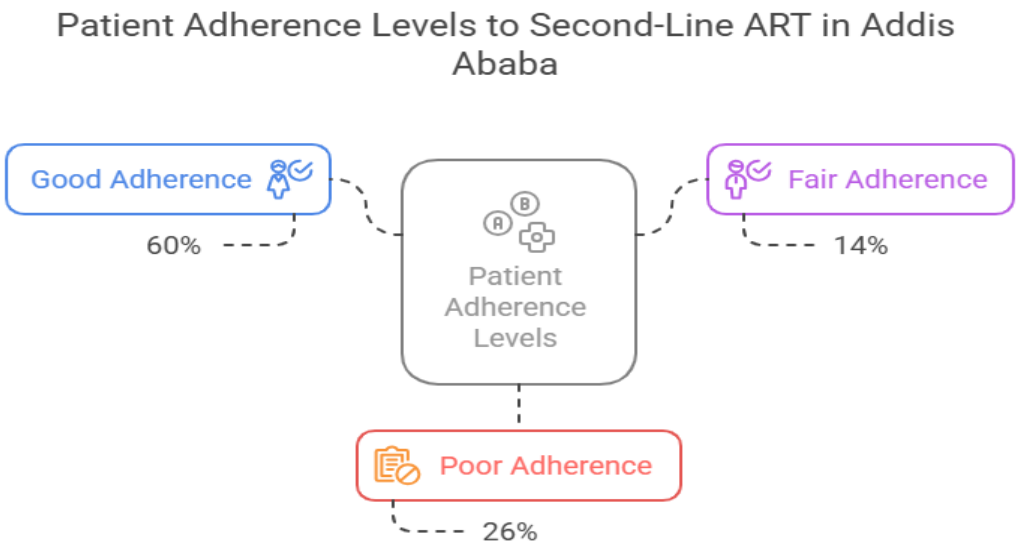


Figure 16. Patient adherence level to second line ART at last visit among adult HIV-positive patients at selected hospitals in Addis Ababa, Ethiopia, 2018-2022 (n=369)

4.14 FACTORS AFFECTING LEVEL OF ADHERENCE TO SECOND LINE ART

Adhering to the prescribed Antiretroviral Therapy (ART) is crucial for clients to achieve effective treatment success. Non-adherence can lead to second line ART VF due to the inability to achieve viral suppression and can be influenced by various factors. Poor adherence can lead to increased viremia and a higher risk of developing Virological Failure.

Factors influencing adherence include the ART side effects, Opportunistic Infections, patient education, psychosocial support, and others. Identifying and understanding these underlying risk factors are essential for timely intervention and management. This can help minimize the potential costs associated with individuals and the HIV program. It is highly recommended that an adherence rate of 95% and greater can be maintained to achieve optimal viral suppression. In this study, on average, 60% of individuals who are taking second line ART achieved the WHO ≥95% adherence level. Accordingly, this study explored the factors that affect adherence among PLHIV aged 18 years and older taking second line ART in Addis Ababa, Ethiopia.

Given that, clients experiencing opportunistic infections during second line ART treatment are 5.186 times more likely to have poor adherence levels compared to those who did not acquire opportunistic infections (5.186 [1.963-13.698], p-value = 0.001). Additionally, HIV-

positive clients on second line ART who did not disclose their status are more likely to have poor adherence (0.507 [95% CI: 0.265-0.971], p-value = 0.041). Based on the study findings, we recommend that, patients experiencing opportunistic infections during second-line ART should receive strengthened OI screening and prompt treatment, coupled with intensified adherence counseling and close follow-up, as they are significantly more likely to have poor adherence.

Furthermore, clients with bedridden functional status are 0.541 times (95% CI: 0.294-0.994, p-value = 0.048) more likely to have poor level adherence than working patients. Whereas literacy contributed to good adherence, PLHIV with a secondary level of education are 2.5 times (95% CI: 1.061-5.925, p-value = 0.036) more likely to have optimal treatment adherence, Table 11.

Table 11. Factors associated with the level of adherence to second line ART among adult HIV-positive patients at selected hospitals in Addis Ababa, Ethiopia, 2018-2022, (n=369)

Variable/Characteristics	Category /level	Level adherence to second line ART					
		Good	Poor [b]	Unadjusted OR (95% CI)	P- value	Adjusted OR (95% CI)	P-Value,
Sex	Male	87	104	0.870 (0.577-1.314)	0.509	-	-
	Female	75	103	1			
Marital Status	Married	48	114	1			
	No Married [a]	75	132	1.349(0.869-2.096)	0.182	-	-
Educational status	No formal education	19	12	1		1	
	Primary	43	64	0..632 (0.307-1.301)	0.213	0.988 (0.327-2.989)	0.983
	Secondary	79	111	1.488(1.011 - 2.191)	0.044*	2.507 (1.061-5.925)	0.036**
	Tertiary	21	20	1.405(1.053-1.875)	0.021*	1.692 (0.758-3.776)	0.199
Patient linked from	Intra facility	127	166	1	1	1	
	Other facility	35	41	1.188 (1.010-1.396)	0.037*	0.482 (0.242-0.960)	0.038**
Functional status during the last visit of first-line ART(before switching to second-line)	Working	61	35	1	1	1	
	Ambulatory	39	44	0.278 (0.166-0.465)	<0.001*	0.335(0.173-0.648)	0.001**
	Bedridden	62	128	0.546 (0.323 - 0.926)	0.025*	0.541(0.294-0.994)	0.048**
HIV disclosure	Disclosed	128	181	1		1	
	Not Disclosed	34	26	0.541(0.309 – 0..945)	0.031*	0.507 (0.265-0.971)	0.041**
The patient took TPT/INH while on 2nd line	Yes	76	86	2.382 (1.822 - 3.113)	<0.001*	8.262 (4.632-4.737)	<0.001 **
	No	181	26	1			
2nd line ART regimen change experience	Yes	23	158	0.534 (0.309-0.309)	0.024*	0.663(0.347-1.266)	0.213
	No	139	49	1			
LTFU from HIV care while on 2nd-line ART	Yes	55	86	1.309(1.114-1.539)	0.001*	0.710 (0.373-1.351)	0.297
	No	107	121	1		1	
Had experienced any drug side effects while on 2ndl	Yes	16	27	0.731(0.379-1.408)	0.348		
	No	146	180	1		1	
developed OI while on 2nd line ART	Yes	7	39	1		1	
	No	155	168	5.571 (2.492-12.456)	<0.001*	5.186(1.963-13.698)	0.001**

[a] never married+ divorced+widowed+separated, [b] poor= Poor +faire,*significance at COR,** significance at AOR

4.15 EFFECT OF EAC ON HIV VIRAL LOAD SUPPRESSION AMONG SECOND LINE ART

An Enhanced Adherence Counseling (EAC) is a counseling intervention designed for PLHIV, particularly those with high viral load test results. This method involves monitoring viral load outcomes, addressing barriers to second line ART adherence, and facilitating psychosocial support. It is managed by well-trained ART service providers who utilize a client-centered and non-judgmental approach rather than a provider-initiated modality.

To declare and confirm the patient as an ART virological failure, they must go through three months of EAC after a patient has two consecutive viral load measurement results greater than or equal to 1000 copies per mL of RNA in a sampled blood specimen.

Among the study records of PLHIV, 89 (24%) individuals had a high viral load. Of these, 34 (38%) achieved HIV viral suppression through Enhanced Adherence Counseling (EAC), while 55 did not. Thus, this research highlighted and underscored the significance of promptly applying EAC for a reasonable number of clients in reducing high HIV viral loads among PLHIV who experienced high HIV viral load in the course of second line ART follow-up. It is concordant with published research, with a notable percentage of records of PLHIV achieving viral suppression after completing EAC sessions, 40.9% (35.7%-46.5%), depending on the specific study and population involved. Table 12, Figure 17.

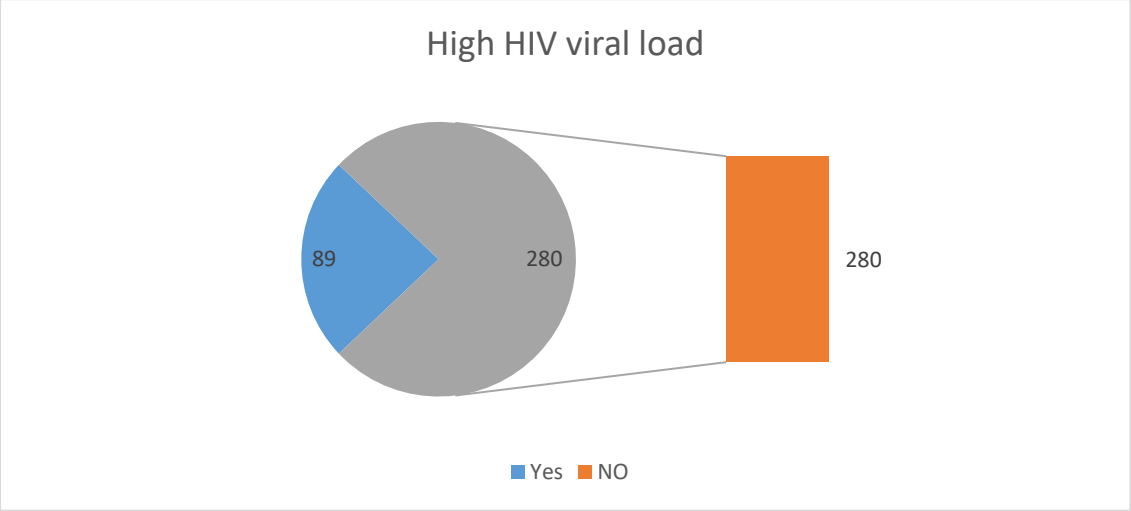


Figure 17. Proportion of clients with documented high viral load during 2nd-line ART (before EAC) among adult HIV-positive patients at selected hospitals in Addis Ababa, Ethiopia, 2018-2022, (n=369)

After the Enhanced Adherence Counseling (EAC), 34(38%) out of 89 clients with high HIV viral loads became HIV virus-suppressed after adhering to the program for 3 to 6 months. The EAC was designed for PLHIV who have unsuppressed viral loads (≥ 1000 copies/ml) after six months of antiretroviral therapy (ART). This counseling session typically lasts between 3 to 6 months. It aims to improve adherence through timely follow-up, identifying and addressing potential barriers to treatment, and any difficulties the patients may be experiencing (Figure 18).

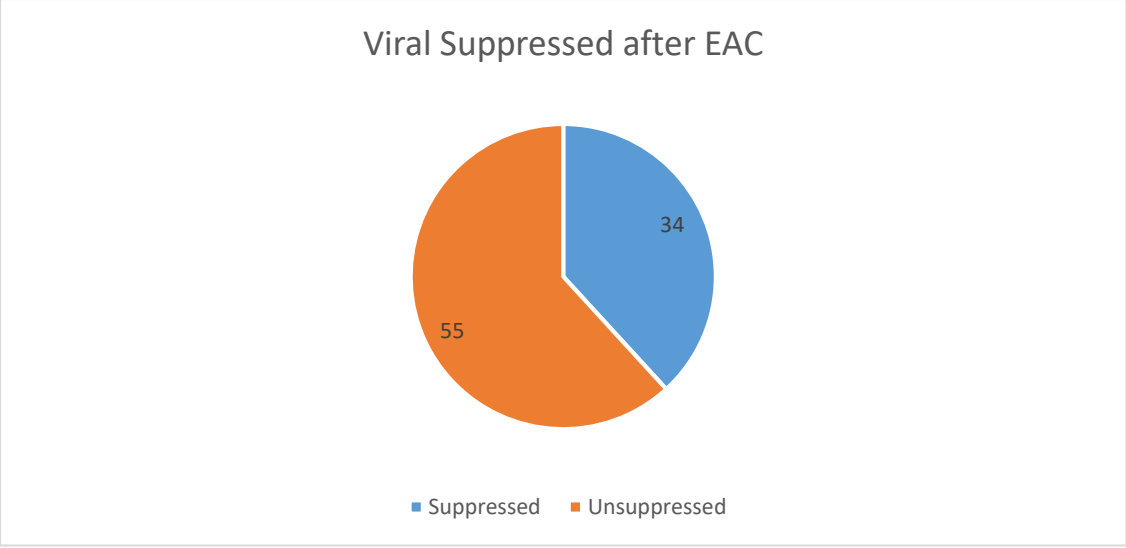


Figure 18. Magnitude of viral load suppression after EAC at selected hospitals in Addis Ababa, Ethiopia.

Table 12. Second line ART Clinical and Laboratory follow-up information, Addis Ababa, Ethiopia.

Variable	Category	Frequency	Percent
Patient developed OI	Yes	46	12.5
	No	323	87.5
Received CPT	Yes	301	81.6
	No	68	18.4
Received INH/TPT	Yes	257	69.6
	No	112	30.4
High VL documented /during 2nd line ART	Yes	89	24
	No	280	76
2nd VL suppressed after EAC(N=89)*	Yes	34	38
	No	55	62

***Note**: *With the EAC effect, 34 out of 87 clients (38%) achieved virological suppression, reducing their initially high viral load. This research highlights and underscores the significance of promptly applying EAC without neglecting its role in reducing high HIV viral loads among clients.*

4.16 TIME TO SWITCH TO THIRD-LINE AMONG SECOND LINE VIROLOGICAL FAILURE

The overall cumulative probability of VF to second line ART among adult HIV-positive patients at selected hospitals in Addis Ababa, Ethiopia, 2018-2022, (n=369) was 4.9% (95% CI 3.1% to 7.6%) at 24 months and 34.2 (29.6, 39.3) at 48 months. It was 34.2% (95% CI 29.6% to 39.3%) at 60 months, it was 80.7% (95% CI 76.6% to 84.6%), and at 72 months, it was 92% (95% CI 88.8% to 94.4%), Table 8. The incidence density was 2.72 per 1000 PM with a 95% CI of [2.11, 3.55] or 33 per 1000 person-years (PY) with a 95% CI of [25.0, 42.0], Appendix 12 and Table 13.

In this study, the occurrences of virological failure were detected at 24, 34, 36, 43, and 48 months of treatment follow-up among adults taking second line antiretroviral therapy, with the highest incidence noted at 36 months during the follow-up period. These findings highlight the importance of closely monitoring patients during the earlier stages of follow-up, particularly within the first 48 months. Early and consistent follow-up efforts are critical, as they help to identify and address potential challenges promptly. After this period, patients tend to achieve greater stability in their treatment regimen, which could ultimately lead to better treatment outcomes and improved overall quality of health. **Tables 12 & 13.**

Table 13. The incidence rates of second line treatment failure in time in 1000 per month among adults living with HIV in Addis Ababa, Ethiopia, 2018-2022 (N=55)

Time in months (at selected months)	Failures #	Incidence Rate	Rate Per1000PMs	95% CI
24	15	0.0432	347.222	209.33 - 575.95

34	01	0.1020	9.8039	1.38 - 69.59
36	24	1.0080	23.8095	15.96 - 35.52
43	01	0.1290	7.7519	1.09 - 55.03
48	14	2.4960	5.6090	3.32 - 9.47
54	0	0.0490	0.0000	--
60	0	6.4200	0.0000	--
66	0	0.1980	0.0000	--
72	0	0.0720	0.0000	--
Total	**55**			

From our study, we observed that all cases of virological failure among adult HIV-positive patients on second line ART at selected hospitals in Addis Ababa, Ethiopia, were transitioned within the recommended timeframe, which is the transition period from the identification of treatment failure to the initiation of appropriate third-line ART within six months. This recent finding underscores the strict follow-up of the recommended international switching time in managing treatment failure, ensuring timely intervention for better patient outcomes, **Table 14**.

Table 14. Average time between high VL documentation and switching to 3rd line ART

Variables	**Months***	**Frequency**	**Percent**
Failed	0	1	0.3
	1	15	4.1
	2	22	6.0
	3	7	1.9
	4	1	0.3
	5	4	1.1
	6	5	1.4
	Total failure	**55**	**14.9**
Not failed	Censored	314	85.1
Total		**369**	**100.0**

***in months, if the patient is confirmed 2nd line ART failure*

A large number of clients were experienced at the range of 24 to 36 months of their ART treatment follow-up. Figure 19.

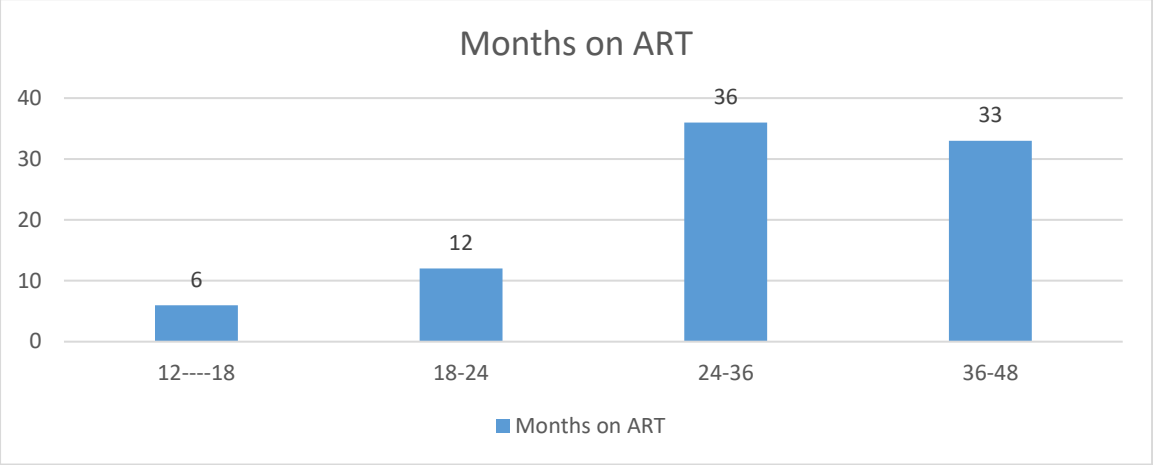


Figure 19. First high VL occur time after initiating 2nd line ART, Addis Ababa, Ethiopia

4.17 WHAT IS THE FATE OF THOSE FAILED CLIENTS?

In this recent study, out of the total 369 enrolled HIV-positive second line ART clients, 55 clients who had a virological failure switched to the third line ART regimen. Accordingly, the majority of the cases, 29 (52.7%), shifted to “other adult third line” ART, followed by 3b, 13 (23.6%), illustrated in Table 15.

Table 15. List of third-line ART regimens dispensed for PLHIV-confirmed second line ART VF in Addis Ababa, Ethiopia, 2018-2022 (N=55)

S.N	Type of third-line ART name	Frequency (#)	In percent
1	Other adult third-line	29	52.7
2	3b (DRV/r + DTG +TDF + 3TC)	13	23.6
3	3c (DRV/r + ABC +3TC + DTG)	6	10.9
4	3a (DRV/r +DTG +AZT +3TC)	5	9.1
5	3e (DRV/r + TDF +3TC + EFV)	2	3.6

4.18 RESULTS FROM THE QUALITATIVE DATA SOURCES

The results from the key informant interview from adult PLHIV taking second line ART who fulfilled the inclusion criteria and FGD from ART providers and program personnel are presented in the following sections. The data analysis has followed the steps indicated in Figure 20.

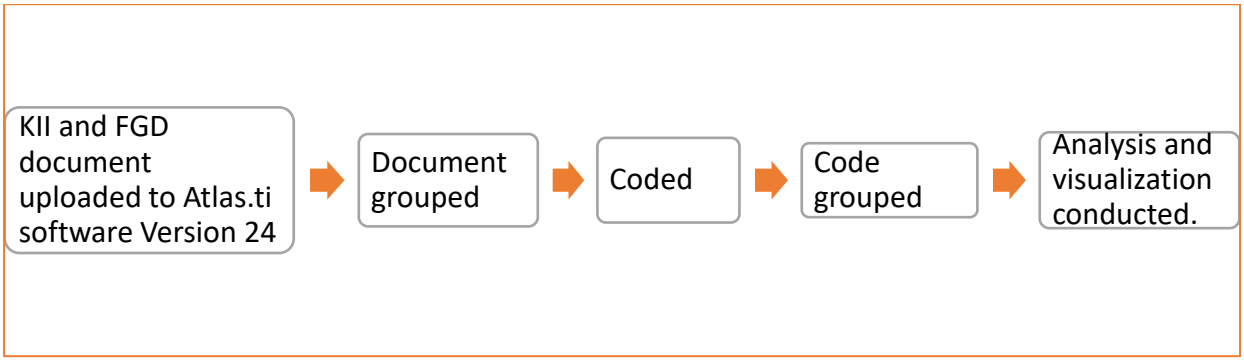


Figure 20. Steps followed for Qualitative data analysis in Atlas.ti Version 24

Bio-data of participants

In the Key Informant Interview (KII) with 15 participants (10 females and 5 males), adults PLHIV who are taking second line antiretroviral therapy (ART) at Zewditu Memorial General Hospital and Yekatit 12 Medical College Hospital participated. The average age of the KII participants was 35.4 years, ranging from a minimum of 24 years to a maximum of 47 years.

For the Focus Group Discussions (FGDs), three discussion sessions were conducted: two at the hospital level with ART service providers and one with program managers. Each FGD consisted of 6 to 7 individuals. In total, 13 individuals participated in the FGDs, which encompass three ART focal persons (2 females) and ART providers (two females and one male included), three adherence counselors (one female), and four case managers (one male).

In the FGD with program managers, a total of 6 individuals participated (5 females and 1 male).

4.18.1 Analysis and findings from key informants' interviews.

The qualitative data has been analysed using the Atlas.ti version 24 software. Accordingly, 19 codes, 5 code groups or themes, and 146 quotations were generated from the 15 KII and 3 FGDs, as indicated in Table 16.

Table 16. KII coding using Atlas. ti for version 24 software, Addis Ababa, Ethiopia

Code Group 1: ART drug side effects	**Code Group 2:** Fear of stigma and discrimination	**Code Group 3:** Feeling of rejection and isolation	**Code Group 4:** Low community awareness of HIV	**Code Group 5:** Poor Adherence

• ART side effect leads to missed doses • Pill Burden	• Disclosure leads to stigma • Discriminatio n leads to poor adherence	• Being HIV positive leads to frustration • Discriminatio n leads to poor adherence • Fear of rejection	• Being HIV positive leads to frustration • Community stigma leads to poor adeherence • Disclosure leads to stigma • Discriminatio n leads to poor adherence • Fear of rejection	• ART side effect leads to missed doses • Pill Burden • Community stigma leads to poor aherence • Disclosure leads to stigma • Distance from the Hospital is a challenge for adherence • Financial problem leads to non-adherence • Nutrition challenge leads to poor adherence • Substance use leads to non-adherence

Based on the qualitative data, the data visualization illustrated the distribution of various codes, including disclosure leads to stigma, ART side effects lead to missed doses, and missing doses due to distance within the documents. Consequently, 14 (93%) of the Key Informant Interview (KII) participants reported that disclosing their HIV status to others could result in stigma. Additionally, 4 (27%) of them noted that the side effects of Antiretroviral Therapy (ART) could contribute to missed doses, as indicated in Figure 21.

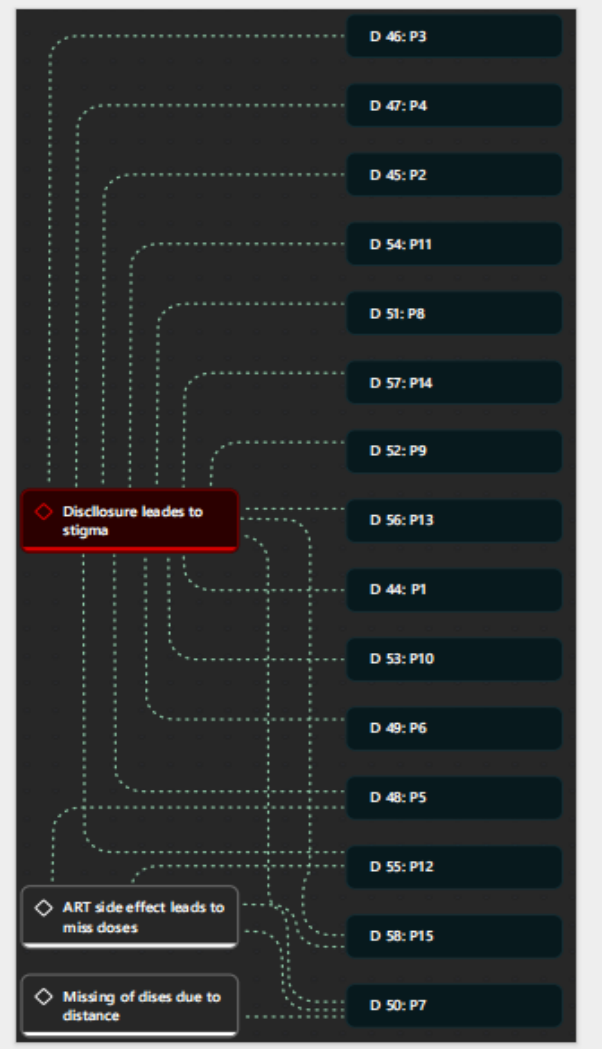


Figure 21. Distribution of Codes-participant networking using Atlas.ti for version 24

The researcher analysed the data using a Sankey diagram illustration to show the relationship between factors affecting ART adherence, including ART drug side effects, community awareness, poor adherence to ART, fear of stigma & discrimination, and fear of rejection and sex. As a result, though poor adherence is associated with both males and females, but males experience higher poor adherence. Factors such as low community awareness of HIV and ART side effects have a stronger connection with males. Feelings of rejection and fear of stigma and discrimination have strong connections with Females. The detail is indicated in Figure 22**.**

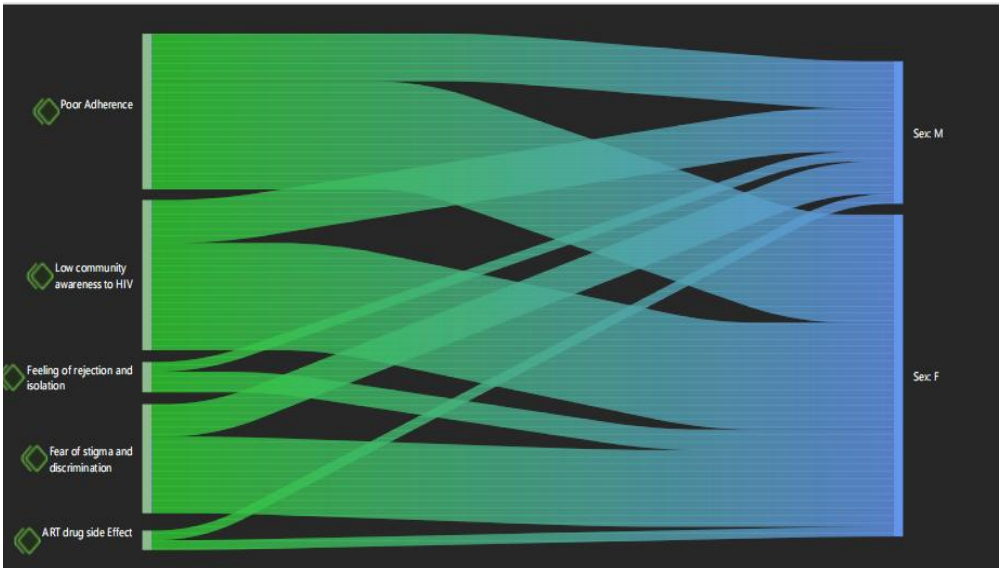


Figure 22. A Sankey diagram shows the connection between sex and factors affecting ART outcome

Each code group or theme is discussed, explained, and the result is presented accordingly.

Theme 1. ART drug side effects and pill burden lead to poor ART Adherence

One of the KII participants stated that;

"*The side effects associated with these medications can be more pronounced, causing discomfort and affecting my quality of life*." *45:2 ¶ 5 in P2*. Report generated from Atlas. ti.

The other KII participant raised,

"…*taking medication for such a long period is very tough and sometimes feels boring."*

Adding that, ***"…*** *there are days when I feel too tired or overwhelmed by the daily routine of taking my medication, but I remind myself of their importance".*

Other participants also said*, "Sometimes, I forget or get caught. second line ART is more challenging than first-line treatment due to the increased number of pills, leading to treatment fatigue*."

The other participants said *"…, However, the pill burden is challenging me. I sometimes worry about the potential long-term side effects of the drug… taking medication for the long term is so difficult… "*

One participant stated missing of her doses during social activities by saying, *"There have been times when I have missed doses of my ART during social activities because I sometimes feel uncomfortable taking them in front of others during social activities due to fear of stigma. These situations have led to missed doses, which I know can affect my health".*

Another participant also added,

"I used to miss doses, and I experienced the negative impact it had on my health."

"…side effects like insomnia and trouble sleeping, which have been affecting my mood and energy level, making it harder to perform my duties at full capacity."

One participant also mentioned that she missed or delayed doses due to fear of social stigma and discrimination, and she said that *"…There are times when I miss or delay doses because of the strict schedule. My fear of stigma and discrimination prevents me from openly discussing my HIV status, even with those close to me. This secrecy means I do not have a support system to remind or encourage me to take my medication consistently, which contributes to my inconsistent adherence. I feel isolated in managing my condition, and the constant worry about others discovering my status adds to my stress, making it even harder to maintain a regular medication routine."*

Theme 2. Fear of stigma and discrimination leads to non-disclosure of HIV status

Many PLHIV choose to keep their HIV status a secret due to fear of stigma and discrimination.

A participant stated that, *"…I've seen how society can stigmatize people living with HIV, and I want to protect myself from that experience." "…I didn't want anyone to know, and this made it especially hard to take my medication in public or around people I knew."*

"*I have chosen not to disclose this information to others because I fear facing stigma and discrimination*." *45:3 ¶ 7 in P2*

"*I have missed doses because of the stigma associated with HIV. The fear of others discovering my status makes me hesitant to take my medication in public or even discuss my condition, leading to missed or delayed doses." 45:9 ¶ 11 in P2.*

A participant in the key informant stated that,"…*the only person that knows my HIV status is my mother. I have chosen to keep it confidential from other people. Disclosing HIV status can sometimes lead to stigma and discrimination, and I want to prioritize protecting myself from those potential experiences by not disclosing my HIV status."*

Theme 3. Feelings of rejection and isolation lead to non-disclosure.

The researcher assessed the feelings of participants in relation to the disclosure of their HIV status to others. A participant expressed the feeling, stating, "*Disclosing my HIV status to others has never been an easy decision. I know that opening up about it could expose me to judgment and stigma, which is something I deeply fear. I worry that people might look at me differently, treat me unfairly, or even reject me entirely. So far, the only person who knows about my HIV status is my father. I trust him completely, and I feel safe sharing this part of my life with him. Beyond that, I have no desire or plan to tell anyone else*." 44:19 ¶ 9 in P1

One key informant stated, "*Except for my family, no one knows about my HIV status. As a college student, I am very cautious about disclosing this information to friends or others. I am concerned that their reactions might not meet my expectations; they could be supportive, or they might respond negatively. Fearing stigma and discrimination, I prefer to keep my HIV status private, sharing it only with my family*." 47:9 ¶ 7 in P4

The researcher assessed the participation of PLHIV in peer support groups. One of the key informants, while acknowledging its importance, expressed concern, stating, *"I am not currently participating in any social support groups. My decision stems from concerns about privacy and confidentiality, as I fear that joining such groups might inadvertently disclose my HIV status to others. Additionally, I worry about facing stigma and discrimination, which are prevalent in my community. However, I acknowledge that support groups can offer benefits, such as emotional support, shared experiences, and practical advice on adhering to antiretroviral therapy. If I were to consider joining a support group, I would find it most beneficial if the group ensured strict confidentiality, provided a non-judgmental environment, and offered flexible meeting times to accommodate my schedule."*

The other KII participant said,

"…I haven't joined any social support groups. It is not that I do not see their value; However, I have some reservations. I am concerned about my privacy and the possibility of unintended disclosure of my HIV status, which could lead to stigma or discrimination

Theme 4. Low community awareness of HIV leads to non-disclosure of HIV status

Participants raised their concern that low community awareness leads to a non-disclosure of their HIV status. A key informant interview expressed,

"*Since the community's awareness about HIV transmission is still low, I avoid carrying my medication to school or the workplace to prevent being seen and possibly stigmatized or discriminated against. Instead, I ensure that I stay at home during my medication time to avoid missing a dose. This decision stems from a fear of judgment and the negative reactions I might face if someone discovers my HIV status. While this approach helps me adhere to my treatment schedule, it limits my flexibility and affects my daily routine, as I have to plan my activities around being at home for my doses. I hope that with increased community awareness and education about HIV, I can take my medication confidently, no matter where I am, without fear of stigma or discrimination*." 44:21 ¶ 20 in P1

The other one said, "*I'm reluctant to disclose my condition to others because I'm afraid of potential discrimination and unsure of how they might react."* 46:8 ¶ 7 in P3

One participant said; *"…Despite increasing awareness about HIV within the community, stigma and discrimination against PLHIV persist. To avoid prejudgment, I choose to keep my HIV status confidential, sharing it only with my family. I also manage my medication privately to prevent any potential discrimination."* 47:11 ¶ 14 in P4.

Theme 5. Lifestyle and behavioral factors leads to poor adherence.

Participants also expressed the lifestyle and behavioral factors affected the adherence to ART medication. One key informant expressed that;

"*There have been times when I have missed doses of my ART during social activities. The fear of stigma associated with taking my medication in front of others has led me to skip doses to avoid potential judgment or discrimination."* 48:6 ¶ 11 in P5.

One PLHIV who lives outside Addis said, "*I am living outside Addis Ababa, sometimes I am encountering difficulty in maintaining my appointment date. Due to this, I am missing some doses of my ART*." 50:1 ¶ 11 in P7.

One of the key informants who lives far from the Hospital said that, "*I have never missed a dose of ART due to difficulties in reaching the health facility. However, I have missed doses because of the stigma associated with HIV. The fear of others discovering my status makes me hesitant to take my medication in public or even discuss my condition, leading to missed or delayed doses. This fear of stigma and discrimination has a significant impact on my adherence to the treatment regimen."*

To address stigma and discrimination and improve patient adherence to ART, community awareness efforts must be strengthened. HIV awareness has declined in recent years, with less media coverage and growing misconceptions in the community, such as the belief that HIV has been eliminated. 12:41 ¶ 25 in F 1

4.18.2 Findings from focus group discussion

Understanding the factors influencing adherence to second line ART is crucial for improving treatment outcomes, patient lifestyle, and ensuring the long-term success of HIV programs. To gain insights from a programmatic perspective as a way of "hearing from the horse's mouth," three different focus group discussion (FGD) sessions were conducted with 6 to 7 participants each, including ART service providers and HIV program managers working at AACAHB regional health bureau, sub-city health department, and two hospital levels.

The findings presented in the following sections offer a comprehensive overview of ART adherence from both a service delivery and programmatic standpoint, highlighting practical, scalable solutions to strengthen adherence support and improve treatment outcomes for PLHIV on second line ART.

The FGD participants identified key barriers mainly associated with psychological, emotional, psychosocial, cultural, and religious factors, explored successful strategies, and proposed innovative solutions to enhance patient adherence to ART. For simplicity and clarity, the researcher presented the findings accordingly.

4.18.2.1 Barriers to ART Adherence Participants from the three FGD thoroughly discussed the factors that negatively affected the adherence to ART. Among the adherence barriers stigma and discrimination been discussed more. Accordingly, an FGD discussant said,

"Many PLHIV are afraid of stigma and discrimination, so they choose to keep their status a secret. Because of this, they miss out on the help they could get from their family, partner, and colleagues, which could have made it easier for them to follow their treatment properly." 12:36 ¶ 10 in F 1.

One of the FGD participants from the Hospital indicated that, "*for many patients, economic difficulties and financial instability make it hard to stay adherent. Some clients travel long distances, even from regional states, to access their ART due to fear of social stigma and discrimination. This creates a significant barrier, as the long journey adds transportation challenges, making it harder for them to consistently adhere to their treatment."* 12:42 ¶ 26 in F 2.

ART providers in the FGD described that "*many PLHIV struggle to accept their HIV-positive diagnosis, experiencing denial, disbelief, or panic. This emotional distress can lead to delayed treatment adherence, potentially affecting their long-term health outcomes*."

Another FGD participant stated that stigma hinders support from others. Participants said, "*Many PLHIV fear stigma and discrimination, mainly perceived stigma, so they choose to keep their status a secret. Because of this, they miss out on the help they could receive from their family, partners, and colleagues, which could make it easier for them to adhere to their treatment."*

In line with this, the study examined various mechanisms aimed at addressing stigma and discrimination, recognizing the significant impact of these issues on the adherence of PLHIV to ART. It explored strategies such as community awareness to reduce misinformation and improve socio-cultural barriers. By tackling these barriers, the study aimed to identify effective approaches to improve ART adherence and overall well-being among PLHIV.

One FGD participant said, "*To address stigma and discrimination and improve patient adherence to ART, community awareness efforts must be strengthened. HIV awareness has declined in recent years, with less media coverage and growing misconceptions in the*

community, such as the belief that HIV has eliminated. In reality, new infections are still under diagnosis. To tackle this, we need to revitalize public education campaigns, stakeholder engagement, engage the media, and increase community-level education about HIV, its transmission, and the importance of treatment adherence." 12:48 ¶ 25 in F 3.

Another participant seconded it, "*While there has been some progress in reducing social stigma and discrimination against PLHIV in the community, challenges still persist…. To truly address this issue and improve patient adherence to ART, a multi-sectorial collaborative approach is essential to create a more supportive and inclusive environment for PLHIV, reduce misconceptions, and foster a culture of respect and acceptance*." 12:49 ¶ 26 in F 3.

Substance addiction identified as a barrier to PLHIV taking ART. From the focus group discussions, an adherence supporter at the hospital level raised, "*We've observed that substance addiction significantly affects patients' ability to adhere to their ART. When individuals struggle with addiction, they often forget or neglect their medication, leading to missed doses and poor treatment outcomes."* 12:23 ¶ 6 in F 1.

Misconceptions about ART also highlighted one of the barriers to good adherence. A case manager at the hospital noted during the FGD that, "Misconceptions surrounding ART, such as fears of side effects and doubts about its effectiveness, often discourage patients from remaining on their treatment."

Hospital-level FGD participants shared religious insight as a barrier to adherence, "*We've encountered instances where certain religious believers patients considered as they have been 'cured' of HIV through prayer, resulting in them discontinuing their ART without consulting us. Additionally, some patients personally believe they are cured after engaging in some religious practices. Consequently, they stop their medication, assuming it is no longer needed. This misunderstanding poses a serious risk to their health because discontinuing ART can lead to disease progression and virological failure*."

The FGD discussion also explored economic problem and distance as barriers to adherence. An FGD discussant from the hospital indicated, "*Many patients face economic challenges and financial instability, which make it hard for them to adhere. Some clients travel long distances, even from regional states, to access their ART due to fear of social stigma and discrimination. This creates a significant obstacle, as the long journey adds transportation*

challenges, making it difficult for them to consistently follow their treatment." 12:45 ¶ 9 in F 1

ART focal persons shared a particular case of a client who traveled 397 KM from a regional state to Addis Ababa for his medication, "…recently, a client missed his appointment simply because he couldn't find transportation due to road inaccessibility." 12:36 ¶ 10 in F 2.

The shortage of second line and third-line ART is another issue. A case manager remarked, "*Sometimes when the hospital faces stock outs, patients are often referred to other health facilities to collect their treatment. However, this process can be discouraging for them and may lead some to miss doses."*

Other factors for poor adherence mentioned was food insecurity. A case manager expressed that, *"…there are patients experience food insecurity, with some even requesting food support from us. When patients lack proper nutrition, the risk of treatment interruption increases."* 12:31 ¶ 23 in F 1.

4.18.2.2 Successful strategies to improve adherence to ART

The study explored successful strategies for improving patient adherence to ART. Participants highlighted several effective approaches, including the Differentiated Service Delivery (DSD) model, such as three-Month Multi-Month Dispensing (3MMD), which reduces the burden of frequent hospital visits. Other key strategies included adherence support programs, youth programs, Enhanced Adherence Counseling (EAC), and pill counts for monitoring and encouraging treatment adherence.

As a result the ART focal highlighted the following, "*For patients with Advanced HIV Disease (AHD), specialized care and follow-up services have been established to ensure better health outcomes. Moreover, Community ART Groups (CAGs) and Peer Community ART Groups (PCAGs) have proven to be highly effective, as they provide peer support and motivation. These strategies, implemented by the government and development partners, have significantly contributed to improving ART adherence*." 12:29 ¶ 17 in F 1.

One of the ART provider said, *"…the 3MMD model allowing stable patients to receive three months' worth of medication at once, reducing frequent hospital visits*." 12:27 ¶ 15 in F 2.

An adherence supporter said, "…*We've also seen positive outcomes from Enhanced Adherence Counseling, where we provide continuous support for patients struggling with adherence and Pill counts help us monitor whether patients are taking their medication correctly*."

ART provider also added, "…*the CAG program facilitates patients' support each other in managing their treatment and similarly the PCAG have been very effective as patients find it easier to stay on ART when they are encouraged by others who share the same experience*." 12:29 ¶ 17 in F 2

4.18.2.3 Challenges associated with implementing the best identified Strategies

The study also looks at the challenges associated with implementing the above-mentioned strategies at the hospital and programmatic levels. Accordingly, the FGD participants noted that despite the effectiveness of these strategies, some programs are regressing due to inadequate funding for the ART program and shortages of second- and third-line ART.

One of the ART focal said, "…*Due to the shortage of second line ART drugs, we are unable to implement the 3MMD DSD model. Currently, we only provide second line ART on a monthly basis. If we had an adequate supply of these medications, we preferred and could extend patients' appointments to two or three months, making it possible to fully implement the 3MMD DSD model*." 12:37 ¶ 19 in F 1

The study also explored the required resources to improve PLHIV adherence. Accordingly, FGD participants raised adequate human resources, improved infrastructure, uninterrupted ART drug supply, financial support, and nutrition support.

One of the hospital ART focal persons said, "…*We need adequate and skilled healthcare providers to deliver comprehensive and quality adherence counseling and follow-up services*." 12:46 ¶ 21 in F 1.

The other adherence counselor said, "…*private adherence counseling rooms foster trust and uphold privacy, allowing patients to openly discuss their concerns without fear of stigma or judgment*." She also added, "…*Improved infrastructure, like adequate and comfortable*

waiting areas equipped with TV screens, can improve patient engagement and education by providing valuable information about HIV and ART adherence." 12:39 ¶ 21 in F 2

In relation to second line ART supply, one of the ART providers said, "… *giving patients a longer refill period, like the 3-month multi-month dispensing (3MMD), really helps. It reduces the number of visits to the hospital, which is important for those who live far away or have work commitments. When patients do not have to come to the Hospital every month just for a refill, they are more likely to continue taking their medication properly. It also reduces the workload for health workers, allowing them to focus on those who need more attention, like new patients or those struggling with adherence*." 12:40 ¶ 22 in F 1.

Concerning nutrition, a case manager says, *"…there are patients who experience food insecurity, with some even requesting food support from us. When patients lack proper nutrition, the risk of treatment interruption increases. Providing nutrition support, whether through direct food assistance or linkage to social programs, can play a crucial role in improving adherence rates and enhancing overall patient well-being*." 12:31 ¶ 23 in F 1.

4.18.2.4 Use technology to improve patient adherence to ART

Furthermore, the study explored technology-driven initiatives aimed at improving ART adherence among PLHIV. FGD participants highlighted the use of Short Message Service **(**SMS), particularly for patients with a high viral load, as well as phone alarm reminders to support medication adherence. Additionally, the implementation of the SMART Care electronic medical record initiative was emphasized as a critical strategy for tracking missed appointments and identifying patients lost to follow-up.

To further strengthen adherence support, a hospital adherence supporter recommended introducing an online system for real-time high viral load test notifications and remote adherence counseling. She added that such a system would ensure timely interventions and enhance ART adherence.

4.18.2.5 Overall effectiveness of the ART program

In the current extreme variability and scarcity world, having an effective and efficient ART program is crucial for sustainably controlling HIV/AIDS. It significantly lowers viral loads, reduces the occurrence of opportunistic infections, and enhances the quality of life and

survival rates for PLHIV. Accordingly, the study assessed the overall effectiveness of the ART program from the perspective of FGD discussants. The FGD participants noted that the effectiveness of the HIV program is being evaluated through management reviews, periodic program performance assessments, catchment area meetings, and joint supportive supervision.

As a result, a program expert stated, "*The success of the ART program has played a crucial role in saving the lives of PLHIV. Mortality due to HIV has significantly decreased compared to previous years, which indicates the effectiveness of the program*." 12:43 ¶ 30 in F 1.

Another ART focal also emphasized, "*We can measure the success of the ART program through viral load results. The viral load suppression rate is close to 95%, demonstrating that the ART program has been highly successful."*

4.19 TRIANGULATION AND INTERPRETATION OF QUANTITATIVE AND QUALITATIVE FINDINGS

The Triangulation enhances the credibility of research by combining quantitative and qualitative data to confirm patterns and reduce bias. Quantitative analysis reveals measurable trends, while qualitative insights delve into underlying reasons and lived experiences. This approach creates a comprehensive perspective, leading to more accurate conclusions and targeted interventions. Properly interpreted triangulated data strengthens evidence-based decision-making, helping to shape effective policies, interventions, and strategies across various sectors.

Quantitative findings on the magnitude of second-line ART virological falire and its risk factors among PLHIV, are explained by qualitative KII findings on factors affecting, and quantitative findings on significant factors associated with the level of second-line ART VF among adult PLHIV are explained by qualitative FGD findings on barriers to second line ART adherence to second-line ART and the relationship between factors .

Accordingly, in this research, the researcher interprets and triangulates the quantitative and qualitative findings are organized into four themes for clarity and ease of understanding for fellow readers.

Theme 1: Effect of non-disclosure of HIV status.

The findings of this study offer an insightful understanding of the factors influencing second line virological failure among PLHIV. Quantitative data from this study revealed a statistically significant association between non-disclosure of HIV status to anyone and a potential for an increased risk of virological failure. This finding is strongly supported by our recent qualitative data from hospital-level ART providers and program managers participating in FGDs. It emphasizes that the lack of social support associated with non-disclosure hinders adherence to medication regimens. They highlighted those individuals who disclose their status to partners, relatives, or parents often benefit from emotional, practical, and reminder support, positively impacting treatment adherence.

Despite the seemingly positive aspects of disclosure indicated by the quantitative data and focus group discussions, KII respondents expressed concerns. They warned that in areas where community awareness about HIV is low and social stigma and discrimination are prevalent, disclosure may lead to non-adherence to treatment. They explained that fear of negative social consequences, such as rejection, isolation, and discrimination, might cause individuals to miss their doses, especially when participating in social activities or when away from home, where they may have more control over their privacy and medication routines. The KII findings suggest that in areas where community understanding and acceptance of HIV are limited, the act of disclosure, while potentially beneficial for some, could create significant barriers to adherence for others due to the anticipated or experienced negative social impacts.

The triangulation of these findings regarding HIV status disclosure reveals a nuanced relationship between disclosure, social context, and virological outcomes. Non-disclosure appears to be a significant risk factor for virological failure. Therefore, the lack of essential social support and the potential negative consequences of disclosure in stigmatizing environments cannot be overlooked.

Interventions that promote disclosure as a strategy to improve adherence and prevent virological failure must be carefully tailored to the specific context. These interventions should be accompanied by strong efforts to raise community awareness about HIV, reduce stigma and discrimination, and create supportive environments for individuals living with HIV. Additionally, healthcare providers should be proficient in assessing the unique

circumstances of each patient and support them in making informed decisions about disclosure. This should involve considering both the potential benefits of social support and the risks associated with stigma in their specific social contexts. Additional further research should investigate how social support and perceived stigma mediate the relationship between disclosure and virological outcomes to refine understanding of these dynamics.

Theme 2: Impact of transfer to higher-level care and geographical distance on second line Virological failure.

The quantitative analysis of this study identified that being a transferred-in client from another health facility for ART care is a significant risk factor for virological failure on second line therapy. This finding aligns strongly with insights gathered from the qualitative research components, including FGDs and KIIs.

Participants in the FGDs, which included healthcare providers and program managers, highlighted several key reasons why transferred-in clients could be at risk for virological failure. They explained that transfers to higher-level facilities often occur when patients on second line ART experience recurring comorbidities that their initial health facilities are unable to manage. This suggests that transferred-in clients may already have a more complex clinical history and potentially compromised health status, making it more challenging to achieve virological control.

Both the FGD and KII highlighted that geographical distance to the ART health facility significantly affected patient's outcome. Transfers to nearby facilities are sometimes implemented for patients residing far from their original clinic. However, the qualitative data demonstrate a concerning consequence of distance: patients living far away, regardless of whether they were transferred or not, are more prone to second line virological failure due to difficulties in adhering to their medication schedules and maintaining consistent engagement with care. This can manifest as missed ART doses and an increased likelihood of being lost to follow-up. The act of transferring, particularly if it disrupts established routines and support systems, may exacerbate these challenges for clients already vulnerable due to distance. Additionally, transferring patients can disrupt their established routines and support systems, potentially worsening the difficulties faced by those already vulnerable due to distance.

The concordance between quantitative and qualitative findings of this study provided a robust understanding of the association. Therefore, interventions designed to improve outcomes for patients on second line ART, particularly those who have been transferred in, should take into account the multifaceted reasons behind their transfer. Enhanced support systems to ensure adherence for patients living in distant areas, regardless of transfer status, are crucial. Moreover, receiving facilities should be particularly attentive in assessing the needs of transferred-in clients, considering their prior clinical history and potential challenges in maintaining consistent care. Strategies to facilitate a smooth transition and address potential barriers to adherence for this population are essential to optimize virological outcomes.

Theme 3: Burden of Side Effects and Second line ART Regimen Change

The quantitative findings of the study indicate that a change in second line ART regimen is a significant contributing risk factor for subsequent second line virological failure. Notably, the primary reason for these regimen changes was the occurrence of ART side effects/toxicity. This quantitative result finds strong convergence with the insights derived from the qualitative component of the research. Both KIIs and FGD participants consistently highlighted drug side effects or toxicity as a major barrier to adherence, which they identified as a leading cause of second line virological failure.

Discussants from both KIIs and FGDs explained that the experience of intolerable side effects often leads patients to deviate from their prescribed ART schedule. This leads to missed doses of ART, an effort to alleviate the experienced discomfort. This pattern of non-adherence undermines the effectiveness of the second line ART regimen and consequently increases the likelihood of virological failure.

The concordance between the quantitative identification of regimen change as a risk factor and the qualitative articulation of how side effects lead to non-adherence provides a coherent understanding of second line virological failure.

Therefore, interventions aimed at improving outcomes for patients on second line ART must prioritize the timely and effective management of drug side effects and toxicities. This includes proactive monitoring for potential adverse events, providing comprehensive patient

counseling on managing side effects, exploring alternative regimens with better tolerability when appropriate, and offering strong support systems to help patients maintain adherence even when experiencing discomfort. Addressing the root cause of regimen changes, drug intolerance is crucial to preventing subsequent virological failure in PLHIV taking second line ART.

Theme 4: Impact of LTFU on second line virological outcome

The quantitative data clearly shows a strong association between patients who have been LTFU in their HIV care and an increased risk of experiencing second line virological failure. This indicates that interruptions in consistent care negatively impact treatment success.

The qualitative segment of the research suggests that experiences of stigma and discrimination can lead patients to disengage from care, resulting in missed antiretroviral therapy (ART) doses and ultimately contributing to virological failure. This underscores the significant role that psychosocial factors play in treatment adherence.

The convergence of both quantitative and qualitative data reveals a clear link between disruptions in care, specifically LTFU, and an increased risk of virological failure. While quantitative studies have established this correlation, qualitative research provides deeper insights into the reasons behind LTFU, highlighting the complex relationship of stigma and discrimination.

4.20 SUMMARY OF RESEARCH FINDINGS

The overall magnitude of virological failure among PLHIV taking second line ART aged 18 years and older from 2018 to 2022 in Addis Ababa, Ethiopia, is 14.9% (55/369) of the total study subjects, with 20,187 person-months (PM) of observations.

The summarized incidence density was 2.72 per 1,000 PM, with a 95% confidence interval (CI) of [2.11, 3.55], or 33 per 1,000 person-years (PY) with a 95% CI of [25.0, 42.0]. The cumulative probability of failure at 24 months was 4.5% (95% CI 3.1% to 7.6%), and at 48 months, it was 34.2% (95% CI 29.6% to 39.3%).

The findings indicate that the probability of having risk of VF in patients receiving second line ART was higher among those patients transferred in, with suboptimal adherence to ART, a

history of regimen change, coupled with non-disclosure of HIV status, and being lost to follow-up (LTFU) from HIV care while on second line ART.

Contributing factors to poor adherence were explored from adult PLHIV taking second line ART, ART service providers, and HIV program managers. Stigma and discrimination, low community awareness of HIV, distance, socio-economic, and socio-cultural issues are explored as the major barriers.

Besides the barriers, program improvement solutions were also proposed by the FGD discussants, in which community awareness programs, implementing and sustaining the DSD model, nutrition support, and calling up donors to improve the ART program were among the strategies mentioned by the ART service providers and program managers.

People living with HIV (PLHIV) face numerous challenges, including the burden of long-term medication, side effects, and the fear of stigma, which leads to missed doses and secrecy about their status. Many refrain from disclosing their HIV status, even to close family, due to fears of discrimination, resulting in limited emotional and practical support.

CHAPTER 5

DISCUSSION

In this section, the researcher analyzes and interprets the recent research findings in light of the latest available literature, identifying them as either concordant or discordant, to provide a clear insight to fellow readers.

5.1 MAGNITUDE OF SECOND LINE ART VIROLOGICAL FAILURE

This study assessed the magnitude of virological failure among people living with HIV (PLHIV) taking second line ART, aged 18 years and older, from 2018 to 2022 in Addis Ababa, Ethiopia. It was found that 14.9% (55/369) of the total study subjects, which is concordance with a study with an overall prevalence rate of VF of 15.4% in Ethiopia (Masresha, Kidie, Alen, Mulaw, Feleke, Kassaw, and Dejene 2023:6) and done in Pune, India, with a virological failure of 15% (59/400) of the study participants (Salvi, Raichur, Kadam, Sangle, Gupte, Nevrekar, Patil, Chavan, Nimkar, Marbaniang, and Mave 2022:3).

The finding is also significantly higher than the rates observed in other studies with a VF of 44 (12.22%) in Ethiopia (Zakaria et al 2022:5) which is more concordance and supported by previous studies carried out in a similar sub-Saharan countries, in Rwanda, with a virological failure 12% for 26 months (Ndahimana, Riedel, Mwumvaneza, Sebuhoro, Uwimbabazi, Kubwimana, Mugabo, Mulindabigwi, Kirk, Kanters, Forrest, Jagodzinski, Peel, Ribakare, Redfield and Nsanzimana 2016:4), and in Tanzania, a study reported a 12.18% prevalence of virological failure among participants on second line ART over six months of follow-up conducted by Gunda et al. in 2019 (Gunda et al 2019:3). However, it was found far from the recent WHO-recommended target, which sets a threshold for virological failure (VF) at less than 10% (WHO 2021:197). and also the 95% UNAIDS viral suppression target by 2025 (Joint United Nations Programme on HIV/AIDS (UNAIDS 2023:1).

Moreover, the finding of this study revealed that, is slightly lower as compared with a previous similar studies done in Ethiopia with a pooled prevalence of virological failure of 15.95% done by Aytenew (Aytenew, Asferie, Ejigu, Birhane, Tiruneh, Kassaw, Asnakew, Legas, Munie, Belay, Ewunetu, Kefale, and Kebede 2024:4) and a study done in Tanzania reported a virological failure rate of 29.72% over a two-year follow-up period (Mwavika et a*l* 2024:7).

This finding was slightly lower than that of a study conducted in China, which reported a cumulative virological failure rate of 18.45% among the high/low-level viremia group (Qin et al 2021:4), and a cohort study conducted in Malawi showed that 32% of participants experienced virological failure while on second line ART (Gupta-Wright et al 2020:4).

The variability difference across all magnitudes of VF in these studies may be attributed to differences in study designs, which might arise from disparities in health system-related gaps, variations in country context and development, urban complexities, population characteristics, methodological approaches, and study settings.

5.2 RISK FACTORS CONTRIBUTING TO VIROLOGICAL FAILURE

Virological failure in an HIV treatment regimen occurs when individuals living with HIV are unable to suppress viral replication despite starting treatment, or could rebound after an initial suppression. This failure can lead to increased risks of disease progression, medication toxicity, and drug resistance. It is often associated with risk predictors that contribute to high rates of virological failure (Musana et al 2021:7).

In this context, several risk factors were found to be significantly associated with VF, including poor adherence, noncompliance with medical care, lost to follow-up, transfer in from other health facilities for follow-up, having a history of frequent regimen changes, and drug toxicity.

Adherence is defined as ‘the act of following the provider's instructions regarding the timing, dosage, and frequency of medication intake’ (Cramer et al 2008:3). Similarly, a study by Aytenew (Aytenew et al 2024:4), and it’s supported by another similar study conducted by Opoku in Ghana (Opoku, Sakyi, Ayisi-Boateng, Enimil, Senu, Ansah, Aning, Ojuang, Wekesa, Ahmed, Okeke and Sarfo 2022:5), which is concordant with this research finding as clients with poor adherence to ART present a significant risk factor for VF, with an AOR of 6.641 (95% CI: 1.077, 40.95, P-value: 0.041).

Similarly, this study found that individuals who were transferred in from other health facilities were 2.726 times more likely to exhibit a high viral load and at a higher risk of virological failure than those who had care at their original enrolled health facility. This could be due to a lack of continuity of follow-up clinical monitoring, unformed patients to clinical provider relationship, communication gaps between referring and receiving health facilities. Perceived

patients safety and comfort variability in care quality, and logistic and related administrative factors and which could increase the potential of treatment disruption and worsening the virological failures (Tian 2023:11; Yayehrad, Getachew and Muluken 2024:5).

Thus, transferred-in patients were prone to related challenges that elevate the risk of virological treatment failure. Having standardized referral systems, enhancing digitalizing record-sharing systems, and providing robust individualized adherence support are some of the most essential prioritized activities for improving treatment outcomes.

Loss to follow-up was another risk factor associated with non-suppressed virological failure among PLHIV. Patients who are lost to follow-up (LTFU) from their HIV care while on second line antiretroviral therapy (ART) face a significantly higher risk of virological failure, with an adjusted odds ratio (AOR) of 6.007 (95% CI: 2.778–12.990, p-value < 0.001), compared to those who adhere consistently to their treatment care. Evidence from Ethiopia (Alemu, Tesfie, Abuhay, Mengistu, Awoke, Kefale, Beyene, and Nibret 2024: 7; Endebu, Taye and Deressa 2024:4), Nigeria (Endebu, Taye and Deressa, 2024) and South Africa further highlights LTFU as a key contributing factor to virological non-suppression (van Liere, Lilian, Dunlop, Tait, Rees, Mabitsi, Ranoto, Struthers, McIntyre, and Peters 2021:6). This underscores the importance of maintaining comprehensive follow-up care to minimize virological failure and improve patient outcomes.

This could lead to drug resistance mostly because of frequent interruption or on and off, interrupted adherence, missed opportunities for timely drug and treatment adjustments, and loss of re-engagement. Hence, to overcome this, a proactive retention strategy, targeted and differential service modalities for the strong re-instatement and engagement in the treatment follow-up are very crucial, as indicated in this research qualitative study participants highlighted as well.

Patients who have experienced regimen change of their second line ART follow-up are twice as likely (AOR: 2.05; 95% CI: 1.08–3.88) to experience virological failure as compared to clients with fewer regimen change experiences. This finding was supported by a similar study conducted in China found that individuals who modified their ART regimen were 1.728 times more likely to exhibit a high viral load than those who adhered to their original treatment regimen (Qin et al 2021).

This could be psychological fatigue, cross-resistance with residue of drugs in absorbance by the client's circulation system,

Loss of trust in the treatment and diminished confidence in its effectiveness , which could lead to accumulative drug related treatment failure vulnerabilities.

Regimen changes during ART follow-up may lead to virological failure, while drug interactions can affect drug levels, efficacy, and toxicity. Addressing adherence, monitoring interactions, and selecting appropriate regimens are key to preventing second line ART failure. Continuous monitoring and personalized care are essential for better outcomes (Huang, Xu, Sun, LGao, Cai, Liu, Ding, Wei, Ma, Wang, Liu, Chen, Chen, Zhao, Yu, Song, Chen, Wu, Qin and Li 2019:4).

Thus, identifying and timely mitigating these contributing risk factors was at most important to improve the PLHIV quality of life.

5.3 ADHERENCE TO ART

5.3 .1 LEVEL OF ADHERENCE TO AR

Study results indicated that optimal adherence to the prescribed ART drugs was a significant factor in successful viral load suppression. The recent study indicates that clients with poor adherence to ART are a significant risk factor for virological treatment failure, with an AOR of 6.641 (95% CI: 1.077, 40.95, p-value: 0.041). It is in concordance with studies in Ethiopia shown that individuals with poor adherence are significantly more likely to experience virological failure compared to those with good adherence. Patients with poor adherence were six times more likely to develop VF compared to those with good adherence (Ambaw et al 2024:9,10).

This finding is also supported by research in South Africa stated that non-adherence to ART is the most identified cause for second line ART VF (Levison et al 2012:5).

The focus group discussions and key informant interview (KII) findings in this study revealed that stigma and discrimination, particularly perceived stigma, remain significant risk factors for non-virological suppression among HIV-positive clients on second line antiretroviral therapy (ART). This finding is supported by a study conducted in Rwanda, reinforcing the evidence that stigma serves as a significant barrier to ART adherence and may potentially

drive virological failure (Niyonsenga, Habimana and Nsanzabera, 2025:20). This can contribute to suboptimal adherence to treatment and loss of engagement in care due to fears of disclosure and uncertainty about the consequences. As a result, this can lead to suboptimal health outcomes and poor quality of life. Previous studies, including those conducted by Perger and Madiba also identified that stigma had significantly associated factor for poor adherence that could lead to a virological failure (Madiba, Wu, Tan, Chen, Wang, Liao and Jiang 2024:7 and Josiah 2019:4,5; Perger, Davtyan, Foster, Evangeli, Berman, Kacanek, Puga, Sekidde and Bhopal 2024:8).

Besides, individuals experiencing drug toxicity in their treatment follow-up course that can lead to suboptimal adherence to the prescribed regimen of ART have non-virological suppression, which directly and potentially leads to virological failure, compared with those who did not, which is supported by other studies (Lailulo et al 2020:7; Ambaw et al 2024:10).

Furthermore, findings in this research underscores the importance and role of EAC in HIV ART viral suppression among second line ART clients, as 38% of the study participants achieved HIV viral suppression through EAC. It is a structured intervention aimed at helping patients achieve and sustain viral suppression. It focuses on identifying and addressing the suboptimal adherence barriers by developing personalized plans to support medication adherence (Ambaw et al 2024:9,10). Poor adherence to ART remains a significant risk factor for virological failure, resulting in increased HIV viral load, the development of drug resistance, and a heightened risk of HIV transmission. The effectiveness of EAC is attributed to its individualized clients' counseling schedule that overcomes adherence hurdles, which aligns with findings from previous similar studies conducted in Ethiopia (Diress, Dagne, Alemnew, Adane and Addisu 2020:4) , in Nigeria (Obasa, Ijaiya, Okwor, Dare, Emerenini, Oladigbolu, Anyanwu, Akinjeji, Brickson, Zech, Ogundare, Atuma, Strachan, Fayorsey and Curran 2024: 5). and in Cameron (Agbornkwai, Bita, Mabouna, Esa, Ngongheh, Ketum, Akateh, Ngunyi, Tanah, Wolloh and Tadzong-Awasum 2022:6).

Recognizing the timing and likelihood of treatment failure can reduce unnecessary complications and prevent the loss of overlooked conditions. It enables proactive clinical management, allowing clinicians to anticipate treatment failure and implement timely interventions before the patient's health deteriorates. This approach helps safeguard treatment options, enhances long-term viral suppression, and improves overall patient

outcomes. Additionally, it facilitates earlier detection of resistance mutations, enabling the refinement of subsequent antiretroviral therapy (ART) regimens. Such insights contribute to optimizing the effective duration of available therapies.

Accordingly, this study revealed that a total of 55 (14.9%) ART clients developed second line treatment failure in 20,187 person-months of the total analysis time at risk and under person per month (PM) of observations. The overall incidence density was 27.2 per 10000 PM or 33 per 1000 person-years. This is more in line with a study by Abuhay as virological failure with developed second line virological failure, with a median follow-up time of 29 months, withan incidence density of 37 per 1,000 person-years(PY) (Abuhay Endalew, Birhan and Muche 2024:5)

Likewise, this result point out that the time to second line treatment failure was longer compared to findings from previous research studies. Alene M. et al. reported a median time of 13.23 months, while Pujades-Rodríguez observed 11.9 months. The variation could be attributed to differences in the criteria used to define treatment failure and the study periods covered by the respective studies (Pujades-rodrı, Balkan, Arnould, Brinkhof and Calmy 2010:5; Alene, Awoke, Yenit and Tsegaye 2019:4).

5.3 .2 LEVEL OF ADHERENCE from Health Belief Model (HBM) perspective TO ART

Perceived susceptibility:

Several participants expressed limited understanding of their likelihood of experiencing secnd line ART VF. This low perceived susceptibility may explain the suboptimal adherence of seen in the study. Similar patter have been reported in Ethiopia, where PLHIV in rural area and those who did not disclose their HIV status were less adherent to ART (Angelo and Alemayehu 2021:6). The qualitative finding from recent study also reflected, persistent stigma and fear of disclosure which discourage some participants taking their medication outside their homes during some social activities. This aligns with studies from Sierra Leone and Uganda demonstrating that stigma reduces perceived control and disrupts adherence behavior (Lahai et al 2022:5 and Bukenya et al 2019:5). Thus, the current study findings confirm that, perceived susceptibility is shaped by social barriers such as, stigma and fear of disclosure, which continue undermine the second line ART outcome.

Perceived Severity:

Although most participants acknowledged the seriousness of HIV infection, many didn't clearly understand the consequences of second line ART VF. Patients with comorbidity or advanced clinical stage in this study were more likely to report adherence challenges, supporting findings from Angelo and Alemayehu (2021:6) that comorbid illness and WHO clinical stage II reduces adherence to ART. The limited awareness about the clinical severity and long term consequences of VF suggested a gap in patient education. The poor perceived severity may prevent individuals from fully appreciating the importance of strict adherence to second line regimen thereby increasing the vulnerability to second line ART VF.

Perceived Benefit:

The study showed that, patient who received adequate counseling and directly collected their ART medication from health facility were more motivated to adhere. This supports evidence from Nepal, where direct engagement with ART centers improved adherence (Neupane, Dhungana, and Ghimire, 2019:4). Competing responsibilities and forgetfulness, also seen in Peru (Leyva-Moral, Loayza-Enriquez, Palmieri, Guevara-Vasquez, Elias-Bravo, Edwards, Feijoo-Cid, Davila-Olano, Rodriguez-Llanos and Leon-Jimenez. 2019:8) were identified in this study as factors diminishing the perceived benefits. These findings highlight that, perceived benefits alone are not sufficient unless supported by reminder, support and patient centered support system.

Perceived barriers:

The current study identified several barriers influencing adherence to second line ART, consistent with the HBM construct of perceived barriers. Drug toxicity, pill burden, side effect ad complexity of second line regimen discouraged consistent use. Findings from Cameron and Ethiopia supported these (Buh, Deonandan, Gomes, Krentel, Oladimeji and Yaya 2023:16) and Nega, Taye, Million, Rodrigo and Eshetie 2020:4-7). Distance from health Facility, transportation cost and economic strain further complicated adherence especially patients with unstable income. These structural barriers overshadowed perceived benefits for many patients. Moreover, drug related toxicities contributed directly to VF reflecting

Global evidence that adverse effects remain a leading cause of ART discontinuation that leads to poor adherence

5.4 TIME TO SWITCH TO THIRD-LINE ART

A timely transition and switching to the appropriate next regimen is highly important, as the recent “WHO consolidated guidelines on HIV prevention, testing, and treatment” (WHO 2021:150) recommend prompt switching to the next appropriate regimen to halt the worst viral replication. Accordingly, a timely transition to the appropriate regimen is most important to achieve viral suppression. In this research, patients who experienced failure with their second line ART were switched to the appropriate third-line regimen within six months after verified failure. The findings of this study were in line with a study done in Ethiopia also indicated the timely initiation of third-line ART lowered the viral load to an undetectable level (Ketema et al 2021:3)**.** A study in South Africa found that the median time to switch to third-line ART after failing second line ART was more than 16 months. Though this is far from the recommended time to transition from the second, the main reasons for the delay were the time it took to request a drug resistance test after confirmed virological failure, review the test results, and decide on third-line ART by clinicians**.** (Majova 2022:3)**.**

A similar study done by Demeke A. et al. revealed the average time for switching to the next regimen among HIV-infected adults on second line ART was a median time of 5 months, and it indicates that the risk of switching is higher among HIV infected adults as the HIV viral RNA is higher (Alemu, Moges, Boneya, Asrade, Tsega and Tewachew 2022:9).

As a result, enhancing access to third-line antiretroviral therapy (ART) and ensuring its timely initiation hold significant potential to improve the quality of life for individuals experiencing virological failure with second line ART. By addressing delays and barriers to third-line therapy, patients can benefit from more effective viral suppression, reducing the risks associated with prolonged virological failure. This proactive approach could contribute to better clinical outcomes, minimize complications, and ultimately enhance the overall well-being of affected individuals. This was supported by the study (kitaw, Abate, Yilak, Tilahun, Faris, Walle, and Haile 2024:5).

Prompt initiation of appropriate third-line ART following second line treatment failure significantly enhances virological outcomes, increasing viral suppression rates and reducing

mortality. Incorporating new drug classes, third-line ART effectively lowers viral loads in patients unresponsive to second line therapy. Timely intervention minimizes drug resistance and safeguards future treatment options (Chimbetete et al2018:6).

5.5 STRENGTHS AND LIMITATIONS OF THE STUDY

5.5.1 Strength of the study

The study was conducted in a hospital setting, and also within the routine ART program setting, and it encompasses professionals working in an actual ART program, and also includes patients' real experience, which reflects ground reality.

This recent research presents both the prevalence and contributing risk factors by employing a quantitative and qualitative mixed research design that addresses critical public health issues in Ethiopia and bridges the existing literature gaps.

Additionally, it analysed the records of PLHIVdetailed first-line ART historical data of socio-demographic and clinical treatment-related risk factors that greatly influence second line virological failure, offering valuable insights for very specific, real-time targeted intervention.

Moreover, the researcher develops a guideline for “timely management of Virological failure in adults on second line ART in Addis Ababa, Ethiopia” using existing literature and recent research findings.

5.5.2 Limitations of the study

While interpreting, inferring, and applying the findings of this research, fellow readers should take into account the following inherent limitations:

- Drug resistance testing constraints: Due to the limited capacity for drug resistance testing, the specific risk factors contributing to virological failure could not be thoroughly identified.
- Low-level viremia assessment: This study did not account for low-level viremia. Instead, we used and categorized viral loads based on a threshold of 1,000 copies/mL, primarily due to resource limitations.
- Recall bias in qualitative analysis: In the qualitative aspects of this study, there might be a potential recall bias, as participants may inaccurately remember past events, affecting

the reliability of findings. To mitigate this, we utilized a pre-tested, validated questionnaire and encouraged participants to base their responses on recent experiences.

- Incomplete and missing data: The secondary data records contained missing entries and potential errors in data recording. Consequently, these incomplete data points were excluded from the final analysis to ensure accuracy and reliability, which might have affected the fair distribution of the participant study recruitment.

5.6 OVERALL SUMMARY OF THE RESEARCH PROCESS

The overall process of the research has been summarized and visually represented by the infographic in Figure 23.

This infographic offers a thorough visual overview of the pre-analytical, analytical, and post-analytical activities carried out throughout the research process. It starts with selecting study participants and records, confirming their eligibility, monitoring HIV viral status, followed by Enhanced Adherence Support Counseling (EAC), and the prompt initiation of appropriate treatment for adult HIV-positive patients in Addis Ababa, Ethiopia, in 2024.

The figure is designed to guide readers through the process clearly and accessibly, improving their understanding of each step involved.

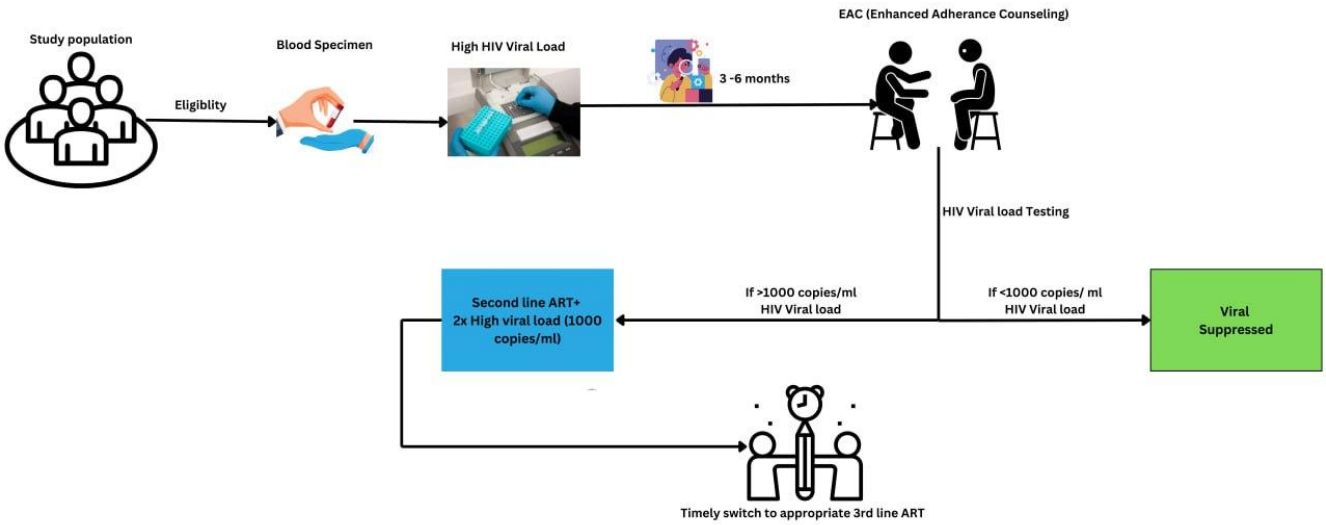


Figure 23. Info graphic abstract on second line ART VF in adult HIV positive patients in Addis Ababa, Ethiopia, 2024

CHAPTER 6

GUIDELINE FOR TIMELY MANAGEMENT OF VIROLOGICAL FAILURE IN ADULT PATIENTS ON SECOND LINE ART IN ADDIS ABABA, ETHIOPIA

6.1 INTRODUCTION

This chapter presents information on the management of virological failure in adults on second line ART in Addis Ababa, Ethiopia. Both the WHO and Ethiopian national guidelines define VF on second line ART as a viral load above 1000 copies/mL based on two consecutive measurements taken 3 months apart, following enhanced adherence support after the first high viral load. Second line ART must be taken for at least 6 months before virological failure can be determined (WHO 2016:104, FMOH Ethiopia 2018:105).

The determination of ART failure may involve clinical and immunological criteria; however, virological failure, identified through quantitative viral load testing, represents the earliest and most direct indicator of suboptimal treatment response. Viral load, by directly quantifying active HIV replication, provides a more reliable metric for patient management compared to indirect clinical observations and CD4 cell counts, which can be influenced by various factors (Assefa et al 2017:5).

This direct measurement facilitates the timely identification of treatment failure, often preceding the onset of clinical manifestations or substantial declines in CD4 counts, thereby enabling prompt interventions to mitigate the risk of drug resistance and disease progression. Furthermore, viral load determination serves as a strong predictor of disease progression and susceptibility to opportunistic infections, establishing its role as the gold standard for monitoring ART efficacy and guiding critical therapeutic decisions (FMOH Ethiopia 2018:165-166; Shoko and Chikobvu 2019:7-8).

This guideline is primarily developed based on the current study's triangulated findings from quantitative data and qualitative insights from patients, health care providers, and program managers. This integrated approach, combined with researcher analysis and a review of relevant literature, ensures a statistically sound and contextually sensitive guide for patients,

providers, and program managers, policy makers, ultimately aiming to optimize patient care in Addis Ababa.

6.2 BACKGROUND AND PRINCIPLES OF THE GUIDELINE DEVELOPMENT

According to the WHO “Handbook for the Development of Guidelines," a guideline is defined as any summarized information that comprises recommendations for clinical practice or public health policy to assist healthcare providers, recipients, and other stakeholders in making informed decisions for optimal health outcomes (WHO 2023:2-4).

The development of this guideline has adopted the WHO principles for guideline development, with careful consideration for PLHIV experiencing virological failure on second line ART, ART providers or health care workers, as well as policy makers and program managers.

The development of this guideline was guided by principles ensuring its quality and applicability: it addresses unanswered questions and unmet needs with transparent recommendations; incorporates multidisciplinary expertise and stakeholder input; minimizes bias through rigorous methods and current evidence; bases recommendations on a comprehensive assessment of benefits and harms; utilizes the most recent evidence; and allows for local adaptation. Recognizing the diverse stakeholders, including policy makers, HIV program managers, providers, and patients. The guideline’s structure and content are aligned with Ethiopia’s existing health infrastructure, informed by consultations and the active engagement of key stakeholders in HIV program management at all levels.

The guidelines are evaluated and validated by the experts from Universities, program managers, health care providers, social and adherence support team and provides summarized guidance for the timely management of virological failure in patients on second line ART in Addis Ababa, Ethiopia. It emphasizes prompt and thorough assessment of key contributing factors, utilizing timely diagnostics. Action should be swift and evidence-based, leveraging local resources and capabilities.

WHO handbook for development of guideline (WHO 2014:14) listed the following principles for process of guideline development:

- Guidelines address an area of uncertainty and an unmet need for guidance.

- Guidelines reflect the core WHO value of the “right to health.”
- The process of developing recommendations is explicit and transparent: the user can see how and why a recommendation was developed, by whom, and on what basis.
- The process of developing guidelines is multidisciplinary and includes all relevant expertise and perspectives, including input from stakeholders.
- The processes and methods used in each step of guideline development aim to minimize the risk of bias in the recommendations.
- Recommendations are based on a systematic and comprehensive assessment of the balance of a policies or intervention’s potential benefits and harms and explicit consideration of other relevant factors.
- The evidence used to develop WHO guidelines is publicly available.
- Recommendations can be implemented in, and adapted to, local settings and contexts.
- Guidelines should be tailored to a specific audience. (The audiences that WHO guidelines can target include public health policy-makers, health programme managers, health-care providers, patients, caregivers, the general public and other stakeholders).

6.3 PURPOSE AND OBJECTIVES OF DEVELOPING GUIDELINES

6.3.1 Purpose

The primary purpose of this guideline is to present updated, evidence-based guidance on the timely diagnosis and treatment of VF in patients on second line ART to minimize or prevent the negative effects of treatment failure and its subsequent effects. Also, it serves as a handbook and a vital tool to institutionalize recent trends, changes, and new developments in ART clinic implementation to ensure and maintain desired quality of life, in this way delivering updated information, raising awareness and prioritizing action at various levels of the healthcare system, including health facilities, health bureaus, and the ministry of Health.

6.3.2 Objectives

This guideline has key objectives, which include, but are not limited to, the following:

- To outline the basic steps for the timely identification, assessment, and management of virological failure in HIV infected adults receiving second line ART.
- To standardize and improve the management of second line ART virological failure across healthcare professionals working in the field.
- To equip healthcare providers with the knowledge and tools necessary for the timely detection and management of virological failure in adults on second line ART, thereby reducing the incidence of associated adverse outcomes.
- To provide evidence-based recommendations based on the most commonly defined risk factors contributing to second line ART virological failure
- To update recommendations for timely switching to the next treatment regimen (ART) to facilitate viral suppression and treatment success.
- To improve the implementation of prevention mechanisms for adverse outcomes related to virological failure, as carried out by healthcare providers.
- To highlight recent evidence on how enhanced adherence counseling can optimize virological suppression and enhance the effectiveness of treatment strategies for adults on second line ART.
- To commend policymakers and other relevant stakeholders on the high priority given to issues of timely screening, diagnosis, and management, and to avoid failure of virological treatment and associated adverse events.

6.4 SCOPE OF THE GUIDELINE

A guideline's scope is determined by the range of preparation that the guideline covers, the important areas that the recommendations are intended to address, and potential benefits and harms. The scoping of the guideline focuses on what the guideline will incorporate and will not incorporate (WHO 2021:417). As a result, the development of the guideline's scope began with identifying potential issues based on research findings, encompassing topics related to the timely identification, monitoring, and management of virological failure and related adverse outcomes. In general, the primary objectives of these guidelines are to offer a solution-oriented approach for the early detection and management of virological treatment failure and its related adverse outcomes.

6.5. HOW TO USE THE GUIDELINE

This guideline is designed to be a vital resource for reference and training, contributing to improved national practices in the management of Virological failure. It will be beneficial for all stakeholders involved in ART programs across the public and private health sectors, including physicians, nurses, public health professionals, pharmacists, laboratory professionals, adherence support teams, case managers, and data managers. For simplicity of understanding and flow of information, the document is structured into five sections:

- **Section 1** provides brief background information on virological failure, its contributing factors, and key concepts.
- **Section 2** outlines strategies for promptly managing virological failure and halting the contributing factors.
- **Section 3** emphasizes the importance of adherence counseling, including enhanced adherence and its critical role in viral suppression.
- **Section 4** details the importance of timely switching to the next level of treatment in response to treatment failures.
- **Section 5** summarizes the validation process and the way forward

The guideline winds up with annexures that include examples of monitoring tools and logs/checklists (Annex 6.13), as well as a brief list of references/included with the main references. The guideline is designed to promote and ensure the timely management of treatment failures among HIV positive patients taking a second line ART treatment.

The HIV program is a comprehensive, multi-layered and multi-sectorial package that requires prompt action from individual and collaborative engagement from all stakeholders, aligning with their respective roles and responsibilities. These guidelines were developed based on the findings of the current study, expert opinions, researcher discernments, and review of relevant updated literatures.

6.6. GUIDELINE FOR THE TIMELY DETECTION AND DIAGNOSIS OF VIROLOGICAL FAILURE

6.6.1 Identification and monitoring of Virological failure

ART treatment failure can be monitored using different approaches. Of these, the following three most recommended approaches are used for monitoring and evaluating ART treatment failure (WHO 2021:193):

- **Clinical:** When suspected, the emergence of new or worsening clinical symptoms associated with advanced HIV disease should be confirmed with a viral load if accessible or with the CD4.
- **Immunologic:** It is based on immunological function, measuring the number of immune cells, mainly CD monitoring should be confirmed with viral load if accessible or with clinical failure.
- **Virological:** This is the most preferred monitoring and /or diagnostic method, done by quantifying the HIV RNA level in the blood of sample or viral load test.

Table 17. Type and classification of treatment failure: virological, immunological, and clinical failure for the decision to switch ART regimens. (Adopted from ART refresher training manual, July 12, 2022)

Type of failure	Definition	Remark
Virological failure	Viral load >1000 copies per mL in a two consecutive VL laboratory results within 3 months gaps with EAC following the first VL test	Before any clinical or immunological failures appear, this is the first indication of failure. Before a regimen is deemed unsuccessful, a person must be taking ART for at least six months. Due to the possibility of VL blips, VL testing should not be performed during an acute infection or fever. Refer to the instructions below.
Immunological Failure	The CD4 count should be at or below 250 cells/mm3, followed to the clinical failure. or continuous CD4 counts less than 100 cells/mm3 for children	Without a concurrent infection to temporarily lower the CD4 cell count. At least two CD4 readings below the threshold are considered persistent. For diagnosing people with VF, the current WHO clinical and immunological criteria have a low sensitivity and a positive predictive value.
Clinical Failure	Treatment failure may also be determined by a new or recurring clinical event that indicates severe immunodeficiency (WHO clinical stage 4 condition and some WHO clinical stage 3 problems, pulmonary TB, and serious bacterial infections). following six months of successful therapy	It is the final presentation that occurs after immunological and virological failures. This condition must be distinguished from immune reconstitution inflammatory syndrome, which can arise after starting ART.

Adopted from: WHO Consolidated guideline 2021

Virological failure is defined as the inability to achieve or suppression of HIV viral replication to an RNA level < 1000 copies/mL with in two consecutive measurements taken 3 months apart, following enhanced adherence support after the first high viral load required, Annex 1. The second line ART must be taken for at least six months before VF can be determined (WHO 2016:104, FMOH Ethiopia 2018:105).

Why is monitoring of clients on ART important?

In the context of Ethiopia's constrained access to advanced and expensive third-line ART, the identification and monitoring of VF among patients on second line ART are not only essential for individual long-term health but also represent a critical public health measure to avert further drug resistance and maintain the efficacy of current treatment options. Below are the benefits of second line ART Monitoring:

- Timely identification and management of virological failure.

Second line ART regimens have been used when first-line ART has failed in suppressing the virus. Regular monitoring of the second line ART, especially using viral load testing, is important in the early detection of Virological failure if the treatment is not working. If the second line ART could not suppress the amount of virus in the blood, the immune system of patients get weakened and prone to opportunistic infections that may leads to morbidity and mortality. Therefore, timely identification of second line ART failure can allows for timely interventions before clinical deterioration happen.

- Ensure adherence

ART monitoring mainly includes adherence counseling and support. In Ethiopia context, PLHIV engaging with ART providers and adherence supporters during their follow up visits. During these times, patients are reminded about the importance of regularly and timely taking of their ART that is the key for maintaining viral suppression and preventing transmission of HIV. In the other hand, unsuppressed viral load is an indication for poor adherence to second line ART. Therefore, regular monitoring will gives an opportunity to assess the patient’s adherence to the prescribed medication, learn the challenges faced by the patients, and provide targeted adherence counseling and support to improve the adherence level. If there are also misconceptions about the ART, it allows for improving patient literacy.

- Preventing HIV transmission

The primary aim of ART is to reduce the amount of virus to an undetectable level. Recent studies showed that individuals who maintain an undetectable viral load have zero risk of

transmitting HIV to their sexual partners (CDC Guide 2024:34). This concept is known as U=U. Therefore, ART monitoring will allow individuals to be aware of their HIV Viral Load status and become confident in not transmitting HIV to others.

- Public Health importance

Individuals with unsuppressed HIV viral load, if the virus is resistant to second line ART, potentially can transmit drug-resistant virus to others, challenging the future treatment effort, especially in Ethiopia, where the drug resistance test is not available for monitoring the ART program. Therefore, effective monitoring of 2nd-line ART can minimize the risk.

- Inform the national ART program

The monitoring data from clients taking second line ART can provide cherished information to the national program about the effectiveness of current second line ART regimen, the need of drug resistance testing to monitor the ART program, prevalence of second line Virological Failure, and the need of adjustment to existing ART guidelines.

- Prevent ART drug resistance.

Even though HIV drug resistance testing is not routinely available for ART monitoring purposes in Ethiopia, regular monitoring of ART through Viral load testing can play a vital role in preventing or minimizing drug resistance, if viral replication is not fully suppressed while the patient is taking second line ART.

Suboptimal adherence level, non-disclosure, lost follow-up, baseline clinical incompliance to the recommended standards and protocols, drug toxicity, transfer-in, stigma and discrimination, and drug stock out were some of the identified contributing risk factors for virological failure (McGowan 2023:7-8). Thus, timely halting these most identified risk factors and designing a way-out modality is essential.

If patients do not adhere to their medication regimen or if the virus develops resistance to the medications being used, there is a risk of viral rebound. This means that the amount of the virus in the blood can increase significantly, leading to high viral loads that can be detected during testing. A viral load test is a precise and quantitative virological analysis that measures the presence of HIV in the bloodstream. Viral load is defined as the number of

copies of HIV's genetic material, specifically its RNA, found within a given volume of blood. This crucial test serves as a key indicator of the effectiveness of ART in monitoring disease progression.

By understanding viral load levels using the standardized high viral load for (Annex 3) and the ART follow-up form (Annex 2), healthcare providers can assess how well the treatment is working and make necessary adjustments to improve patient outcomes. Compared to clinical and immunological failure, VF is the earliest indication of ART failure. Detailed in figure 24.

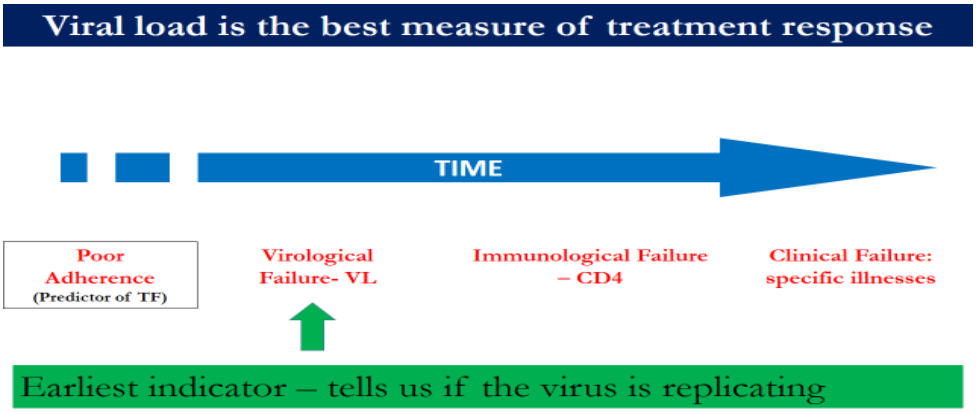


Figure 24. Type of treatment failure by timeline, 2025

6.6.2. Important aspects regarding the criteria for virological ART treatment failure:

- **Viral Load Benchmark**: A viral load that exceeds 1,000 copies/mL is typically considered a cutoff value for virological failure.
- **Verified through repeat testing**: One should not rely on a single test to declare Virological failure; at least two consecutive viral load tests, 3 months apart and indicating levels above 1,000 copies/mL, are crucial.
- **Enhanced Adherence Counseling**: Providing Enhanced Adherence Counseling during the testing interval is essential to ensure that the patient follows their prescribed medication regimen.

Important Considerations:

- Clinical context: Depending on the specific clinical circumstances, the benchmark for virological failure may be adjusted somewhat.

- Drug resistance testing: If virological treatment failure is confirmed, further evaluation with drug resistance testing is often needed to assist in adjusting the treatment plan. It is highly advised to perform this promptly if the resources allow.
- Monitoring Immunity: Although it is not the only sign of treatment failure, keeping track of immunological health and cell counts can offer supplementary insights regarding the immune response. Figure 25.

Treatment Monitoring Algorithm

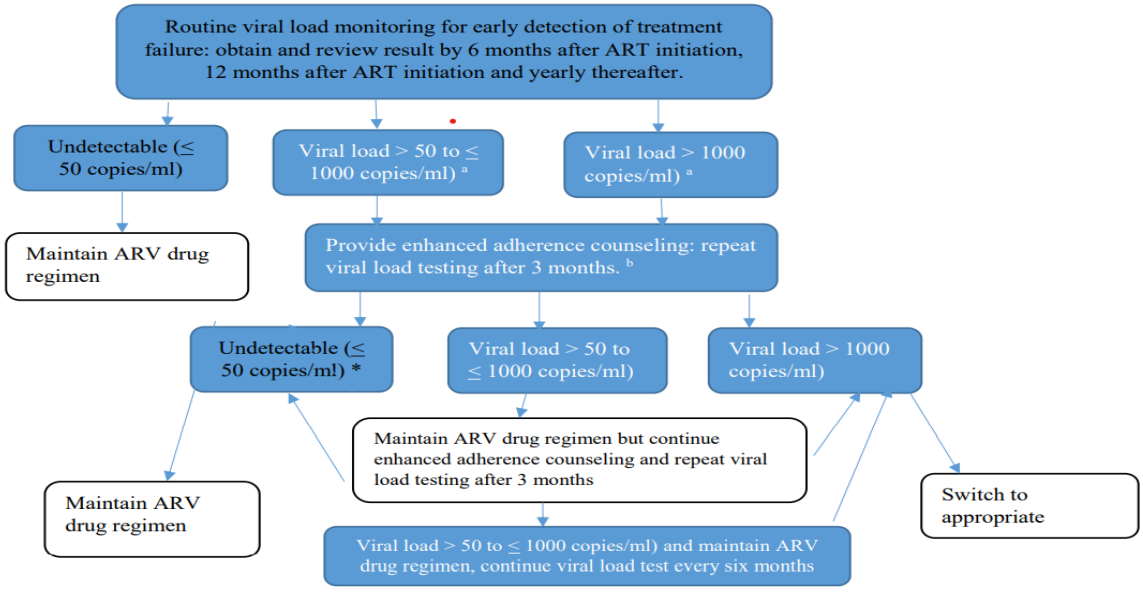


Figure 25. Treatment monitoring algorithm adopted from the National training participant manual

6.7 RISK FACTORS RELATED TO VIROLOGICAL FAILURE: PROMPTLY IDENTIFY AND MANAGE

Several factors contribute to virological failure; thus, it is vital to identify and address them in a short time to ensure a higher success rate in treatment and improve the quality of life. It is mostly linked to risk factors such as miserable adherence, regimen change history, lost follow-up, drug toxicity, opportunistic infections while on ART, low level of CD4+ lymphocytes count at start of ART, adherence, and clinical stage.

In the current study, the overall rate of virological failure among PLHIV who were receiving second line ART, aged 18 years and older in Addis Ababa, Ethiopia, from 2018 to 2022, based on 369 participants, was 14.9%. The study also assessed the associated factors for

the virological failure among participants on second line ART at Zewdtu Memorial Hospital and Yekatit 12 Medical College referral hospital. Accordingly,

Poor adherence [AOR of 6.641 (95% CI: 1.077, 40.95, p-value: 0.041)], clients transferred in [AOR of 2.726 (95% CI: 1.235, 6.016; p-value: 0.013)], patients LTFU from HIV care while on second line ART [AOR of 6.007 (95% CI: 2.778, 12.990, p-value < 0.001) were associated risk factors for second line ART VF.

For different reasons, patients can change their regimen without switching to the next level. HIV patients who have not experienced a second line ART regimen change during the follow-up were found that less likely to experience virological failure.

6.8 STRATEGIES FOR PROMPTLY MANAGING VIROLOGICAL FAILURE AND HALTING THE CONTRIBUTING FACTORS

Effective and timely management of virological failure is essential to prevent disease progression, improve quality of life, preserve immune function, prevent drug resistance, reduce the risk of HIV transmission, and ensure long-term cost-effectiveness of HIV care. Addressing the underlying causes for VF is crucial in ensuring the optimal treatment outcomes and the ART program as well.

If resources permit, conducting drug resistance testing is the most preferred and critical step in identifying mutations that may compromise treatment efficacy, enabling informed decisions on selecting appropriate antiretroviral therapy. By implementing these strategies promptly, healthcare providers can improve individual patient outcomes while contributing to broader public health efforts to curb HIV transmission and resistance development.

6.9. ADHERENCE AND ITS ROLE IN VIRAL SUPPRESSION

6.9.1. Type of Adherence and Addressed Adherence

The WHO described adherence as "the degree to which an individual's actions in taking medications, adhering to a diet, and/or implementing lifestyle modifications align with the agreed-upon recommendations from a healthcare professional" (WHO 2015:13), which needs to be sustained over an extended period.

Adherence involves a mutual decision-making process between the patient and health care provider. For optimum adherence, the patient should take the prescribed drug at the right

dose, in the right frequency, and right time and in the correct route. For a better outcome, the adherence program should be supported by psychosocial and economic support.

The qualitative part of the current study revealed that disclosure of HIV status to others, perceived stigma and discrimination, distance to health facility, nutritional problems, and socio-economic problems were mentioned as contributing factors for poor adherence. The other factors mentioned by the health care providers and program managers include, shortage of second line ART to implement the differentiated service Delivery model like 3-month multi-month dispensing (3MMD), a lack of community-level support groups like CAG, PCAG, and Nutrition support.

How to Promote Adherence?

Different modalities can be adopted to ensure effective adherence and a higher treatment success rate through tailored-based approaches. The following are some of the modalities:

- Encourage disclosure
- Provide reminder tools
- Link to adherence support to develop a plan
- Arrange a treatment supporter or assistance
- Establish a trustworthy relationship with every client.

We should also promote more proven interventions that have shown benefits in enhancing adherence and achieving HIV viral suppression**:**

- Support from peers
- Text messages
- Installing devices for the reminder
- Therapy focused on cognitive-behavioral approaches
- Training in behavioral skills and adherence to medication
- Combination medications with fixed doses taken once daily

- Implement the differentiated HIV service delivery (DSD) model by taking various contexts into account.

6.9.2. Barrier to ART Adherence

Complying with the prescribed ART is crucial for patients to achieve effective treatment success. Non-adherence can lead to drug-resistant HIV due to the inability to achieve viral suppression and can be influenced by various factors. Identifying and understanding these underlying risk factors are essential for timely intervention and management. This can help minimize the potential costs associated with the program, including the number of PLHIV who need to switch to more advanced third-line ART, which could compromise their overall quality of life.

HIV/AIDS ART adherence barriers can be summarized as drug issues, social issues, and health-related issues:

- Drug-related Issues: drug toxicity/side effect, side effects, pill burden, need to have food as a prerequisite.
- Socio-economic Issues: perceived stigma and discrimination, linked to sin, language barriers, alcohol and substance use, lack of support, economic crisis, distance from the ART clinic, transport cost, low literacy level, drug stock out during routine visit, and rescheduling following this, busy schedule, religious belief,
- Health-related Issues: opportunistic infections, stress, uncovered health insurance, disclosure, comorbidity, depression, lack of symptoms, poor quality services.

Maintaining an adherence rate of 95% or greater is strongly advised to ensure optimal viral suppression. The recent study revealed that the average adherence level among PLHIV on second line ART was 60%. As a result, we investigated the factors influencing adherence among individuals aged 18 and older living with HIV who are undergoing second line ART in Addis Ababa, Ethiopia.

Given that, clients experiencing opportunistic infections during second line ART treatment are 5.186 times more likely to have poor adherence levels compared to those who did not acquire opportunistic infections (5.186 [1.963-13.698], p-value = 0.001).

Literacy level also contributes to good adherence. HIV-positive clients with a secondary level of education are 2.5 times (95% CI: 1.061-5.925, p-value = 0.036) more likely to have good adherence. Furthermore, clients with bedridden functional status have the opportunity of poor adherence than patients with good adherence with 0.541 times (95% CI: 0.294-0.994, p-value = 0.048), more likely to have poor outcomes of adherence, table 11.

6.9.3. Enhanced adherence counseling (EAC)

Enhanced Adherence Counseling (EAC) is a structured intervention designed to support patients with HIV in improving treatment adherence, mainly those experiencing high viral load results, which helps patients achieve viral suppression (Gill et al 2019:7).

PLHIV receiving second line ART and exhibiting viral load result $\geq$ 1000 copies/ml after six months of treatment should undergo enhanced adherence counseling and repeat testing after three to six months to assess potential treatment failure. Certain factors that the health care providers taken in to account are summarized in Table 18.

Table 18. Summary of EAC components, Adopted from "National-Comprehensive-HIV-guideline", pages 77-78

Sessions	Activities to be done
1st Session (When the viral load result >1000 is received, Day 0)	• Examine the cognitive, behavioral, emotional, and socio-economic impediments to adherence • Understanding of treatment • Medications: dosage, timing, and storage requirements, side effects and incentive • Conduct mental health evaluations. **Action:** • Discuss ways to minimize risks. • Discover the patient's support networks. • Help the patient develop a plan for adherence to attack the identified challenges. • Arrange referrals and suggest connection with others when required.
2nd Session (30 days after the first session)	○ Review the adherence plan developed during the initial session and discuss any difficulties experienced in implementing it. ○ Identify further possible limitation and newly arising issues. **Action:** • Support the patient to modify the adherence plan to address the identified issues. • Make referrals and connect with others when needed.
3rd Session (60 days after the first session)	○ Examine the adherence plan from the initial and subsequent sessions and talk about any difficulties encountered. ○ Recognize additional potential gaps and new concerns that may have arisen. **Action:** ✓ Help the patient adjust their adherence plan to tackle the issues identified. ✓ The decision regarding repeat VL testing will depend on the current level of adherence: ✓ If adherence is satisfactory, schedule repeat VL testing for a month later and discuss potential next steps, highlighting the importance of both the patient and the health facility in enhancing adherence. ✓ If there are ongoing adherence challenges, connect the patient to suitable client-centered care.
4th Session (90 days from the first session)	○ Take the second VL sample. ○ Try to get a prompt the VL result as early as possible. ○ Communicate the VL result to the patient promptly up on receipt. **Action**: 1. If VL is < 50 copies/ml, maintain the current regimen and encourage adherence 2. If VL is 50-1000 copies/ml, continue the current regimen and the monthly EAC for the next 3 months then repeat the viral load testing. If the low-level viremia (50–1000 copies/ml) persists, maintain ARV drug regimen and continue viral load test every six months. 3. In addition, continue the routine follow-up support and link to adherence support services. If VL is > 1000 copies/ml, switch to an appropriate regimen on a timely manner.

Once the patient experienced high viral load, the health provider should strictly follow the patients based on the standardized EAC session observation checklist and logbook (Annex 4 & 5). Selected activities and important steps that would be done in EAC, as depicted in figure 26 as follows:

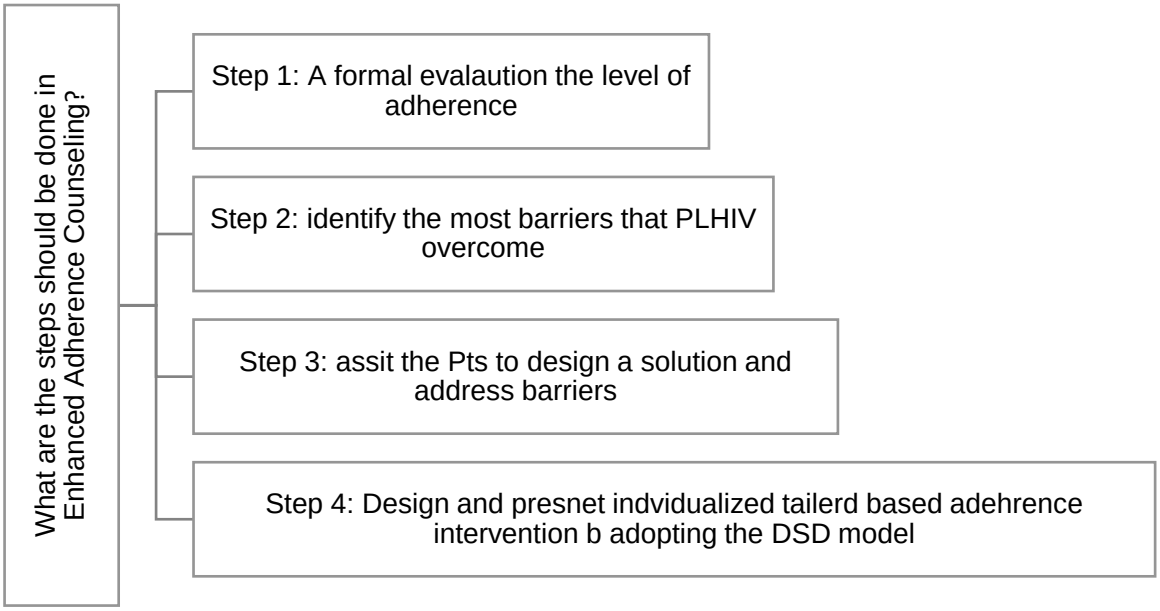


Figure 26. Selected activities that would be done in EAC

6.9.4 Rationale for adherence counseling

- Poor adherence is the most common identified risk factors for ART failure.
- The identification of non-adherence is challenging and requires specific interventions.

Outcomes of optimum adherence to ART:

- HIV suppression
- Decline risk of drug-resistance
- Improved patient overall quality of life
- Reduced HIV transmission

Why do we provide EAC to patients on second line ART?

EAS is specifically designed for individuals receiving second line ART and experiencing high viral load to reinforce consistent medication adherence. By ensuring patients follow their prescribed treatment regimen more effectively, EAC plays a pivotal role in achieving sustained viral suppression. Maintaining low viral loads is essential in managing HIV, reducing disease progression, preventing drug resistance, and preventing treatment failure, which could otherwise necessitate more advanced and complex therapeutic interventions. In addition to improving individual health outcomes, this strategy supports larger public health initiatives to prevent HIV transmission and the emergence of resistance.

A study indicates that from the 209 patients who showed high viral load and enrolled in EAS, 96 (46%) patients had achieved viral suppression (Wedajo, Degu, Deribew, and Ambaw 2021:5).

A concordant finding was noted from the recent study finding: after the Enhanced Adherence Counseling (EAC), 34(38%) out of 89 patients, having high HIV viral loads, became virally suppressed after 3 to 6 months of EAC. The EAC is designed for PLHIV who have unsuppressed viral loads (≥ 1000 copies/ml) after six months of antiretroviral ART. This counseling session typically lasts between 3 to 6 months and aims to improve adherence through regular follow-up, identifying and addressing potential barriers to treatment, and any difficulties the clients may be experiencing, Fig. 26 and 27.

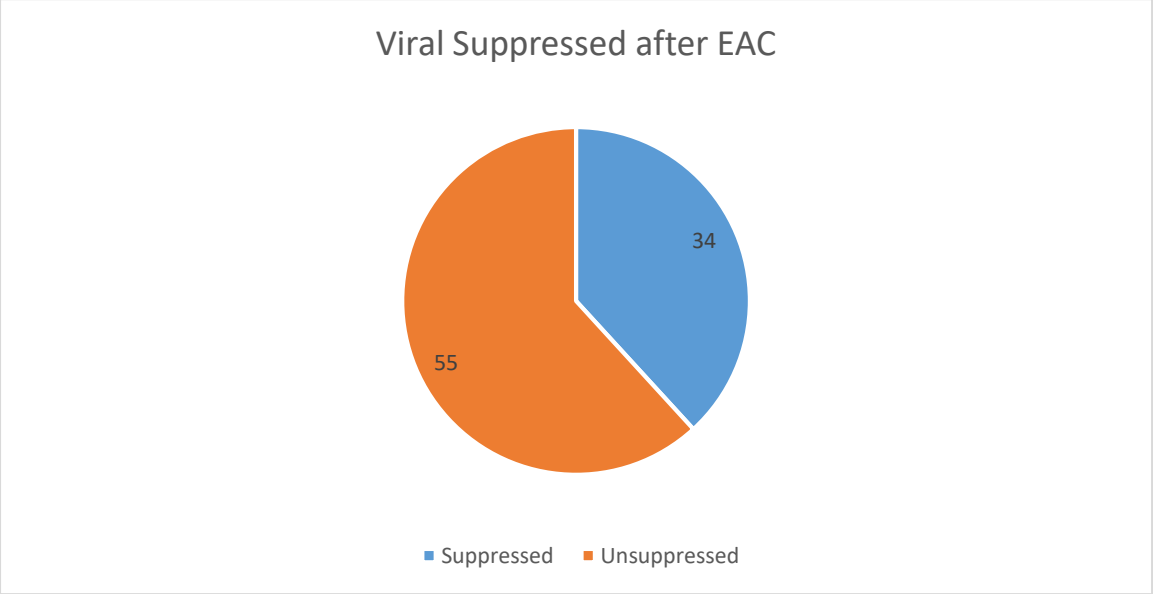


Figure 27. Magnitude of viral load suppression after EAC at selected hospitals in Addis Ababa, Ethiopia, 2024.

Guidance for Switching ART Regimens for Treatment Failure

- To prevent premature switching, confirm the diagnosis of therapy failure.
- Evaluate adherence levels and remove any obstacles.
- Address problems with drug interactions.
- Avoid adding a medicine to a treatment plan that isn't working!
- Use at least two new medications in the new regimen, ideally one from a new drug class;
- Take resistance and cross-resistance into account, and
- Seek guidance from knowledgeable specialists.

6.10 TIMELY SWITCHING OF TREATMENT IN RESPONSE TO FAILURES

Once second line virological failure is confirmed, patients should be switched to the appropriate third-line ART in promptly as possible

Before transitioning to the appropriate third-line ART regimen, healthcare providers must ensure that the following important requirements are met:

- Two consecutive viral load measurements > 1000 copies/ml, conducted with a minimum interval of three months.

- The initial viral load assessment should take place at least six months post-transition to the second line treatment.
- The patient must remain on the second line therapy for at least six months with proper adherence prior to the first viral load evaluation.
- Increased support for adherence should be implemented, and the patient should be monitored monthly for three months.
- The subsequent viral load test should be conducted three months after the introduction of enhanced adherence support..

If the patient is clinically unwell, the timing of the algorithm should be adapted to the clinical urgency. Since the next regimen option is very limited, the process for switching to a third-line regimen should strictly adhere to the set and established principles.

Strict Monitoring after Switching to the appropriate third line ART

Upon failure of second line ART, the client should be switch to the appropriate next level regimen, and subsequently the following activities should take place:

1. Viral load monitoring: measure the viral load after 3 months after switching to the new regimen.

2. Adherence Support: Continue the proactive adherence counseling and support to ensure the success of the new regimen.

6.11 VALIDATION OF THE GUIDELINES

The aim of validating these guidelines was to ensure that they contained acceptable and achievable values. The validation process for the guidelines commenced with the search for criteria to assess them and adapting it for this particular study. In this effort, Thomson and Dowding (2014:43) provided guidance to the researcher. The principles that guided this process are:

- **Clarity** – user-friendly, explicit, and exact
- **Clinical applicability** – beneficiary population is identified using evidence
- **Clinical flexibility** – exclusions and patient options are noted.
- **Cost-effectiveness** – It should be affordable to improve one's health.

- **Meticulous** – Participants, presumptions, and procedures should all be precisely documented.
- **Reproducibility** – Another group ought to use the same information and evidence to offer comparable suggestions.
- **Reliability** – In comparable circumstances, other HPs would apply the principles similarly.
- **Representatively-** the development of the guidelines was assisted by concerned groups and all major disciplines
- **Scheduled review** – at what time and by what means they will be reexamined
- **Specificity**- specific and focused
- **Utilization review** – methods in which adherence may be monitored should be indicated.
- **Validity** – correct interpretation of available pieces of evidence.

The overview contains the subject, objectives of the research, context of the issue, and the methods employed, along with the suggested guidelines. The reviewers/evaluators were invited to assess the guidelines and rate them based on the established criteria (Table 19) for validation of the developed guidelines.

The evaluators were purposely selected for their expertise in ART and HIV/AIDS programs. This group included two senior academic professors (Associate and Assistant) from the Infectious and Tropical Diseases Department of Addis Ababa University. Additionally, two ART hospital program managers and service providers, two sub-city level HIV/AIDS program managers, from regional health bureau an Adherence Manager, and an HIV/AIDS program Quality Improvement advisor were invited. Finally, two hospital-based ART adherence supporters also invited and participated.

Table 19. Guideline evaluators' background information

S#	Profession and assigned recent position/ role	Qualification
1	Associate Professor	PhD, MSC
2	Assistant Professor	PhD, MSC
3	Regional Health Bureau Adherence Manager	MD, MPH
4	Regional Health Bureau HIV/AIDS QI Manager	MD, MPH, MHP,MSC
5	Sub city HIV/AIDS program manager (2)	MD, MPH, MHP,
6	Hospital-Based HIV/AIDS ART program manager	MD, MPH
7	Hospital-Based HIV/AIDS ART program manager	BSc, MPH
8	Hospital-Based HIV/AIDS ART program manager	MD
9	Hospital-based adherence supporter	BSC

A four-point Likert scale (i.e., strongly disagree, disagree, agree, and strongly agree) was employed for the assessment of the guideline. The 10 evaluators were instructed to utilize the provided options to evaluate, score, and determine whether each guideline fulfilled the required standards. When appropriate, the evaluators were asked to include written comments.

Table 20. WHO Standards and scoring point's evaluators used to validate the guidelines.

Standards	Score (from lowest (1) to highest (4)				Remark
	Strongly disagree(1)	Disagree (2)	Agree (3)	Strongly agree (4)	
Clarity The guideline is specific and easily understandable					
Reliability In comparable circumstances, different health professionals would apply the guidelines in a similar manner					
Validity Exact interpretation of available evidence					
Cost-effectiveness The guideline can generate health improvements at an acceptable cost					
Specificity It is precise and focused					
Clinical flexibility Exemptions are identified					
Applicability The target users are clearly defined					
Achievability Can be executed by the healthcare professionals in ART clinics					
Utilization review Techniques in which adherence may be monitored should be indicated					
Relevance The guideline is appropriate for execution in the ART clinic					

The guideline was evaluated using a scoring system with a minimum threshold of 10 points and a maximum possible total score of 40. Guidelines that received a score of 32 or higher were deemed suitable, as this represents an 80% acceptance rate. A panel of ten evaluators was tasked with assessing each guideline, providing scores, and offering suggestions for improvement.

For classification purposes, guidelines that received an "Agreed" or "Strongly Agreed" rating were considered well-structured, practical, and suitable for implementation. Among the ten evaluators, seven assigned a rating of 4 on the Likert scale, contributing to a cumulative

score of 28. Two evaluators rated the guideline at 3 on the Likert scale, adding 6 points to the total score. Additionally, one evaluator provided a summarized Likert scale score of 2.

Overall, the preferred Likert scale ratings (3 and 4) combined to yield a total score of 34 points, accounting for 85%, exceeding the expected threshold. The evaluators' scores demonstrated a high level of consistency, with the majority exceeding 32 points. However, one guideline received a lower score (2-disagreed), indicating non-compliance concerns regarding its applicability in routine ART treatment for virological failure in Ethiopia. In response to the evaluators' feedback, necessary modifications were incorporated into the final version of the guideline to ensure its suitability for practical use.

Validation Workshop

In addition to professional/expert evaluation, we had a half-day validation workshop in a small group of professionals, encompassing health care providers working on ART at the hospital level, sub-city level, at city administration, faculty members, adherence supporters, case managers to enrich the guideline more. Accordingly, their valued comments and feedback were considered in this final version using annex 6.

6.12 Guidelines Revision

According to the WHO guideline development guide, all guidelines should be kept up to date to ensure consistency with the best available evidence. This requirement is particularly critical and challenging in public health emergencies, where new data and field experience are continually emerging. The technical unit with primary responsibility for the rapid advice guideline is expected to remain abreast of new information and to continuously assess its potential impact on existing recommendations. If evidence emerges indicating that current recommendations require modification, the guideline should be revised in a timely manner (WHO, 2014:166).

Accordingly, revision of this guideline will follow established recommendations and will be undertaken at one-year intervals to incorporate emerging data and new evidence. The review and updating process will be aligned with both WHO and national guideline updates to ensure continued consistency with current standards and best available information.

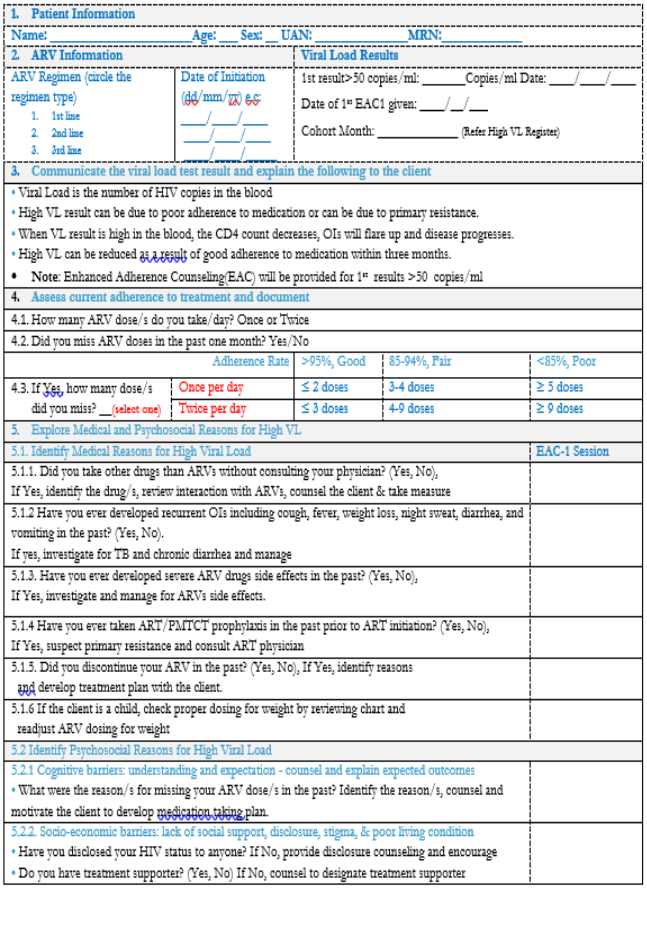
6.13 CONCLUSION OF THE CHAPTER

This guideline has been developed to enhance to improve the understanding and proficiency of healthcare professionals, program managers, and adherence supporters in the prompt management of virological failure in patients receiving second line ART. It serves as a valuable resource for training materials.

Additionally, it can assist in everyday service delivery when dealing with treatment failures in virological suppressed clients as an operational job aid. The guideline highlights the importance of providing enhanced adherence counseling and making timely decisions to switch to the appropriate treatment line of ART. By adhering to this guideline, health care professionals can help patients achieve long-lasting viral suppression, better health outcomes, and an enhanced quality of life.

6.14 ANNEXURES FOR THE GUIDELINE (Adopted from MOH ART Guideline)

Annex 1. ART Follow-up form for clients with high viral load



1. Patient Information

Name: _____ Age: ___ Sex: __ UAN: _____ MRN: _____

2. ARV Information

ARV Regimen (circle the regimen type)	Date of Initiation (dd/mm/yr) e.g:	Viral Load Results
1. 1st line 2. 2nd line 3. 3rd line	___/___/___ ___/___/___ ___/___/___	1st result>50 copies/ml: _____Copies/ml Date: ___/___/___ Date of 1st EAC1 given: ___/__/__ Cohort Month: _____ (Refer High VL Register)

3. Communicate the viral load test result and explain the following to the client

- Viral Load is the number of HIV copies in the blood
- High VL result can be due to poor adherence to medication or can be due to primary resistance.
- When VL result is high in the blood, the CD4 count decreases, OIs will flare up and disease progresses.
- High VL can be reduced as a result of good adherence to medication within three months.
- Note: Enhanced Adherence Counseling(EAC) will be provided for 1st results >50 copies/ml

4. Assess current adherence to treatment and document

4.1. How many ARV dose/s do you take/day? Once or Twice

4.2. Did you miss ARV doses in the past one month? Yes/No

Adherence Rate		>95%, Good	85-94%, Fair	<85%, Poor
4.3. If Yes, how many dose/s did you miss? __(select one)	Once per day	≤ 2 doses	3-4 doses	≥ 5 doses
	Twice per day	≤ 3 doses	4-9 doses	≥ 9 doses

5. Explore Medical and Psychosocial Reasons for High VL

5.1. Identify Medical Reasons for High Viral Load	EAC-1 Session
5.1.1. Did you take other drugs than ARVs without consulting your physician? (Yes, No), If Yes, identify the drug/s, review interaction with ARVs, counsel the client & take measure	
5.1.2 Have you ever developed recurrent OIs including cough, fever, weight loss, night sweat, diarrhea, and vomiting in the past? (Yes, No). If yes, investigate for TB and chronic diarrhea and manage	
5.1.3. Have you ever developed severe ARV drugs side effects in the past? (Yes, No), If Yes, investigate and manage for ARVs side effects.	
5.1.4 Have you ever taken ART/PMTCT prophylaxis in the past prior to ART initiation? (Yes, No), If Yes, suspect primary resistance and consult ART physician	
5.1.5. Did you discontinue your ARV in the past? (Yes, No), If Yes, identify reasons and develop treatment plan with the client.	
5.1.6 If the client is a child, check proper dosing for weight by reviewing chart and readjust ARV dosing for weight	
5.2 Identify Psychosocial Reasons for High Viral Load	
5.2.1 Cognitive barriers: understanding and expectation - counsel and explain expected outcomes • What were the reason/s for missing your ARV dose/s in the past? Identify the reason/s, counsel and motivate the client to develop medication taking plan.	
5.2.2. Socio-economic barriers: lack of social support, disclosure, stigma, & poor living condition • Have you disclosed your HIV status to anyone? If No, provide disclosure counseling and encourage • Do you have treatment supporter? (Yes, No) If No, counsel to designate treatment supporter	
5.2.3 Behavioral barriers: attitude, motivation, confidence & skills educate, motivate, and empower client to manage medication taking and develop reminder • What do you do to remind yourself to take drugs on time? • Are you confident to take your ARV openly at home? If no, advise reminder mechanisms	
5.2.4 Psychological/Emotional barriers: common mental illness: depression, PTSD, substance abuse, and psychosis – link to psychiatric clinic for psychotherapy & treatment • Have you ever felt sad for more than 2 weeks? Have you ever lost interest in activities that usually give you pleasure for more than 2 weeks? Have you regularly taken alcohol or chew Khat? If yes, counsel the client to avoid alcohol and/or Khat.	

6. Follow-up EAC Sessions

6.1. Assess current adherence to treatment and circle adherence rate		Subsequent EAC Sessions						Repeat three EAC Sessions for clients whose confirmatory viral load > 50 and ≤ to 1000 copies/ml(Low Level Viremia)								
		Rate at EAC-2			Rate at EAC-3			Rate at EAC-1			Rate at EAC-2			Rate at EAC-3		
		>95% Good	85 to 94% Fair	<85% Poor	>95% Good	85 to 94% Fair	<85% Poor	>95% Good	85 to 94% Fair	<85 % Poor	>95% Good	85 to 94% Fair	<85% Poor	>95% Good	85 to 94% Fair	<85 % Poor
6.2. If Yes, how many dose/s did you miss?	One per day	≤ 2	3-4	≤ 2	3-4	≥ 5	≤ 2	≤ 2	3-4	≤ 2	≤ 2	3-4	≤ 2	≤ 2	3-4	≤ 2
	Two per day	≤ 3	4-9	≤ 3	4-9	≥ 9	≤ 3	≤ 3	4-9	≤ 3	≤ 3	4-9	≤ 3	≤ 3	4-9	≤ 3

7. Follow-up status of identified Reasons for High VL	EAC 2 Date: __/__/___	EAC 3 Date: __/__/___	EAC-1 Date: __/__/___	EAC-2 Date: __/__/___	EAC-3 Date: __/__/___
7.1. Medical reason/s(Y/N)					
7.2 Psychosocial					
7.2.1 Cognitive barriers(Y, N):					
7.2.2 Socio-economic barriers(Y,N):					
7.2.2. Behavioral Barriers(Y,N)					
7.2.3. Psychological/ emotional(Y,N):					

8. Outcome of EAC Sessions

Did the patient attend all the appointments? (Yes No) If no, any reason?

_____

Note: Client should have three consecutive good adherences before confirmatory(2nd) VL test

2nd Viral Load

Date ordered: __/__/___, 2nd Viral Load Result: _____ copies/ mL, Date Received __/__/___,

Measure Taken

1. Continue 1st Line, 2. Continue 2nd line 3. Continue Third line 4. Switched to 2nd Line, 5. Switched to 3rdLine

Comment: _____

ART Physician:/ART clinician _____ **Date:** ___/___/_____

Annex 2. HIV CARE/ART FOLLOW-UP FORM

HIV CARE/ART FOLLOW-UP FORM MINISTRY OF HEALTH

ጤና ሚኒስቴር – ኢትዮጵያ
MINISTRY OF HEALTH-ETHIOPIA

Facility Name _____ Name: _____ Age _____years (Months for Children <5 years)

Sex ☐ M F ☐ _____Address: Region_____ Woreda/Sub city_____ Kebele_____ House No._____Telephone _____

Patient Card No_____ Unique ART No. _____ Date confirmed HIV+ (Retesting): _____/_____/_____(DD/MM/YY)

Type of HIV Test ☐ Rapid HIV tests ☐ DNA/PCR (for children) Client readiness: (date client is ready)_____/_____/_____(DD/MM/YY) Height (Adult) in cm: _____

S/US	Follow up date dd/mm/yy	Months on ART	Weight (Kg) Edema+/-	BMI (MUAC for pregnant woman or bedridden)	Pregnancy status / FPmethod If child Length/ Height/ Head Circumference for < 3years	Functional Status W,A,B Developmental Milestone (A,D,R)	WHO Stage (1-4 / T1- T4	TB Screen - P/N	Xpert-MTB/ RIF(1) LF-LAM(2) Sent (√)	Xpert-MTB/ RIF(1) LF-LAM(2) Result P/N	TB Treatment / TB Prophylaxis	Dispense Dose (TPT drugs)	Adherence for TPT (G,F,P)	Side effect for TPT drugs (see side effect at back 1-13)	Cx Ca screening & Treatment Type of Cx Ca Screening (0-7)	Cx Ca screening & Treatment Management of cervical lesions (0-5)	Oth/ HIV related cancers	Assessed & Managed for pain	CD4/mm^3 or % if < 5 Yrs.	VL result (copies/ml)	Hgb. ALT/ AST/ Cr/ CrAg	Co-trimoxazole Preventive therapy Adherence (G,F,P)	Co-trimoxazole Preventive therapy Dispense dose	Fluconazole preventive therapy(FPT) (Dispensed Dose)	Other medications / or nutritional supplements dispensed	Assess & counsel for ARV Adherence Adherence (G,F,P)	Assess & counsel for ARV Adherence Why Fair or Poor?	ARV drugs Dispense Dose/ code	ARV drugs Side effect	ARV drugs Reason for change	Client sets HIV prevention plan Disclosure for Children	Enrolled to DSD Model (DD/MM/YY) Type of DSD(write code 1-10)	Next Visit Date dd/mm/yy

Back page

S/US

S=Scheduled US=Unscheduled

TB SCREEN

SCREENFOR TB AT EVERYVISIT

Adult &Adolescent

1. Current Cough?
2. Fever?
3. Night sweats.
4. Weight loss?

P=(Positive screen)-Yes to any of the above---Evaluate for TB.

N= (Negative screen)- No to all the questions above---assess for IPT eligibility

Children0-14years old

1. Current Cough?
2. Fever?
3. Weight loss or poor weight gain?
4. Contact history with TB patient?

P=(Positive screen)-Yes to any one of the four---evaluate for TB

N=(Negative screen)-No to all four--assess for eligibility to IPT

Xpert MTB/ RIF (1)

P= Positive N= Negative

LF- LAM (2)

P= Positive N= Negative

TB PROPHYLAXIS TREATMENT

6H1-6=Currently on INH prophylaxis (Number refers to months on 6H)
6H-C=Completed treatment
6H- DC=discontinued for any reason
3HP1-3=Currently on 3HP prophylaxis (Number refers to months on 3HP)
3HP-C=Completed treatment
3HP- DC=discontinued for any reason
TB RX1-6=Currently on Anti-TB(numbers refer to months on Rx)
TB RXDC=discontinued TB Rx for any reason
TB Rx C=Completed anti TB Rx

OI/ Opportunistic Cancers

NOI=No OI or Opportunistic cancer
Z=Zoster
BP=Bacterial Pneumonia
PTB=Pulmonary Tuberculosis
EPTB=Extra pulmonary tuberculosis
TO= Thrush oral
EC=eaophageal candidiasis
UM=ulcers-mouth
DC or DA=Diarrhea Chronic/Acute
PCP=Pneumocystiaspneumonia
CT=CNS Toxoplasmosis
CM=Cryptococcal Meningitis
NHL=Non Hodgkins Lymphoma
KS=Kaposi's Sarcoma
CC=Cervical cancer
O=Other

Months on ART

Duration in months since initiation of ART:
0=ART Initiation date
1week=1 week
2weeks=2 weeks
3weeks=3 weeks
1= 1 month
2=2 months
If not started on ART (Pre-ART) leave this column blank

Pain Assessment &Management

Assess for Pain &Manage as
NP= No pain
S1= WHOStep1
S2= WHOstep2
S3= WHOstep3

Nutritional Status (adults)

BMI (wt/(ht2)) (for non-pregnant/non postpartum)
1= Normal(18.5-24.99kg/m2)
2= Mild (17-18.49kg/m2)
3=Moderate malnutrition (16-16.99kg/m2)
4=Severe malnutrition (<16kg/m2)
5=Over weight (25-29.99 kg/m2)
NB: write the codes (1,2,3,4 or 5)

MUAC (for pregnant/ postpartum /bedridden)
1= Normal (>23cm)
2=Moderate malnutrition (19-23cm)3=-Severe malnutrition (<19cm for pregnant and postpartum /<18cm for bedridden)

ADHERENCE

Estimate adherence using the table below:

Adherence	%	# Missed doses	
G (Good)	≥95%	(of 30 doses) <2 doses	(of 60 doses) ≤3 doses
F (Fair)	85-94%	2-4doses	4-9 doses
P (Poor)	<85%	≥5 doses	≥10 doses

If Fair or Poor adherence, in why column note reason:

1. Toxicity/ Side effects
2. Share with others
3. Forgot
4. Felt better
5. Too ill
6. Stigma, discloser
7. Drug stock out
8. Lost/ ran out of pills
9. Delivery/ travel problems
10. Inability to pay
11. Alcohol
12. Depression
13. Other

Pregnancy Status/Family PlanningMethod

P=Pregnant(If pregnant, give estimated due date(EDD))
PMTCT=Referred to PMTCT &indicate linkage
WP=want to become pregnant
No FP=not pregnant& is not using any FP methods
FP=On Family Planning (enter code):
1=Condoma
2=Oral contraceptive pills
3=Injectable
4= Implant
5=Intrauterine device
6=Vasectomy/ tubal legation
7=Abstinence(no sex)

Length / height/ HC

Measure length/height in cm for children younger than14 years at EVERY visit.
Measure head circumference In cm for children younger Than 3 years of age at EVERY visit

Nutritional Status(Children)

WH
1=Normal/ Appropriate (> -1Z-score)
2=Mild(<-1and> -2Z-score)
3=MAM- Moderate Acute Malnutrition (<-2and>-3 Z-score)
4=Severe Acute Malnutrition(<-3Z-score)

SIDE EFFECTS

1. No side effects
2. Nausea
3. Diarrhea
4. Fatigue
5. Headache
6. Numbness/tingling/pain
7. Rash
8. Anemia
9. Abdominal pain
10. Jaundice
11. Fat changes
12. Dizzy, anxiety, nightmare, depression
13. Other

REASONS FOR REGIMEN CHANGE

1. Toxicity/ Side effects
2. Due to new TB
3. New drug available
4. Drug stock out
5. Clinical failure
6. Immunologic failure
7. Virologic failure
8. Other

Cervical Cancer Screening& Treatment

Type of Cx Ca Screening result (0- 6):
0. Cx Ca screening not done
1. HPV Negative
2. HPV Positive
3. VIA Negative
4. VIA Positive: eligible for Cryo
5. VIA Positive: Non-Eligible for Cryo
6. Suspicious for Cervical Cancer
7.Referred for screening

Management of cervical lesions (0-4)
0. No treatment / further evaluation & management service given
1. Cryotherapy
2.Thermal ablation treatment
3.LEEP service
4. Further evaluation & management service given to Suspicious for Cervical Cancer
5.Referred

Functional status

W=Working(able to perform usual work in or out of the house, harvest, go to school or, for children, normal activities or playing)
A=Ambulatory (able to perform activities of daily Living)
B=Bedridden (not able to perform activities of daily living)

DEVELOPMENTAL MILESTONES FOR CHILD

A=Appropriate:
Sitting without support 3 to9months
Standing with assistance.....5to 11months
Hands and knees crawling 6 to1 3months
Walking with assistance .....7 to14 months
Standing alone.....8 to17 months
Walking alone..... 9 to18 months
Delay: Failure to attain milestones for age
Regression: Loss of what has been attained for age

Nutritional Status(Older children &adolescents)

BMI for age(5-18yrs)
1=Normal/appropriate (>-1Zscore)
2=Mild(<-1and> -2Zscore)
3=Moderate malnutrition(<-2and>-3Zscore)
4=Severe malnutrition(<-3Zscore)
*BMI forage for older children and adolescents.

REASONSFOR STOPPINGREGIMEN

1. STOP=Stopped ART
2. If STOP, In why column, note reason:
3. Toxicity/side effects
4. Treatment failure
5. Poor adherence
6. Illness, hospitalization
7. Drugs out of stock
8. Patient lack finances
9. Other patient decision
10. Other

VIRAL LOAD

Mark "" under VL column when requested/ specimen collected,

Write the amount and interprat as Suppressed- if the viral load is< 50 copies per ml, Low level viremia: if viral load is between 50 and 1000 copies per ml and High Viral Load - if the viral load is >1000 copies per ml for clinical intervention

Client readiness

Enter the date (dd/mm/yy) client is ready for ART initiation when client is counseled, adhesrnce barriers addreseed and client is willing to start ART

Client Set HIV Prevention Plan

D =Agreed to Disclose to partner/family/friend,
PT= Agreed to bring partner for testing
ChT=agreed to bring children for testing,
SSex=discussed &agreed to practice safer sex
SubU=Decides to avoid or decrease Substance use
ASS=Assessed for STI
SRX=client managed for STI

For children Fill in stage of HIV disclosure

DS0 = No disclosure
DS1=Satge1, about the illness, taking medicine, keeping healthy,
DS2=Stage2, about germs, body soldiers,
DS3=Stage3, use of terms like CD4, Viral Load, HIV

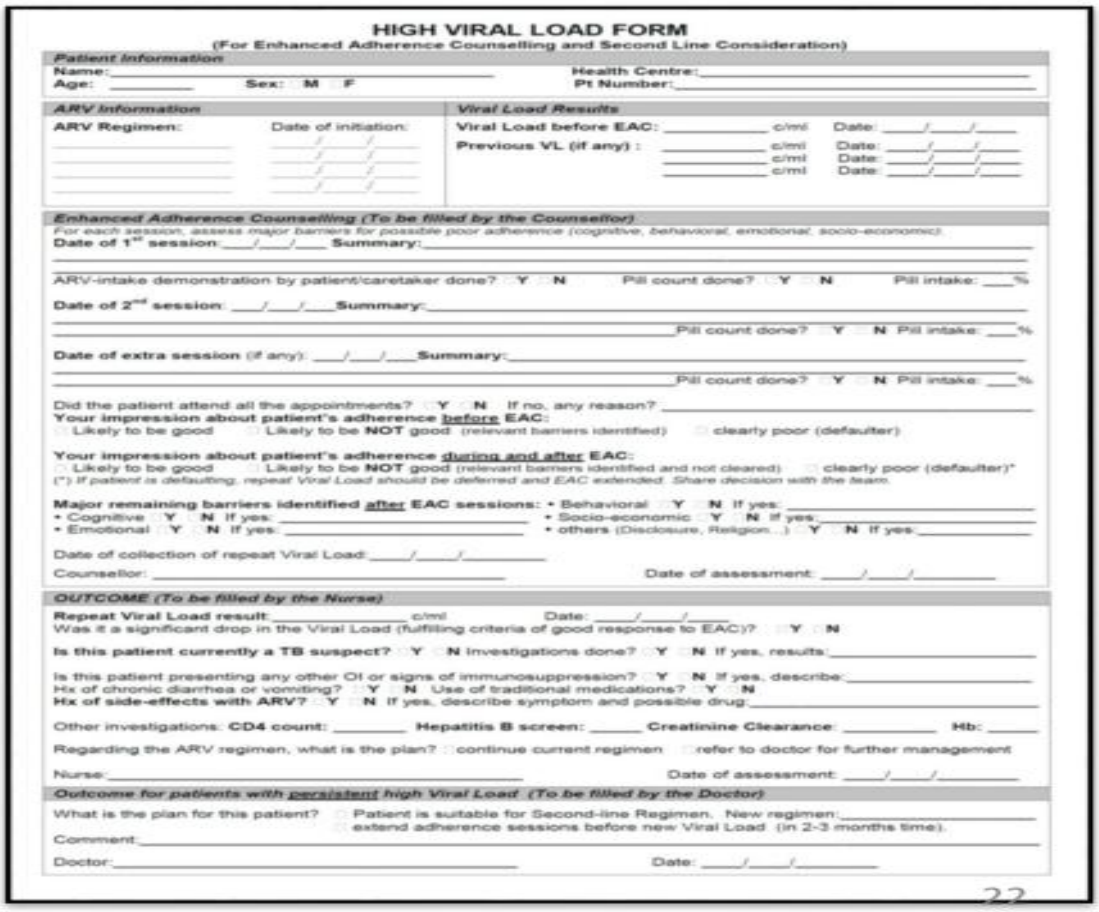
DISPENSE DOSE/ REGIMEN CODE

ADULT FIRST LINE	CHILD FIRST LINE
1d = AZT - 3TC - EFV 1e = TDF - 3TC - EFV 1g = ABC + 3TC + EFV 1j = TDF + 3TC + DTG 1K = AZT + 3TC + DTG 1i = Other specify	4d = AZT+3TC+EFV 4e = TDF+3TC+EFV 4f = AZT +3TC + LPVr 4g = ABC + 3TC + LPVr 4i = TDF + 3TC + DTG 4j = ABC + 3TC + DTG 4K = AZT + 3TC + DTG 4L = ABC + 3TC + EFV 4h = Other specify
ADULT SECOND LINE	**CHILD SECOND LINE**
2e= AZT +3TC +LPVr 2f =AZT+3TC +ATVr 2g=TDF + 3TC+LPVr 2h= TDF + 3TC + ATVr 2i= ABC + 3TC+ LPVr 2j = TDF + 3TC + DTG 2k = AZT + 3TC + DTG 2l= Other specify	5e=ABC+3TC+LPVr 5f=AZT + 3TC + LPVr 5g=TDF + 3TC + EFV 5h=ABC + 3TC + EFV 5i= TDF + 3TC+LPVr 5m= ABC+3TC+DTG 5n= AZT+3TC+DTG 5o= TDF + 3TC + DTG 5j= Other specify
ADULT THIRD LINE	**CHILD THIRD LINE**
3a = DRVr+DTG+AZT+3TC 3b = DRVr+DTG+TDF+3TC 3c=DRVr+ABC+3TC+DTG 3e= DRVr+TDF+3TC+EFV 3f= DRVr+AZT+3TC +EFV 3d = Other specify	6c= DRVr + DTG + AZT +3TC 6d = DRVr + DTG +TDF+3TC 6f = DRVr+DTG+ABC+3TC 6g= DRVr +ABC+3TC+ EFV 6h= DRVr +AZT+3TC+EFV 6e = Other specify

DSD CODE

1. 3MMD
2. ASM(6MMD)
3. FTAR
4. CAG
5. PCAD
6. DSD for Adolescent
7.DSD for KP
8.DSD for MCH
9.DSD for AHD
10.Others

Annex 3. High Viral load form



HIGH VIRAL LOAD FORM
(For Enhanced Adherence Counselling and Second Line Consideration)

Patient Information
Name:_____ Health Centre:_____
Age: _____ Sex: M F Pt Number:_____

ARV Information
ARV Regimen: Date of initiation:
_____ __/__/__
_____ __/__/__
_____ __/__/__
_____ __/__/__

Viral Load Results
Viral Load before EAC: _____ c/ml Date: ____/____/____
Previous VL (if any) : _____ c/ml Date: ____/____/____
_____ c/ml Date: ____/____/____
_____ c/ml Date: ____/____/____

Enhanced Adherence Counselling (To be filled by the Counsellor)
For each session, assess major barriers for possible poor adherence (cognitive, behavioral, emotional, socio-economic).
Date of 1st session: ___/___/___ Summary:_____
_____
_____
ARV-intake demonstration by patient/caretaker done? Y N Pill count done? Y N Pill intake: ___%

Date of 2nd session: ___/___/___Summary:_____
_____Pill count done? Y N Pill intake: ___%

Date of extra session (if any): ___/___/___Summary:_____
_____Pill count done? Y N Pill intake: ___%

Did the patient attend all the appointments? Y N If no, any reason? _____
Your impression about patient's adherence before EAC:
Likely to be good Likely to be NOT good (relevant barriers identified) clearly poor (defaulter)

Your impression about patient's adherence during and after EAC:
Likely to be good Likely to be NOT good (relevant barriers identified and not cleared) clearly poor (defaulter)*
(*) If patient is defaulting, repeat Viral Load should be deferred and EAC extended. Share decision with the team.

Major remaining barriers identified after EAC sessions: • Behavioral Y N If yes: _____
• Cognitive Y N If yes: _____ • Socio-economic Y N If yes:_____
• Emotional Y N If yes: _____ • others (Disclosure, Religion…) Y N If yes:_____

Date of collection of repeat Viral Load:____/____/_____
Counsellor: _____ Date of assessment: ____/____/_____

OUTCOME (To be filled by the Nurse)
Repeat Viral Load result:_____ c/ml Date: ____/____/____
Was it a significant drop in the Viral Load (fulfilling criteria of good response to EAC)? Y N

Is this patient currently a TB suspect? Y N Investigations done? Y N If yes, results:_____

Is this patient presenting any other OI or signs of immunosuppression? Y N If yes, describe:_____
Hx of chronic diarrhea or vomiting? Y N Use of traditional medications? Y N
Hx of side-effects with ARV? Y N If yes, describe symptom and possible drug:_____

Other investigations: CD4 count: _____ Hepatitis B screen: _____ Creatinine Clearance: _____ Hb: _____

Regarding the ARV regimen, what is the plan? continue current regimen refer to doctor for further management

Nurse:_____ Date of assessment: ____/____/_____

Outcome for patients with persistent high Viral Load (To be filled by the Doctor)
What is the plan for this patient? Patient is suitable for Second-line Regimen. New regimen:_____
extend adherence sessions before new Viral Load (in 2-3 months time).
Comment:_____
Doctor:_____ Date: ____/____/_____

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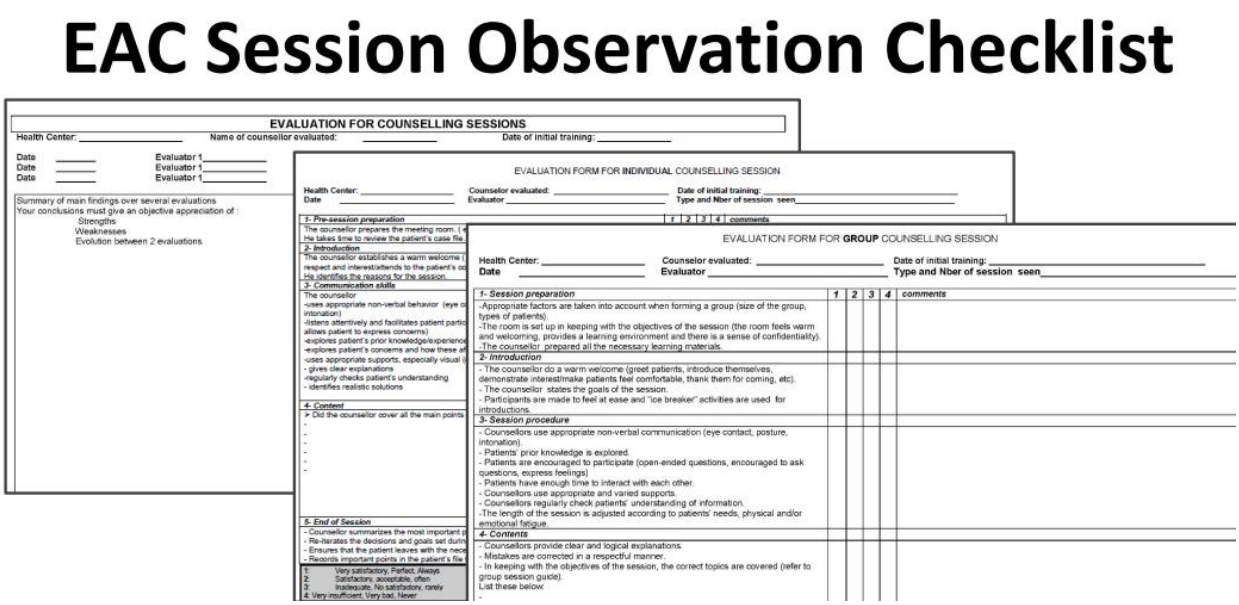
Annex 4. EAC Logbook

ART number	First name	Surname	DOB (DD/MM/YYYY)	Sex	Current ART regimen	Reason for VL test (R= routine T= targeted)	Date first VL taken (DD/MM/YYYY)	First VL Result (copies/mL)	Date results received by facility	Date patient received high VL result	1st EAC Date	2nd EAC Date	3rd EAC Date	Additional EAC Date

Additional EAC Date	Date follow-up VL taken	Follow-up VL result (copies/mL)	Date results received by facility	Date client received follow-up VL result	MDT Case Review Date	Outcome: ①Switched regimen ②Remained on current regimen ③Other (e.g., transferred out, deceased, referred) specify: _____	ART regimen, if switched	Outcome Date	Due date for follow-up VL date post ART switch	Date follow-up VL taken	Follow-up VL result (copies/mL)

Annex 5. EAC session observation checklist



Annex 6. Agenda and meeting minute for the half-day validation workshop

Meeting Schedule

Time	Activity	Participants	Moderator
8:30 AM - 9:00 AM	Registration	Supervisor	
9:00 AM - 9:10 AM	Welcoming Speech	PI	
9:10 AM - 9:20 AM	Opening and introduction	PI	Supervisor
9:20 AM - 10:00 AM	Evaluation Summary	Evaluating team Coordinator	Supervisor
10:00 – 10:20 AM	Break		
10:20 AM - 11:20 AM	Discussion	All Evaluators	PI
11:20 AM - 12:20 PM	Accommodate the discussion points	Supervisor	PI
12:20 PM – 12:30 PM	Closing remark	PI	Supervisor

Meeting Minute

Date:

Venue:

List of Participants:

Meeting Chair:

Meeting Secretary:

Agenda:

- Validating the guideline

Proceeding:

Recommendations:

CHAPTER 7

CONCLUSION AND RECOMMENDATIONS

7.1 CONCLUSION

Antiretroviral therapy (ART) failure in HIV-positive adults is a major public health concern, especially in resource-limited settings, as it can lead to increased mortality risk and the development of drug resistance. Continuing with failing ART therapy can exacerbate the situation.

Virological failure of second line HIV treatment can increase the risk of drug resistance, creating a significant challenge in managing HIV infections. Patients who experience treatment failure while on second line antiretroviral therapy (ART) may suffer from poorer health outcomes and may need to seek more expensive treatment alternatives. It can lead to further health complications, a decline in quality of life, and the need for more expensive treatments.

The research analysis is based on the extent and contributing risk factors of second line VF among adult HIV-positive patients at selected hospitals in Addis Ababa, Ethiopia. The study involved 369 participants, showing that a significant number of treatment failures, 14.9% (55/369) ART clients who developed second line treatment failure in 20,187 person-months of the total analysis time at risk and under person per month (PM) of observations. The overall incidence density was 27.2 per 10000 PM or 33 per 1000 person-years, underscoring the importance of careful monitoring and adjustment of treatment plans.

Several factors were found to be significant risk factors for VF, including poor adherence, lost to follow-up, transfer in from other health facilities for follow-up, having a history of frequent regimen changes, perceived stigma and disclosure, and drug toxicity.This research finding is higher than the WHO-recommended target and threshold of less than 10%.

This research underscores the importance and role of EAC in HIV ART viral suppression among second line ART clients. It is a structured intervention aimed at helping patients achieve and sustain viral suppression. It focuses on identifying the suboptimal adherence barriers by developing personalized plans to support medication adherence.

Given that treatment options are limited, ART treatment failure is particularly concerning in resource-limited settings, such as Ethiopia. Therefore, it is essential to monitor patients and make timely decisions regarding treatment adjustments actively. This approach can enhance patients' quality of life and efficiently and effectively use available resources.

7.2 RECOMMENDATIONS

The researcher drew several recommendations to policymakers, stakeholders, and fellow researchers regarding the timely and appropriate management of HIV care and treatment programs, ensuring the best quality of life for PLHIV.

Regular virological monitoring is necessary to detect timely treatment failure and strategies that support patients to have a timely switch without undue delays, as soon as virological failure should be prioritized

Early prompt identification of patients who had lost follow-up experience, regimen change history, and transfer in from other health facilities, ensuring adherence, addressing non-disclosure, and managing high viral loads will be crucial in decreasing ART failure. Patients exhibiting these issues will require more frequent clinical monitoring to lower the chances of treatment failure.

Further study should be highly recommended on the determination of the level of viremia and specific genomic-based drug resistance among virological failure.

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APPENDICES

Appendix 1. PARTICIPANT INFORMATION SHEET (phase 2a)

Date_____

Title: VIROLOGICAL FAILURE AMONG HIV-INFECTED ADULTS TAKING SECOND LINE ANTIRETROVIRAL TREATMENT (ART) IN ADDIS ABABA, ETHIOPIA.

Dear Prospective Participant

My name is **Bekelech Bayou Feyissa** and I am doing research with **Professor Geoffrey Setswe**, a senior faculty member in the Department of Health Studies towards a doctoral degree at the University of South Africa. We are inviting you to participate in a study entitled Virological Failure Among HIV-Infected Adults Taking Second line Antiretroviral Treatment (ART) In Addis Ababa, Ethiopia.

WHAT IS THE PURPOSE OF THE STUDY?

I am conducting this research to find out the prevalence and predictors of second line ART virological failure to design strategies to improve the quality of life of PLHIV.

WHY AM I BEING INVITED TO PARTICIPATE?

You are being invited to participate in this key informant interview because you are a person living with HIV on second line ART. I am interested in learning more about your experiences on adherence of second line ART, including the challenges and opportunities you face, as well as your perspectives on current treatments and services. Your feedback will be used to inform the development of strategies and improved interventions for PLHIV on second line ART.

WHAT IS THE NATURE OF MY PARTICIPATION IN THIS STUDY?

You are participating in interviews. Interviews will be conducted in person. The interviewer will ask you questions about your experiences, thoughts, and feelings, and challenges related to second line ART adherence.

CAN I WITHDRAW FROM THIS STUDY EVEN AFTER HAVING AGREED TO PARTICIPATE?

Participating in this study is voluntary and you are under no obligation to consent to participation. If you do decide to take part, you will be given this information sheet to keep and be asked to sign a written consent form. You are free to withdraw at any time and without giving a reason.

WHAT ARE THE POTENTIAL BENEFITS OF TAKING PART IN THIS STUDY?

Individuals and groups who are going to participate in this research will contribute to the outcome of the study. At the end of the research, the researcher will develop a strategy that will benefit the life of PLHIV and HIV service provision. Participation will be ensured upon obtaining individuals' consent.

ARE THEIR ANY NEGATIVE CONSEQUENCES FOR ME IF I PARTICIPATE IN THE RESEARCH PROJECT?

The research has no negative consequences or harm to participants.

WILL THE INFORMATION THAT I CONVEY TO THE RESEARCHER AND MY IDENTITY BE KEPT CONFIDENTIAL?

You have the right to insist that your name will not be recorded anywhere and that no one, apart from the researcher and identified members of the research team, will know about your involvement in this research OR your name will not be recorded anywhere, and no one will be able to connect you to the answers you give. Your answers will be given a code number, or a pseudonym and you will be referred to in this way in the data, any publications, or other research reporting methods such as conference proceedings.

HOW WILL THE RESEARCHER(S) PROTECT THE SECURITY OF DATA?

Hard copies of your answers will be stored by the researcher for a period of five years in a locked cupboard/filing cabinet by the researcher for future research or academic purposes; electronic information will be stored on a password-protected computer. Future use of the stored data will be subject to further Research Ethics Review and approval if applicable. After five years, the information will be destroyed hard copies will be shredded and electronic copies will be permanently deleted from the hard drive of the computer.

WILL I RECEIVE PAYMENT OR ANY INCENTIVES FOR PARTICIPATING IN THIS STUDY?

Participating in this research will not have any reward or payment or incentive.

HAS THE STUDY RECEIVED ETHICS APPROVAL

This study has received written approval from the Higher Degrees Committee of the Department of Health Studies of the University of South Africa (UNISA) and the Addis Ababa City Administration Health Bureau (AACAHB) research review committee. A copy of the approval letter can be obtained from the researcher if you so wish.

HOW WILL I BE INFORMED OF THE FINDINGS/RESULTS OF THE RESEARCH?

If you would like to be informed of the final research findings, please contact Bekelech Bayou Feyissaa on +251 9 11707322 or email bekelechbayou@gmail.com. The findings are accessible for 2026.

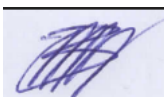
Should you require any further information or want to contact the researcher about any aspect of this study, please contact Bekelech Bayou Feyissaa contact # +251 9 11707322 and email bekelechbayou@gmail.com.

Should you have concerns about the way in which the research has been conducted, you may contact Professor Geoffrey Setswe, email xxx. Alternatively, contact the CREC chairperson of the Research Ethics Board of the University of South Africa (UNISA), Prof KB Khan on 012 429 6549 or email address khankb@unisa.ac.za.

Or Addis Ababa Health Bureau, EREC: **Phone Numbers:** +251 115517011/+251 11 551-9366 **Email:** info@moh.gov.et, 1234 Sudan Street, Addis Ababa, Ethiopia

Thank you for taking time to read this information sheet and for participating in this study.

Thank you.



Bekelech Bayou Feyissa

Appendix 2. CONSENT TO PARTICIPATE IN THIS STUDY- Phase 2b.

I, _____ (participant name), confirm that the person asking my consent to take part in this research has told me about the nature, procedure, potential benefits, and anticipated inconvenience of participation.

I have read (or had explained to me) and understood the study as explained in the information sheet.

I have had sufficient opportunity to ask questions and am prepared to participate in the study.

I understand that my participation is voluntary and that I am free to withdraw at any time without penalty.

I am aware that the findings of this study will be processed into a research report, journal publications and/or conference proceedings, but that my participation will be kept confidential unless otherwise specified.

I agree to the recording of Interview.

I have received a signed copy of the informed consent agreement.

Participant Name & Surname…… (please print)

Participant Signature……..Date……

Researcher's Name & Surname……(please print)

Researcher's signature……..Date……

Appendix 3. Key Informant Interview Questions Guide

The goal of these questions is to get a comprehensive understanding of the PLHIV's adherence level and the challenges they face in taking their ART. This information can be used to develop interventions to improve adherence and help PLHIV achieve optimal health outcomes.

The participants will be PLHIV age 18 years and above taking second line ART.

Category	Questions
Drug-related	• How often do you take your medication? • What challenges do you face in taking your medication? • How do you feel about the long-term commitment of taking second line antiretroviral therapy?
Disclosure-related	• How did you feel about disclosing your status to others? • What are the challenges you face in disclosing your HIV status? • What are the benefits and risks of disclosing your HIV status?
Social support-related	• How support group help you in taking your ART? • What would you like to see in a support group or organization for PLHIV?
Distance from HF	• Have you ever missed a dose of your ART drugs because of difficulty getting to the HF?
Stigma and discrimination-related	• How stigma or discrimination affected your adherence to ART? • How do you cope with stigma and discrimination?

For any information, the contact address of the principal investigator and CREC chairperson has been indicated below.

Information	Principal Investigator	CREC Chairperson
Name	Bekelech Bayou Feyissa	Prof KB Khan
Contact #	+251 911707322	+012 429 6549
Email	20265433@mylife.unisa.ac.za	khankb@unisa.ac.za.

Appendix 4. PARTICIPANT INFORMATION SHEET (phase 2b)

Date_____

Title: VIROLOGICAL FAILURE AMONG HIV-INFECTED ADULTS TAKING SECOND LINE ANTIRETROVIRAL TREATMENT (ART) IN ADDIS ABABA, ETHIOPIA.

Dear Prospective Participant

My name is **Bekelech Bayou Feyissa** and I am doing research with **Professor Geoffrey Setswe**, a senior faculty member in the Department of Health Studies towards a doctoral degree at the University of South Africa. We are inviting you to participate in a study entitled Virological Failure Among HIV-Infected Adults Taking Second line Antiretroviral Treatment (ART) In Addis Ababa, Ethiopia.

WHAT IS THE PURPOSE OF THE STUDY?

I am conducting this research to find out the prevalence and predictors of second line ART virological failure to design strategies to improve the quality of life of PLHIV.

WHY AM I BEING INVITED TO PARTICIPATE?

You are invited to a focus group in this study because you are a leading expert in HIV programmes. Your feedback will help us inform policy, develop strategy, and improve interventions for people living with HIV on second line ART.

WHAT IS THE NATURE OF MY PARTICIPATION IN THIS STUDY?

You will be participating in focus groups. Focus groups will have five to seven individuals and the discussion will be led by a moderator. The moderator will ask the group questions about the second line ART service and challenges in related with adherence. The participant will share their experience that helps to develop the strategies.

CAN I WITHDRAW FROM THIS STUDY EVEN AFTER HAVING AGREED TO PARTICIPATE?

Participating in this study is voluntary and you are under no obligation to consent to participation. If you do decide to take part, you will be given this information sheet to keep

and be asked to sign a written consent form. You are free to withdraw at any time and without giving a reason.

WHAT ARE THE POTENTIAL BENEFITS OF TAKING PART IN THIS STUDY?

Individuals and groups who are going to participate in this research will contribute to the outcome of the. at the end of the research, the researcher will develop a strategy that will benefit the life of PLHIV and HIV service provision. Participation will be ensured upon obtaining individuals' consent.

ARE THEIR ANY NEGATIVE CONSEQUENCES FOR ME IF I PARTICIPATE IN THE RESEARCH PROJECT?

The research has no negative consequences or harm to participants.

WILL THE INFORMATION THAT I CONVEY TO THE RESEARCHER AND MY IDENTITY BE KEPT CONFIDENTIAL?

You have the right to insist that your name will not be recorded anywhere and that no one, apart from the researcher and identified members of the research team, will know about your involvement in this research OR your name will not be recorded anywhere, and no one will be able to connect you to the answers you give. Your answers will be given a code number, or a pseudonym and you will be referred to in this way in the data, any publications, or other research reporting methods such as conference proceedings.

In a focus group: While every effort will be made by the researcher to ensure that you will not be connected to the information that you share during the focus group, I cannot guarantee that other participants in the focus group will treat information confidentially. I shall, however, encourage all participants to do so. For this reason, I advise you not to disclose personally sensitive information in the focus group.

HOW WILL THE RESEARCHER(S) PROTECT THE SECURITY OF DATA?

Hard copies of your answers will be stored by the researcher for a period of five years in a locked cupboard/filing cabinet *by the researcher* for future research or academic purposes; electronic information will be stored on a password-protected computer. Future use of the

stored data will be subject to further Research Ethics Review and approval if applicable. After five years, the information will be destroyed hard copies will be shredded and electronic copies will be permanently deleted from the hard drive of the computer.

WILL I RECEIVE PAYMENT OR ANY INCENTIVES FOR PARTICIPATING IN THIS STUDY?

Participating in this research will not have any reward or payment or incentive.

HAS THE STUDY RECEIVED ETHICS APPROVAL

This study has received written approval from the Research Ethics Review Committee of the UNISA and AACAHB. A copy of the approval letter can be obtained from the researcher if you so wish.

HOW WILL I BE INFORMED OF THE FINDINGS/RESULTS OF THE RESEARCH?

If you would like to be informed of the final research findings, please contact Bekelech Bayou Feyissa on +251 9 11707322 or email bekelechbayou@gmail.com. The findings are accessible for 2026.

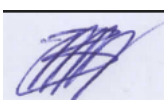
Should you require any further information or want to contact the researcher about any aspect of this study, please contact Bekelech Bayou Feyissa contact # +251 9 11707322 and email bekelechbayou@gmail.com. Should you have concerns about the way in which the research has been conducted, you may contact,

Mrs. Bekelech Bayou Feyissa on +251 9 11707322 or email bekelechbayou@gmail.com.

Alternatively, contact the CREC chairperson of the Research Ethics Board of the University of South Africa (UNISA), Prof KB Khan on 012 429 6549 or email address khankb@unisa.ac.za.

Thank you for taking time to read this information sheet and for participating in this study.

Thank you.



Bekelech Bayou Feyissa

Appendix 5. CONSENT TO PARTICIPATE IN THIS STUDY-Phase 2b.

I, _____ (participant name), confirm that the person asking my consent to take part in this research has told me about the nature, procedure, potential benefits, and anticipated inconvenience of participation.

I have read (or had explained to me) and understood the study as explained in the information sheet.

I have had sufficient opportunity to ask questions and am prepared to participate in the study.

I understand that my participation is voluntary and that I am free to withdraw at any time without penalty.

I am aware that the findings of this study will be processed into a research report, journal publications and/or conference proceedings, but that my participation will be kept confidential unless otherwise specified.

I agree to the recording of Interview.

I have received a signed copy of the informed consent agreement.

Participant Name & Surname…… (please print)

Participant Signature……..Date……

Researcher's Name & Surname……(please print)

Researcher's signature……..Date……

Appendix 6. Focused Group Discussion (FGD) Guide Questions

The goal of this guide is to get a comprehensive understanding of second line ART from a programme perspective, generate new ideas, explore solutions for challenges, and propose strategies.

The participants will be hospital-level ART service providers and HIV program managers working at the sub cities and AACAHB.

- What are the main barriers to PLHIV patient adherence to ART?
- What are some successful strategies that have been used to improve patient adherence to ART?
- What are some challenges that you (HF/Sub cities/RHB) face in implementing these strategies?
- What are some resources that you (HF/Sub cities/RHB) need to improve patient adherence to ART?
- What are some ways that you can propose to address stigma and discrimination to improve patient adherence to ART?
- How can you work with community organizations to improve patient adherence to ART?
- How can you use technology to improve patient adherence to ART?
- How can you measure the effectiveness of strategies to improve patient adherence to ART?

Appendix 7. Checklist/Chart abstraction. /data extraction sheet

Checklist

Baseline information at enrollment to HIV care and support (from ART intake form)		
Unique ART Number (ID)_____		
Part 1: Socio-demographic characteristics		
No	Questions	Coding category
101	Age at enrollment (in years)	_____
102	Gender	☐ Male ☐ Female
103	Marital status	☐ Never married ☐ Married ☐ Divorced ☐ Separated ☐ widowed
104	Educational status	☐ Not education ☐ Primary ☐Junior ☐ Secondary ☐Tertiary.
105	Patient linked from	☐Intra facility (same facility) ☐ Other facility. ☐ Community
Part 2: Baseline information		
201	Previous history of TB before switching to 2nd line ART	☐Yes ☐ No
202	Past HIV PEP	☐ Yes ☐ No
	Past HIV PrEP	☐ Yes ☐ No
203	Weight in KG at the start of first-line ART	_____KG
204	Functional status at enrollment to ART	☐ Working ☐ Ambulatory ☐ Bedridden
205	WHO clinical stage at enrollment	☐ I ☐ II ☐ III ☐ IV
206	CD4 level at the start of 1st-line ART	☐ <50 cell/mm3, ☐ 50-100 cell/mm3, ☐ 100-350cell/mm3, ☐ >350 cell/mm3
207	Baseline VL level at the start of first-line ART (0-6 months)	☐ <1000 copies/ml ☐ ≥1000 ☐ not done
208	First-line ART failure was determined/assessed by:	☐ VL only ☐ CD4 level only ☐ WHO Clinical criteria only ☐ CD4 & WHO clinical ☐ VL & CD4 ☐ VL & WHO clinical ☐ VL, CD4 & WHO clinical.
209	Type of first-line ART failure	☐ Immunological ☐ Clinical ☐ Virological ☐ immunological & Clinical ☐ Virological & immunological ☐ Virological & Clinical
Part 3: Baseline social information		
	Occupation	☐ employed ☐ self-employed ☐ housewife ☐ retiree ☐ student ☐ other
301	Employment status	☐ Employed ☐ Unemployed
302	Religion	☐ Orthodox Christian ☐ Muslim ☐Protestant ☐ Catholic. ☐ other
303	Community support/HIV support group	☐ Yes ☐ NO
304	disclosure status of HIV to the family member (at least one)	☐ Yes ☐ No
305	disclosure status of HIV to friends other than family member	☐ Yes 2. No
306	Condition of husband/wife	☐ Healthy☐ Chronically ill ☐ Dead ☐ Unknown

307	HIV status of spouse	☐ Negative ☐ Positive ☐ Unknown.
308	If the HIV status of the spouse is positive, was/is on ART?	☐ Yes ☐ No
Part 4: Knowledge of ART		
401	Understanding of HIV transmission	☐ NA ☐ - 3. + ☐ ++ ☐ +++
402	Understanding of ART medication	☐ NA ☐ - ☐ + ☐ ++ ☐ +++
Part 5: Risk behavior.		
501	Sexual behavior	☐ Has regular sexual partner ☐ Has casual partners.
502	If casual partners, number of casual partners in the past year (12 months).	☐ 1 ☐ 2 ☐ 3 ☐ >3
503	Condom use	☐ NA ☐ Never ☐ Rarely ☐ Mostly ☐ Always. ☐ No response.
504	Tobacco use	☐ NA ☐ - ☐ + ☐ ++ ☐ +++
505	Alcohol	☐ NA ☐ - ☐ + ☐ ++ ☐ +++
506	Soft drink	☐ NA ☐ - ☐ + ☐ ++ ☐ +++
507	Hard drink	☐ NA ☐ - 3. + ☐ ++ ☐ +++
Part 6: ART assessment and plan		
601	OI prophylaxis at base line	☐ Not given ☐ CPT ☐ INH ☐ TPT ☐ Fluconazole.
602	Which 1st line regimen did the client start?	☐1a (d4t+3Tc+NVP), ☐ 1b (d4t +3tc +EFV) ☐ 1c (AZT + 3TC +NVP) ☐ 1d (AZT+3tC+EFV) ☐ 1e (TDF+3TC+EFV) ☐ 1f (TDF+3TC+NVP) ☐ 1g ☐ 1J
603	Has the patient ever Lost from HIV care while on 1st line ART?	☐ Yes ☐ No
604	Did the patient experience a regimen change while on 1st line ART?	☐ Yes ☐ No
605	If yes to question 603, to which regimen the drug/s was/were changed?	☐ 1a (d4t+3Tc+NVP), ☐ 1b (d4t +3tc +EFV) ☐ 1c (AZT + 3TC +NVP) ☐ 1d (AZT+3tC+EFV) ☐ 1e (TDF+3TC+EFV) ☐ 1f (TDF+3TC+NVP) ☐ 1g, ☐ 1J
606	What was the patient 1st line-ART regimen during the switch to 2nd-line ART.	☐ 1a (d4t+3Tc+NVP), ☐ 1b (d4t +3tc +EFV) ☐ 1c (AZT + 3TC +NVP) ☐ 1d (AZT+3tC+EFV) ☐ 1e (TDF+3TC+EFV) ☐ 1f (TDF+3TC+NVP) ☐ 1g, ☐ 1J
Part 7: HIV care/ART follow-up information (from HIV care/ART follow-up form)		
701	Date Confirmed 1st-line ART Failure	_____/_____/_____(dd/mm/yy EC)
702	Date 2nd line ART started	_____/_____/_____(dd/mm/yy)
703	Type of 2nd line ART regimen dispensed (coded)	☐ AZT+CTC+ATV/r or LPV/r ☐ (AZT + 3TC +DTG or ATV/r or LPV/r ☐ TDF+3TC+DTG or ATV/r or LPV/r ☐ TDF+3TC+LPV/r or ATV/r
704	Had the patient experienced any drug side effects of 2nd line ART?	☐ Yes ☐ No

705	Had the patient experienced 2nd line ART regimen change?	☐ Yes ☐ No
706	If yes to Q 705, to which regimen was switched?	AZT+CTC+ATV/r or LPV/r ☐ (AZT + 3TC +DTG or ATV/r or LPV/r ☐ TDF+3TC+DTG or ATV/r or LPV/r ☐ TDF+3TC+LPV/r or ATV/r
707	Has the patient ever been LTFU from HIV care while on 2nd-line ART?	☐ yes ☐ No
708	Number of months on 2nd ART	_____months
709	Number of episodes of good adherence for ARV during the follow-up visits	_____
710	Number of episodes of fair adherence for ARV during the follow-up visits	_____
711	Number of episodes of poor adherence for ARV during the follow-up visits	_____
712	Has a high VL been documented while the patient is taking 2nd-line ART	☐ Yes ☐ No
713	If yes to Q **708**, what is the date of the first high VL documented	_____(DD/MM/YY)
714	At what month did the first high VL occur after initiating 2nd line ART	☐ 0-6, ☐ b/n 6-12, ☐ 12-18, ☐ 18-24, ☐ 24-36, ☐ 36-48
715	Date 1st EAC given	_____(DD/MM/YY)
716	Date 2nd EAC given	_____(DD/MM/YY)
717	Date 3rd EAC given	_____(DD/MM/YY)
718	Date 2nd follow-up VL test result documented	_____(DD/MM/YY)
719	2nd Viral load measurement result	☐ <1000 ☐ ≥1000
720	Has 2nd line ART failure been confirmed?	☐ Yes ☐ No
721	If yes to Q # 721, did the 2nd line ART switch to the next level (3rd line)?	☐ Yes ☐ No ☐ On EAC
722	If yes to Q # 719, which ART regimen has the patient switched?	☐ DRV/rC +TDF +3TC +EFV ☐ DRV/r + TDF +3TC + DTGe ☐ DRV/r + TDF +3TC + DTGf ☐ DRV/r + AZT +3TC + DTG ☐ DRV/r + AZT +3TC + EFV
723	What is the time between high VL documentation and switching to 3rd line ART (in months, if the patient is confirmed 2nd line ART failure)	☐ 0-6, ☐ 6-12, ☐12-18, ☐ 18-24, ☐ >24

724	What is the time between the confirmation of 2nd line ART failure and switching to 3rd line ART (in months).	☐ 0-6, ☐ 6-12, ☐12-18, ☐ 18-24, ☐ >24

Part 8: Clinical and Laboratory monitoring follow-up information while the patient is on 2nd-line ART.

		month							
	Indicators	Baseline	6 M	12M	18M	. 24M	30M	36M	At last visit
801	Weight in KG								
802	Functional status (W,A,B)								
803	BMI								
	WHO clinical stage (I, II, III, IV)								
804	OI (in number)								
805	CPT (yes, NO)								
806	Adherence to CPT (G, F, P)								
807	TPT/INH (Yes, No)								
808	Adherence to TPT (G, F, P)								
809	2nd line ART regimen (in number)								
810	ART adherence (G,F,P)								
811	VL test result								
812	CD4 count in cell/mm^3								
813	Hemoglobin (gm/dl)								
814	WBC count (cell/ml)								
815	TLC								
816	ALT								
817	AST								

Note: Keys for

504-507

-Not use, + light use (eg. smoking a few cigarettes per week), ++moderate use, +++ heavy use

Note: Keys for 804 & 807

A. Opportunistic Infections (OI)

1. Oral thrush
2. Herpes Zoster
3. Chronic diarrhea
4. Recurrent upper respiratory infections

5. CNS toxoplasmosis
6. PCP
7. Oral leukoplakia
8. Bacterial pneumonia
9. Pulmonary TB
10. Extra PTB
11. Kaposi's sarcoma
12. Cryptococcus meningitis
13. Lymphoma.

B. 1st line ART regimen

1. D4t-3tc-NVP
2. D4t3tc-EFV
3. AZT-3tc-NVP
4. AZT-3tc-EFV
5. TDF-3tc-EFV
6. TDF-3tc-NVP
7. AZT+3TC+DTG,
8. TDF+3TC+DTG
9. ABC+3TC+DTG,
10. ABC+ 3TC+EFV
11. AZT+3TC+ATVr or LPV/r,
12. TDF+3TC+ATVr or LPV/r
13. Other specify, _____

C. 2nd line ART regimen:

1. AZT+3TC+ATVr or LPV/r,

2. AZT+3TC+ DTG or ATVr or LPV/r

3. TDF+3TC+ DTG or ATVr or LPV/r

4. TDF+3TC+ATVr or LPV/r

5. AZT+3TC+DTG 6. TDF+3TC+DTG

Part 9: Final assessment:

901: Is there any documented 2nd line treatment failure?

1. Yes 2. No

902: What type of evidence of treatment failure did the patient meet?

1. Viral load test ≥ 1000
2. CD4 count dropped to pretreatment baseline
3. CD4 decline ≥50% from the treatment peak CD4
4. Persistent CD4 ≤100
5. New or recurrent stage for and some stage 3 conditions

903: was the type of treatment failure documented?

1. Yes 2. No

904: What type of treatment failure did the patient have?

1. Clinical

2. Immunological

3. Virological

4. 1 & 2,

5. 1 & 3,

6. 2 & 3,

7. 1,2,&3.

905: Did the patient put on 3rd line regimen?

1. Yes

2. No

906: At what month of 2nd line ART did the patient develop treatment failure? ____

907: What is the time interval between 2nd line ART failure switched to 3rd line ART? (in mot

Appendix 8. Appendix 8 Ethics Certificate from Higher degree research and ethics committee of UNISA.

UNISA university of south africa

COLLEGE OF HUMAN SCIENCES RESEARCH ETHICS REVIEW COMMITTEE

16 August 2024

NHREC Registration # : Rec-240816-052
CREC Reference # : 20265433_CREC_CHS_2024

Dear Mr Bekelech Bayou Feyissa

Decision:
Ethics Approval from 16 August 2024 to 15 August 2025

Researcher(s): Name: Mr. B. B. Feyissa
Contact details: 20265433@mylife.unisa.ac.za
Supervisor(s): Name: Dr. E. L. Davids
Contact details: davidel@unisa.ac.za

Title: Virological Failure Among HIV-Infected Adults Taking Second-Line Antiretroviral Treatment (ART) In Addis Ababa, Ethiopia.
Degree Purpose: PhD

Thank you for the application for research ethics clearance by the Unisa College of Human Science Ethics Committee. Ethics approval is granted for one year.

The ***medium-risk application*** *was reviewed by* College of Human Sciences Research Ethics Committee, in compliance with the Unisa Policy on Research Ethics and the Standard Operating Procedure on Research Ethics Risk Assessment.

The proposed research may now commence with the provisions that:

1. The researcher(s) will ensure that the research project adheres to the values and principles expressed in the UNISA Policy on Research Ethics.
2. Any adverse circumstance arising in the undertaking of the research project that is relevant to the ethicality of the study should be communicated in writing to the College Ethics Review Committee.
3. The researcher(s) will conduct the study according to the methods and procedures set out in the approved application.
4. Any changes that can affect the study-related risks for the research participants, particularly in terms of assurances made with regards to the protection of participants' privacy and the

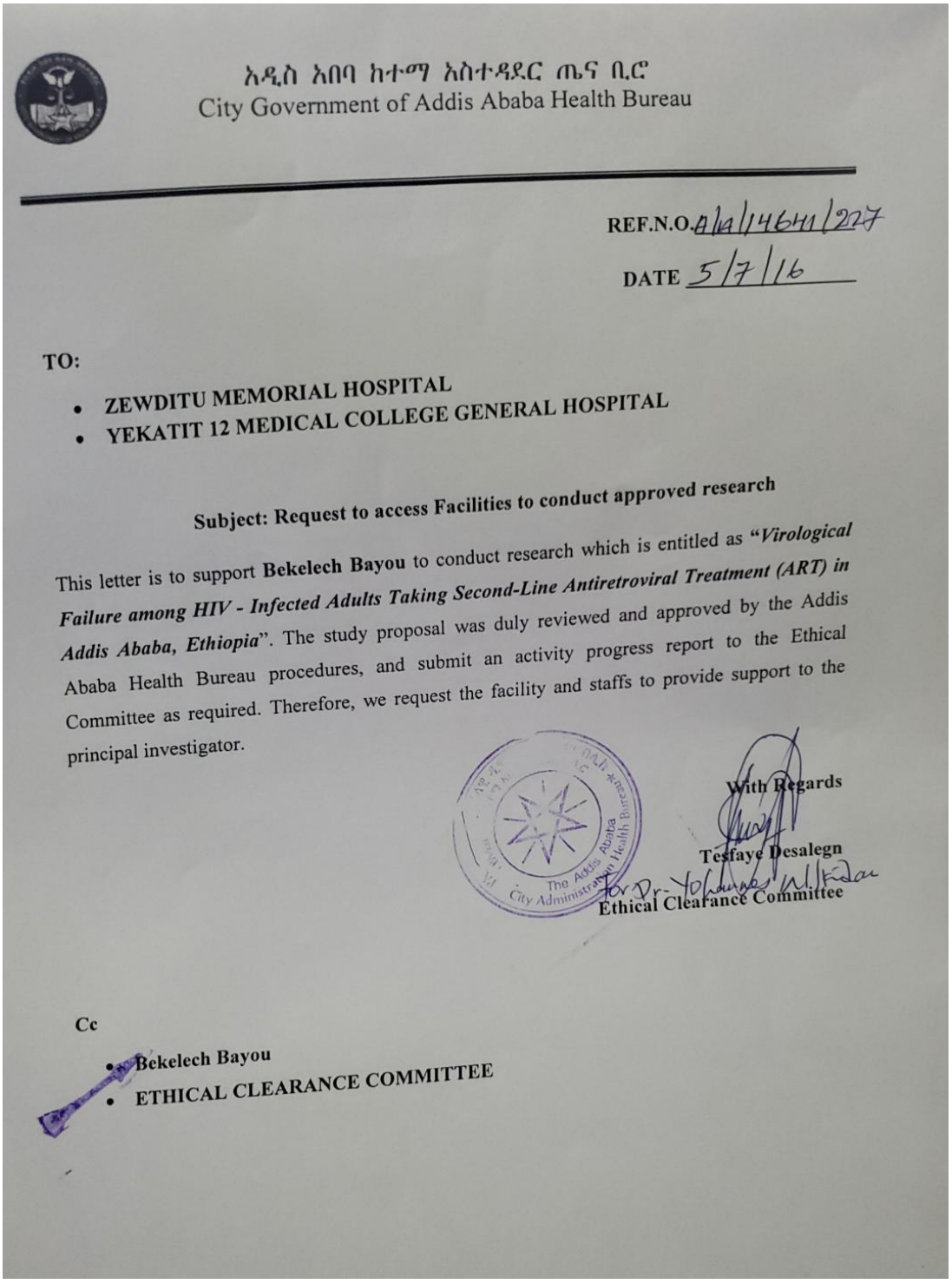
University of South Africa
Preller Street, Muckleneuk Ridge, City of Tshwane
PO Box 392 UNISA 0003 South Africa
Telephone: +27 12 429 3111 Facsimile: +27 12 429 4150
www.unisa.ac.za

confidentiality of the data, should be reported to the Committee in writing, accompanied by a progress report.
5. The researcher will ensure that the research project adheres to any applicable national legislation, professional codes of conduct, institutional guidelines and scientific standards relevant to the specific field of study. Adherence to the following South African legislation is important, if applicable: Protection of Personal Information Act, no 4 of 2013; Children's act no 38 of 2005 and the National Health Act, no 61 of 2003.
6. Only de-identified research data may be used for secondary research purposes in future on condition that the research objectives are similar to those of the original research. Secondary use of identifiable human research data require additional ethics clearance.
7. No fieldwork activities may continue after the expiry date **(15 August 2025).** Submission of a completed research ethics progress report will constitute an application for renewal of Ethics Research Committee approval.

Note:
The reference number ***20265433_CREC_CHS_2024*** *should be clearly indicated on all forms of communication with the intended research participants, as well as with the Committee.*

Yours sincerely,

Appendix 9. Permission Letter from Addis Ababa Health Bureau Research Review Committee.



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City Government of Addis Ababa Health Bureau

REF.N.O. አአ/14641/227

DATE 5/7/16

TO:

- ZEWDITU MEMORIAL HOSPITAL
- YEKATIT 12 MEDICAL COLLEGE GENERAL HOSPITAL

Subject: Request to access Facilities to conduct approved research

This letter is to support **Bekelech Bayou** to conduct research which is entitled as "***Virological Failure among HIV - Infected Adults Taking Second-Line Antiretroviral Treatment (ART) in Addis Ababa, Ethiopia***". The study proposal was duly reviewed and approved by the Addis Ababa Health Bureau procedures, and submit an activity progress report to the Ethical Committee as required. Therefore, we request the facility and staffs to provide support to the principal investigator.

The Addis Ababa City Administration Health Bureau

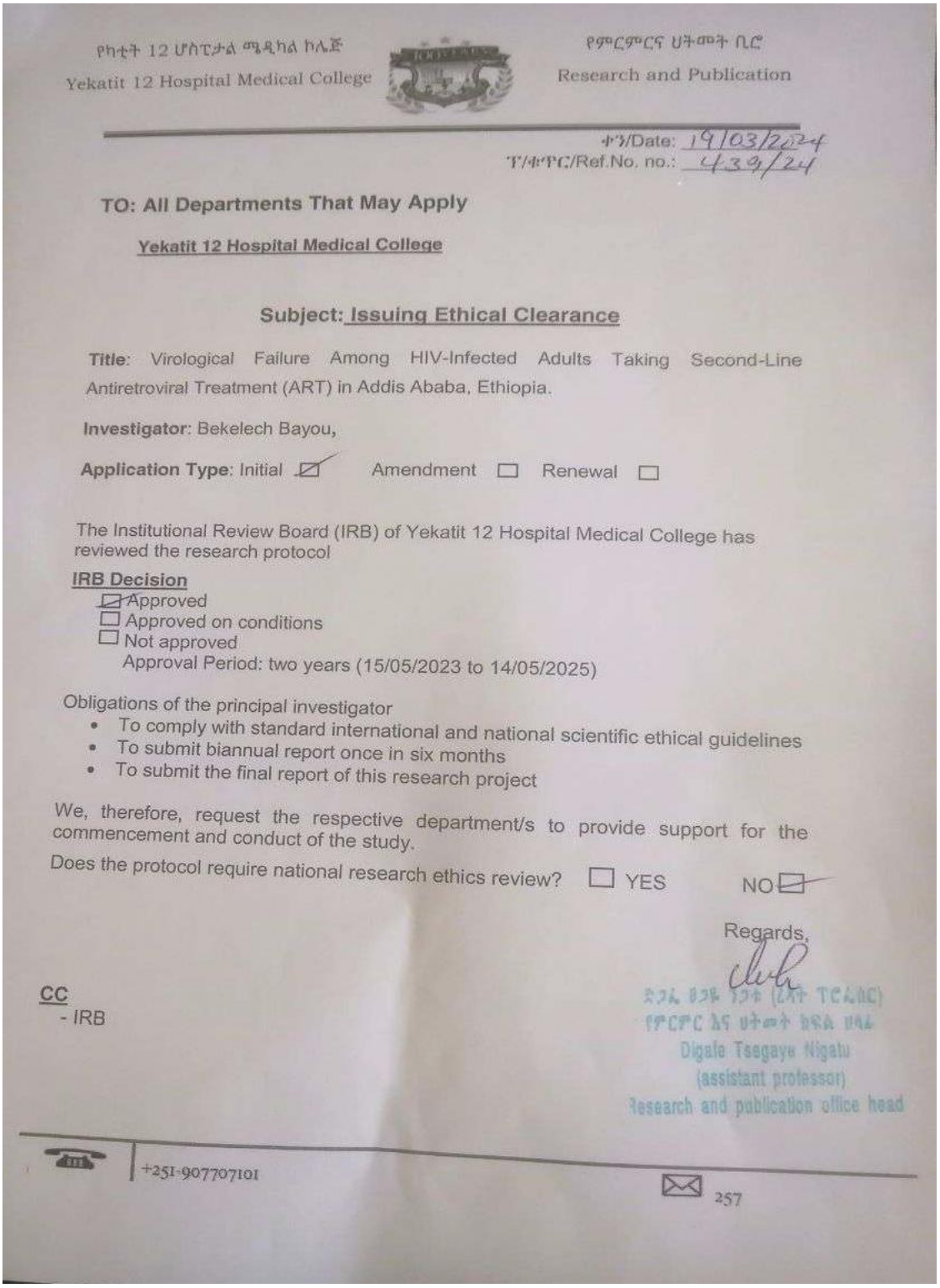
With Regards

Tesfaye Desalegn
for Dr. Yohannes W. Kidan
Ethical Clearance Committee

Cc

- **Bekelech Bayou**
- **ETHICAL CLEARANCE COMMITTEE**

Appendix 10. Letter of ethical approval and permission to use data for ART patients from Yekatit 12 Mediccal College in Addis Ababa.



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Yekatit 12 Hospital Medical College

የምርምርና ህትመት ቢሮ
Research and Publication

ቀን/Date: 19/03/2024
ፕ/ቁ/Ref.No. no.: 439/24

TO: All Departments That May Apply

Yekatit 12 Hospital Medical College

Subject: Issuing Ethical Clearance

Title: Virological Failure Among HIV-Infected Adults Taking Second-Line Antiretroviral Treatment (ART) in Addis Ababa, Ethiopia.

Investigator: Bekelech Bayou,

Application Type: Initial ☑ Amendment ☐ Renewal ☐

The Institutional Review Board (IRB) of Yekatit 12 Hospital Medical College has reviewed the research protocol

IRB Decision

☑ Approved
☐ Approved on conditions
☐ Not approved

Approval Period: two years (15/05/2023 to 14/05/2025)

Obligations of the principal investigator

- To comply with standard international and national scientific ethical guidelines
- To submit biannual report once in six months
- To submit the final report of this research project

We, therefore, request the respective department/s to provide support for the commencement and conduct of the study.

Does the protocol require national research ethics review? ☐ YES NO ☑

Regards,

ድጋሌ ፀጋዬ ነጋቱ (ረዳት ፕሮፌሰር)
የምርምር እና ህትመት ቢሮ ሀላፊ
Digale Tsegaye Nigatu
(assistant professor)
Research and publication office head

CC
- IRB

+251-907707101

257

Appendix 11. Letter of permission to use data for ART patients from Zewditu Memorial General Hospital in Addis Ababa.

To: - ART dep't

Zewditu memorial hospital

Subject: -Request to access departments to conduct approved research

The letter is to support Mr/Ms/Dr. Bekelech Bayou

On the research topic of

Virological failure among HIV-infected adults taking Second-Line Antiretroviral treatment (ART) in ZMH,

the study proposal was duly reviewed and approved by Addis Ababa Health Bureau IRB and the approval letter was left to our department (Training and research directorate).

Therefore we request the department and staffs to provide support to the principal investigator.

With regard

Simench Dakito Gucheto
Training & Research Directorate
Director

Appendix 12. STATA do file

Stata do file.do

Samples STATA output to be considered

```
 8 . stset timemonth, failure(secondlineARTfailure==1)

  Survival-time data settings

          Failure event: secondlineARTfailure==1
  Observed time interval: (0, timemonth]
       Exit on or before: failure

--------------------------------------------------------------------------
        369  total observations
          0  exclusions
--------------------------------------------------------------------------
        369  observations remaining, representing
         55  failures in single-record/single-failure data
     20,187  total analysis time at risk and under observation
                                                At risk from t =         0
                                     Earliest observed entry t =         0
                                          Last observed exit t =        73

 9 .
  end of do-file

10 . do "/var/folders/wn/_qlfywnx0hx6hp_nrnbylb3w0000gn/T//SD00430.000000"

11 . strate, per(100)

          Failure _d: secondlineARTfailure==1
    Analysis time _t: timemonth
```

D	Y	Rate	Lower	Upper
55	201.8700	0.27245	0.20918	0.35487

Notes: Rate = D/Y = failures/person-time (per 100).
Lower and Upper are bounds of 95% confidence intervals.

```
12 .
   end of do-file

13 . strate, per(10000)

          Failure _d: secondlineARTfailure==1
    Analysis time _t: timemonth

  Estimated failure rates
  Number of records = 369
```

D	Y	Rate	Lower	Upper
55	2.0187	27.245	20.918	35.487

Notes: Rate = D/Y = failures/person-time (per 10000).
Lower and Upper are bounds of 95% confidence intervals.

```
15 . strate adherance2, per(100)

          Failure _d: secondlineARTfailure==1
    Analysis time _t: timemonth

  Estimated failure rates
  Number of records = 369
```

adhera~2	D	Y	Rate	Lower	Upper
Good	20	86.6000	0.23095	0.14900	0.35797
Poor	35	115.2700	0.30363	0.21801	0.42289

Notes: Rate = D/Y = failures/person-time (per 100).
Lower and Upper are bounds of 95% confidence intervals.

```
15 . strate adherance2, per(100)

          Failure _d: secondlineARTfailure==1
    Analysis time _t: timemonth

  Estimated failure rates
  Number of records = 369

  +-------------------------------------------------------------+
  | adhera~2    D          Y      Rate     Lower     Upper     |
  |-------------------------------------------------------------|
  |     Good   20    86.6000   0.23095   0.14900   0.35797     |
  |     Poor   35   115.2700   0.30363   0.21801   0.42289     |
  +-------------------------------------------------------------+
  Notes: Rate = D/Y = failures/person-time (per 100).
         Lower and Upper are bounds of 95% confidence intervals.


16 .
  end of do-file

17 . do "/var/folders/wn/_qlfywnx0hx6hp_nrnbylb3w0000gn/T//SD00430.000000"

18 . strate adherance2, per(10000)

          Failure _d: secondlineARTfailure==1
    Analysis time _t: timemonth

  Estimated failure rates
  Number of records = 369

  +-------------------------------------------------------------+
  | adhera~2    D          Y      Rate     Lower     Upper     |
  |-------------------------------------------------------------|
  |     Good   20     0.8660   23.095    14.900    35.797     |
  |     Poor   35     1.1527   30.363    21.801    42.289     |
  +-------------------------------------------------------------+
  Notes: Rate = D/Y = failures/person-time (per 10000).
         Lower and Upper are bounds of 95% confidence intervals.
```