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Predictors of Second-Line Antiretroviral Treatment Virological Failure at Felege Hiwot and University of Gondar Comprehensive Specialized Hospitals Amhara Region, Northwest Ethiopia: A Case-Control Study

Getahun, Ayenew

BAHIR DAR UNIVERSITY

COLLEGE OF MEDICINE AND HEALTH SCIENCES

SCHOOL OF PUBLIC HEALTH

DEPARTMENT OF HEALTH SYSTEM MANAGEMENT AND HEALTH ECONOMICS

PREDICTORS OF SECOND-LINE ANTIRETROVIRAL TREATMENT VIROLOGICAL FAILURE AT FELEGE HIWOT AND UNIVERSITY OF GONDAR COMPREHENSIVE SPECIALIZED HOSPITALS AMHARA REGION, NORTHWEST ETHIOPIA: A CASE-CONTROL STUDY

BY; - GETAHUN AYENEW

A RESEARCH PAPER TO BE SUBMITTED TO THE DEPARTMENT OF HEALTH SYSTEM MANAGEMENT AND HEALTH ECONOMICS, SCHOOL OF PUBLIC HEALTH, COLLEGE OF MEDICINE AND HEALTH SCIENCES, BAHIR DAR UNIVERSITY IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF MASTER OF PUBLIC HEALTH IN GENERAL PUBLIC HEALTH

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DEPARTMENT OF HEALTH SYSTEM MANAGEMENT AND HEALTH ECONOMICS

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Declaration

I, the undersigned, declare that the thesis comprises my work. In compliance with internationally accepted practices, I have acknowledged and refereed all materials used in this work. I understand that non-adherence to the principles of academic honesty and integrity, misrepresentation/fabrication of any idea/data/fact/source will constitute sufficient ground for disciplinary action by the University and can also evoke penal action from the source which have not been properly cited or acknowledged.

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Signature; .....

Date of submission; 12/12/2022

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

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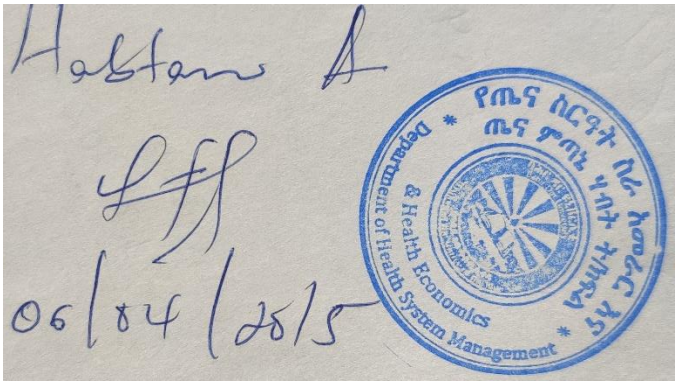

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3TC	Lamivudine
ABC	Aba Cavir
ACR	Albumin–Creatinine Ratio
ADR	Acquired HIV Drug Resistance
AIDS	Acquired Immune Deficiency Syndrome
AMR	Antimicrobial Resistance
ART	Antiretroviral Therapy
ART	Antiretroviral Therapy
ATV	Atazanavir
ATV	Atazanavir
BMI	Body Mass Index
CDC	United States Centers for Disease Control and Prevention
DRV	Darunavir
DRV	Darunavir
DTG	Dolutegravir
EFV	Efavirenz
EIA	Enzyme immunoassay
ETV	Etravirine
FHCSH	Felege Hiwot Comprehensive Specialized Hospital
HIV	Human Immuno Deficiency Virus
HIVDR	HIV Drug Resistance
LPV	Lopinavir
NCD	Non-communicable Disease
NNRTI	Non-Nucleoside Reverse-Transcriptase Inhibitor

NRTI	Nucleoside Reverse-Transcriptase Inhibitor
NVP	Nevirapine
OI	Opportunistic infection
PI	Protease inhibitor
STI	Sexually Transmitted Infections
RAL	Raltegravir
UGCSH	University of Gondar Comprehensive Specialized Hospital
UNAIDS	United Nations Programme on HIV/AIDS
WHO	World Health Organization
FHCSH	Felege Hiwot Comprehensive Specialized Hospital
UGCSH	University of Gondar Comprehensive Specialized Hospital
MAM	Moderate Malnutrition
SAM	Sever Malnutrition

ABSTRACT

Back ground: Second-line HIV treatment failure has become increasing worldwide, mainly in sub-Sahara Africa including Ethiopia. Even though the problem becomes increasing, inadequate information was available about its magnitude and predictors in the current study area.

Objective: To assess the predictors of second line Anti-Retroviral Treatment virological failure among second line ART users.

Method and materials: Institutional based unmatched case control study design was conducted from first September 2021 to December last 2021 at Felege Hiowt and University of Gondar Comprehensive Specialized Hospitals; Amhara region, North West Ethiopia. A total of 216 patients (60 cases and 156 controls) were recruited by Simple random sampling technique with 1:3 cases-to-controls ratio. Patients who had two viral load results ≥1000 copies/ml within a 3-month interval after taking ART drugs for at least 6 months were cases whereas ≤1,000 copies/ mL were controls. The sample size was calculated by using Epi-Info version 7.2.4. Structured questionnaires and check lists were used to gather the required information from patient registration book/ card/ review and face to face interviews. SPSS version 26 was used to summarize the findings. In bivariate logistic regression model, Variables with two-tailed P-value ≤ 0.25 at 95% confidence interval were transferred in to multivariate binary logistic regression mode and P value at ≤ 0.05 was set as statistically significant.

Results: Out of 216 patients recruited, 212 were participated with a response rate of 98.2%. Among the participants, 117 (55.2%) were males and 187 (88.2%) were urban dwellers. 208 (98.1%) of the respondents had age > 24 years, 73 (34.4%) had elementary level of education, 72(34%) had poor ART adherence and 112(52.8) did not disclose their HIV status. Likewise, Most of the patients 147(69.37) didn't used condom. The Predictors were; not disclosing HIV status (AOR=3.4, 95% CI: 1.52 – 7.79), poor adherence level (AOR=5.27, 95% CI: 2.2 - 12.5), not using condom (AOR=4.47, 95% CI: 1.63 – 12.2) and high Viral load (≥1000 copes/ml) when switched to second line ART (AOR=3.56, 95% CI: 1.5 - 8).

Conclusion and recommendations: The Predictors of second line Anti-Retroviral Treatment virological failure were non-disclosure, poor adherence, not using condom and high Viral load (≥1000 copes/ml) at switched to second line ART. Disclosing their HIV status, using condom and improving their adherence level for patients and counselling about the importance of disclosure and good adherence for health care providers are crucial.

Key word: ART Virological failure, Felege Hiwot Hospital, University of Gondar Hospital.

CHAPTER ONE: INTRODUCTION

1.1 Background

Human immunodeficiency virus (HIV) is a single-stranded RNA virus which attacks the body's immune system, specifically the white blood cells called CD4 cells. HIV has been continued to be a major global public health issue, having claimed almost 36.3 million lives so far. About 79.3 million people have become infected with HIV since the start of the epidemic. Only in 2020, there were 37.7 million people (1.7 million children <14 years) living with HIV, 1.5 million People became newly infected and 680 000 people died from AIDS-related illnesses worldwide. However, with increasing access to effective HIV prevention, diagnosis, treatment and care including for opportunistic infections, HIV infection has become a manageable chronic health condition enabling people living with HIV to lead long and healthy lives (1,2)

But the emergence of drug-resistant HIV has the potential to become a major public health threat worldwide as it limits treatment options for people living with HIV. HIV drug resistance (HIVDR) is an alteration in the genetic structure of HIV that affects the ability of a specific drug or combination of drugs to block replication of the virus. HIVDR occurs when the virus starts to make changes (mutations) to its genetic make-up (RNA) that are resistant to certain HIV drugs, or classes of HIV drugs. Now a day's, global prevalence of HIVDR is rising mainly due to resistance to non-nucleoside reverse transcriptase inhibitor (NNRTI) drugs which make up the backbone of first-line antiretroviral treatment regimes. It is also a serious emerging threat to the global scale-up of HIV treatment access, viral load testing access, monitoring of other clinical factors relating to patient care, patient behavior and clinic and program management (3).

Second-line HIV treatment failure has also become highly prevalent in Sub-Saharan Africa (SSA) with alarming rates during the 12–18 month period of treatment start in children (4). Monitoring people on antiretroviral therapy (ART) is important to ensure treatment efficacy and improved health outcomes, successful treatment, identify adherence problems and determine whether ART regimens should be switched in case of treatment failure (2). Second-line ART regimens are used when patients develop treatment failure for the first-line treatment regimens (5). If a person on ART who has taken ART drugs for at least 6 months has two consecutive viral load measurements greater than 1000 copies/ml within a 3-month interval with adherence support between

measurements, the results will confirm failure of the current treatment regimen and the client needs to be switched to appropriate third line regimen (6,7).

Clinical assessment and laboratory tests play a key role in assessing individuals following a positive HIV diagnosis to assess for coinfections, non-communicable diseases (NCDs) and other comorbidities that may have an impact on treatment response. Viral load failure is used as a golden approach to confirm treatment failure. For HIV patients who start ART, Viral load testing should be performed early after initiating ART within 6 months, at 12 months and then at least every 12 months to detect treatment failure. If viral load testing is not routinely available, CD4 count and clinical monitoring may be used to diagnose treatment failure, with targeted viral load testing to confirm virological ART failure where possible. In settings where routine viral load monitoring is available, CD4 cell count monitoring can be stopped in individuals who are stable on ART and virally suppressed (6,8).

1.2 Problem statement

The rise in Antimicrobial Resistance (AMR) is one of the greatest threats to global health. If it is not urgently addressed, it may result in millions of deaths, an increase in new and hard-to-treat infections and increased health-care costs. As a result, combatting AMR, including the threat posed by drug-resistant HIV is a major goal for the global community (9). After 15 years of global scale-up of antiretroviral therapy (ART), rising prevalence of HIV drug resistance in many low and middle income countries poses a growing threat to the HIV response with an increase in mortality, morbidity, HIV incidence and health care costs (3,8). All current antiretroviral drugs (ARVD), including newer classes, are at risk of becoming partly or fully inactive because of the emergence of drug-resistant virus. People receiving ART can acquire HIVDR or people can also be infected with HIV that is already drug resistant (9).

Delayed detection of Virological ART failure has been shown to be associated with the development of drug resistance HIV. This delaines progressively worsens by accumulating DR mutations (DRMs) over time without an appropriate switch in ART regimens. The issue is even more problematic in prevention of mother-to-child HIV transmission (PMTCT) in HIV programs (10).

Globally, the prevalence of DRHIV to NNRTI drugs has significantly increased since 2001. This rise has been observed more rapidly in Eastern Africa with estimated annual incremental increase of 29%, Southern Africa (23%), Western and Central Africa (17%), Latin America (15%) and Asia (11%). In eastern Africa, the Prevalence of pretreatment NNRTI resistance increases from 0% in 1996 to 13% in 2016 (3,11).

Virological ART failure is highly prevalent in sub-Saharan Africa (10). Especially in low-income countries, HIV drug resistance is still a serious threat to their health (12). Among populations receiving NNRTI-based ART with viral non-suppression, the levels of NNRTI and NRTI resistance ranged from 50% to 97% and from 21% to 91% respectively. Estimates of dual class resistance (NNRTI and NRTI) ranged between 21% and 91% of individuals for whom NNRTI-based first-line ART failed (13).

A survey implemented between 2014 and 2018 in 39 countries, showed that Pretreatment HIV Drug Resistance (PDR) to efavirenz/nevirapine among adults starting or restarting first-line ART ranges 10.2% in NEPAL to 25.9% in Honduras. Pretreatment drug resistance among treatment-naive infants newly diagnosed with HIV from 2012 to 2018 was very high, ranging from 34% in Swaziland to 69% in Malawi. Overall, the prevalence of any HIVDR among all individuals receiving treatment between 2014 and 2018 were ranged from 3% in Viet Nam to 29% in Honduras (13).

In Sub Sahara Africa (SSA), Second-line HIV treatment failure has become highly prevalent with alarming rates during the 12–18 month period of treatment start (4). Among patients receiving protease inhibitor (PI) based 2nd-line HIV treatment, 25% experienced virological failure at some point during follow-up in this region in 2016 (14). Another report in the same year in Sub-Saharan Africa showed that second line ART drug resistance mutation were 14% (15). A systematic review and meta-analysis conducted in SSA in 2019 also reported that, Second-line HIV treatment failure was 13.4%. Of which 65% PI-based and 35% was Ritonavir boosted PI-based second-line ART regimens (4).

In resource-limited settings, the prevalence of second-line virological ART failure rates among adults in 2012 were 21.8–33%, 14–38%, 15—38.5% and 10–38.0% at 6, 12, 24, and 36 months of initiation on second-line ART respectively (16). There were 1668 patients with virological failure in south Africa in 2012 (17), 109 patients with confirmed virological failure in Malawi in 2010 (18) and Second-line ART Virological failure was 18% in Rwanda by the end of 2016 (19). Some

Studies in Tanzania and southeast Uganda also indicated that there was a high incidence of virological failure (20).

The number of virological treatment failure is increasing from time to time in Ethiopia (21). It becomes a major challenge for HIV ADIS prevention and control mechanisms (22). The adjusted magnitude of VF among population taking ART in Ethiopia was found to be 11% (23). According to a study done among children and adolescents on second line ART in a pediatric cohort of an Ethiopian tertiary hospital, proportion of treatment failure (TF) were 14 out of 76 patients(24). A high incidence rate of second-line treatment failure (9.86 per 100 person-years or 254/1011) was also noticed in Amhara Region in 2016 (5).

Among the determinants of second line ART failure, poor adherence to ART, high viral load, not disclosure about HIV status , opportunistic infection, low CD4 counts < 350 cell/mm^3, low BMI (< 16 kg/m^2), young age 15– 29 year patients, smoking and drug abuse were the main factors (5,25).

Even if the problem is growing, there is still a paucity of information in developing countries on the factors for second-line ART failure (18). Identifying risk factors of second-line treatment failure remains crucial to reduce the need for third-line drugs (26). Even though the incidence and prevalence of second line ART failure becomes increasing, inadequate information is available about the magnitude and its predictors of second line ART virological failure in the current study area. Most of the previous studies were focused on adults >18 years.

1.3 Significance of the study

Findings of this research will give information about the risk factors of second line virological ART failure in the study area. It will serve as a base line data for treatment centers to address factors related to second line treatment failure. The result might be useful for regional health bureau to set programs and action plans on the need to third line regimens. It will be used as a source of information for researchers. It will also give important recommendations for patients on their treatment.

CHAPTER TWO: LITERATURE REVIEW

2.1 HIV drug resistance

HIV drug resistance (HIVDR) is the ability of HIV to mutate and reproduce in the presence of antiretroviral (ARV) drugs(27). This occurs when the virus starts to make changes (mutations) to its genetic make-up (RNA) that are resistant to certain HIV drugs, or classes of HIV drugs. It is caused by one or more changes (mutation/s) in the genetic structure of HIV that affects the ability of a specific drug or combination of drugs to block replication of the virus. These mutations can lead to changes in certain proteins most commonly enzymes which help HIV to reproduce (replicate) (9).

Resistance can happen either as a result of a prolonged period of time on treatment or more commonly, as a result of suboptimal treatment adherence. These new mutations make copies of themselves gradually increasing the level of the virus (viral load) in the person living with HIV. This indicate that treatment may no longer be effective (3).

Viral load testing is the recommended test to detect ART failure. Vairological ART failure is defined as viral load above 1,000 copies/ml based on two consecutive viral load measurements in a 3-month interval with adherence support following the first viral load test after at least six months of starting a new ART regimen. An individual must be taking ART for at least 6 months before it can be determined that a regimen has failed. Second line antiretroviral therapy virologic failure is defined as patients who are on second-line regimen and have meet the criteria for Vairological ART failure. Third-line ART regimens are used when patients develop treatment failure for the second-line treatment regimens (5,28).

2.2 Second line and third line ART regimens

The following two treatment options can be used for patients who had a treatment failure for first line regimes.

1. Dolutegravir (DTG) in combination with an optimized nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) backbone may be recommended as a preferred second-line regimen for people living with HIV for whom non-DTG-based regimens are failing (Adults and adolescents and Children with approved DTG dosing) (29,30).

2. Boosted protease inhibitors (PI) in combination with an optimized NRTI backbone is recommended as a preferred second-line regimen for people living with HIV for whom DTG-based regimens are failing (30–32).

Table 1. Preferred and alternative second-line ART regimens for adults, adolescents, children and infants, Bahir Dar, Northwest Ethiopia; 2022.

Population	Failing first-line regimen	Preferred second-line regimen	Alternative second-line regimens	Third line regimens
adults and adolescents > 10years	TDFb + 3TC (or FTC) + DTGc	AZT + 3TC + ATV/r (or LPV/r)	AZT + 3TC + DRV/rd	DRV/r b + DTGc (or RAL) ± 1–2 NRTIs
	TDF + 3TC (or FTC) + EFV (or NVP)	AZT + 3TC + DTGc	AZT + 3TC + ATV/r (or LPV/r or DRV/r)d	DRV/r b + 2 NRTIs ± NNRTI
	AZT + 3TC + EFV (or NVP)	TDFb + 3TC (or FTC) + DTGc	TDFb + 3TC (or FTC) + ATV/r (or LPV/r or DRV/r)d	Optimize regimen using genotype profile
Children and infants ≤10 years	ABC + 3TC + DTGe	AZT+ 3TC + LPV/r (or ATV/rf)	AZT + 3TC + DRV/rg	RAL (or DTG)f + 2 NRTIs DRV/rg + 2 NRTIs DRV/rg + RAL (or DTG)f ± 1–2 NRTIs
	ABC (or AZT) + 3TC + LPV/r	AZT (or ABC) + 3TC + DTGe	AZT (or ABC) + 3TC + RAL	
	ABC (or AZT) + 3TC + EFV	AZT (or ABC) + 3TC + DTGe	AZT (or ABC) + 3TC + LPV/r (or ATV/rf)	
	AZT + 3TC + NVP	ABC + 3TC + DTGe	ABC + 3TC + LPV/r (or ATV/rf or DRV/rg)	

3TC: lamivudine; ABC: Abacavir; ATV/r: Atazanavir/ritonavir; AZT: Zidovudine; DRV/r: Darunavir/ritonavir; DTG: Dolutegravir; EFV: Efavirenz; FTC: Emtricitabine; LPV/r: Lopinavir/, ritonavir; NVP: Nevirapine; RAL: Raltegravir; TDF: Tenofovir Disoproxil Fumarate (33).

Sequencing:- if PIs are used in first-line ART: ATV/r (or LPV/r or DRV/r depending on programmatic considerations) + TDF + 3TC (or FTC) and then AZT + 3TC + DTG in Second-line ART. TAF (Tenofovir Alafenamide) can be used as an alternative NRTI in special situations for adults and adolescents. DRAL + LPV/r can be used as an alternative second-line ART regimen for adults and adolescents (33).

Table 2: Summary of sequencing options for first-, second- and third line ART regimens in adults, adolescents, pregnant women and children, Bahir Dar, Northwest Ethiopia; 2022.

Population	First-line regimens	Second-line regimens	Third-line regimens
Adults and adolescents (>10 years)	2 NRTIs + EFV	2 NRTIs + ATV/r or LPV/r	DRV/r b + DTGc (or RAL) ± 1–2 NRTIs
		2 NRTI + DRV/rb	
	2 NRTIs + DTG	2 NRTIs + ATV/r or LPV/r	DRV/r b + 2 NRTIs ± NNRTI
		2 NRTI + DRV/r	Optimize regimen using genotype profile
Pregnant or breastfeeding women	2 NRTIs + EFV	2 NRTIs + ATV/r or LPV/ra	DRV/r b + DTGc (or RAL) ± 1–2 NRTIs
		2 NRTIs + DRV/rb	
Children (0–10 years	2 NRTI + LPV/r	If less than 3 years: 2 NRTIs + RALd	RAL (or DTG)f + 2 NRTIs DRV/rg + 2 NRTIs DRV/rg + RAL (or DTG)f ± 1–2 NRTIs
		If older than 3 years: 2 NRTIs + EFV or RAL	
	2 NRTI + EFV	2 NRTIs + ATV/re or LPV/r	

ATV atazanavir, DRV darunavir, DTG dolutegravir, EFV efavirenz, LPV lopinavir, NNRTI non-nucleoside reverse-transcriptase inhibitor, NRTI nucleoside reverse-transcriptase inhibitor, NVP nevirapine, PI protease inhibitor, r ritonavir, RAL raltegravir (33).

2.3 Types of HIVDR

WHO commonly classify HIVDR into three main categories. 1. Acquired HIV drug resistance (ADR) develops because of viral replication in the presence of ARV drugs. Resistance to commonly used NNRTIs ranged from 50% to 97% and resistance to most commonly used NRTIs ranged from 21% to 91%. 2. Transmitted HIV drug resistance (TDR) is detected among ARV drug–naive people with no history of ARV drug exposure. TDR occurs when previously uninfected individuals are infected with virus that has drug resistance mutations. 3. Pretreatment HIV drug resistance (PDR) refers to resistance that is detected among ARV drug–naive people initiating ART or people with previous ARV drug exposure initiating or reinitiating first-line ART. PDR affects more than 10% of people receiving ART for the first time and rise up to 30% in people who had previous

exposure to these drugs. PDR is either TDR or ADR or both. PDR may have been transmitted at the time of infection (TDR) or may be acquired through previous ARV drug exposure such as among women exposed to ARV drugs for preventing mother-to-child transmission of HIV, among people who have received pre-exposure prophylaxis or among individuals reinitiating first-line ART after a period of treatment interruption (9,34).

2.4 Prevalence of second line ART virological failure and associated factors

HIV drug resistance can arise from a range of different factors, which can be divide into four broad categories – patient, programming, drug regime and virus-specific factors (3).

Patient related factors: A number of individual related reasons may stop a person taking their drugs as prescribed which increases the risk of developing drug resistant mutations. This includes, lack of understanding about HIV treatment, adherence to a prescribed ART, having to take a lot of pills, being forgetful, depression Stigma, disclosure and substance or alcohol abuse. Such factors particularly affect adolescents, because they may find it hard to prioritize their health over social engagements. Children also face unique challenges because they have less treatment options available to them and rely on others to manage their health (3).

Programme related factors: this factors refers to challenges arising from the delivery of large-scale or country-level HIV treatment programmes which in turn affect an individual's ability to stick to a treatment regimen. Factors such as drug supply continuity and retention of patients on treatment are among programmatic driving factors. Poorly resourced treatment programmes may also be the result of weak monitoring and evaluation of care outcomes (3).

Drug and treatment regime related factors: Selection of specific antiretroviral regimes may increase or decrease the likelihood of HIVDR. Because; different types of drugs and drug classes have varying genetic barriers to resistance like; drug potency, pharmacokinetics, drug–drug interactions, tolerance and genetic barrier to resistance. A drug, or combination of drugs, that is not absorbed properly can also result in too low levels in the bloodstream and ultimately allow HIV reproduction and the accumulation of drug-resistance mutations. Interactions between drugs—including common HIV medications can be a major problem in this regard (3,35).

Viral related factors: Virus-related factors refer to resistance that arises by nature of the HIV type or subtype that may affect a drug regime (such as HIV subtype, replication capacity and pre-existing polymorphisms)(3,35).

Different studies showed that the number of people living with HIV (PLHIV) switching from first- to second-line ART regimens and treatment failure on this regimens becomes increasing worldwide (16,36,37).

Rate of second line ART virological failure is also increasing overtime resulting in rising the number of individuals who required third-line ART regimens. This shift is related to several factors. Primarily, poor-adherence to medication due to adverse events or non-continuous medication access and duration of exposure to previous drug regimens. The issue is more worsen in resource limited settings (4,16). Approximately, 22% - 23% of the patients on second-line ART in low-income countries experienced a virologic failure at 12 months after the start of second-line and mortality at 12 months ranges from 5.3% - 10.5% (16). For example, the 3-year probability of virologic failure among children was 19.3% in 2011 in South Africa (38). A Retrospective Cohort Study conducted among individuals on second line antiretroviral therapy in Eastern Uganda also showed that the 5 year cumulative incidence of treatment failure was 23% (39)**.** A cross-sectional study done among children aged <19 years in Dodoma (central Tanzania) reported that, virological treatment failure among children and adolescents living with HIV on ART remained high (34%) (40). Similar study done in Western Kenya in 2018 also showed that virologic failure (VF) was 21% (41).

A study conducted among Asian Children and Adolescents on second line ART reported that, 46% had ≥1, 34% had ≥2, and 23% had ≥3 consecutive episodes of viral failure with Second-Line ART during the 2 years of follow-up. The odds of VF were increased by 5-fold (AOR, 5.22; 95% CI: 1.18–23.05) for patients who had a CD4 count of <350 cells/μL compared to those with a CD4 count of ≥350 cells/μL and Self-reported adherence of <95% (42). Another study done in Cambodia (Southeast Asian) in 2018 also reported that, virological failure for Protease Inhibitor-Based Second-Line Regimen among adult population was 10.3%. factors associated with virological success were CD4 cell count between 201 and 350/mm^3 (OR: 4.66, 95% CI: 2.57–8.47) and >350/mm^3 (OR: 6.67, 95% CI: 4.02–11.06), duration of PI-based regimen >2 years (OR: 1.64, 95% CI: 1.03–2.62), ATV-containing regimen (0R: 1.65, 95% CI: 1.04–2.63) and high level of adherence (OR: 2.41, 95% CI: 1.07–5.41) (43).

A systematic review and meta-analysis showed that, the pooled second-line HIV treatment failure rate was 15.0 per 100 PYs in sub-Saharan Africa (SSA). Baseline values, high viral load (OR: 5.67; 95% CI: 13.40–9.45), advanced clinical stage (OR: 3.27; 95% CI: 2.07–5.19), low CD4 counts (OR:

2.80; 95% CI: 1.83–4.29) and suboptimal adherence to therapy (OR: 1.92; 95% CI: 1.28–2.86) were the factors associated with increased failure rates (44).

Another Multicentered systematic review analysis performed in low and medium income countries showed that out of 928 HIV-infected children on second-line ART, 154 were experienced virological treatment failure. Being adolescent were almost four times more risky to virologic failure compared to younger children (45).

The number of patients on second-line ART in Rwanda has increased substantially in the last decade from 388 patients in 2007 to 7625 by the end of December 2016. Out of 1688 patients initiated second-line ART PI-based regimen in this country, 301(18%) individuals were developed Virological failure. Risk factors associated with virological failure were Age groups 15–29 years and 30–39 years compared to age group 40–59 years (AOR = 2.22 and 1.45), CD4 cell count ≤500 cells/mm3 at ART initiation (AOR= 5.40), WHO stage III & IV as compared to WHO stage I and II (AOR, 1.56), ATV/r compared to LPV/r based second-line regimen (AOR: 1.48) and receiving care at a health center relative to regional or provincial hospital (AOR 1.55) (46).

A 5-year observational retrospective study done in Southwestern Nigeria to assess virological failure in patients on second-line ART showed that, 33 (13.3%) had viral load >1000 RNA copies/ml (unsuppressed viral load or virological failure). Poor adherence to ART was the critical factor chiefly contributing to virological failure (AOR= 2.15; 95% CI: 0.37-7.31) (47).

A case control study conducted in Johannesburg, South Africa in 2016 reported that second line ART Virological failure was predicted by poor adherence (AOR: 4.7; 95% CI: 2.1–10.5), younger age, <40 years (AOR: 0.6; 95% CI: 0.3–1.1), high social instability (AOR: 3.8; 95% CI: 1.30–11.5), self-reported ADR (AOR: 1.9; 95% CI: 1.0–3.5), disclosure to friends/colleagues rather than partner/relatives (AOR 3.4; 95% CI: 1.3–9.1), and medium/high depression compared to low/no depression (AOR 4.4; 95% CI: 1.5–13.4) (25). Virological failure among adult HIV patients receiving PI based second line ART regimens in north western Tanzania was 12.18% in 2018. Determinant factors were age <30 years (AOR = 12.5), being on first line for less than 3 years (AOR = 6.1) and CD4 <200cells/μl at switch to second line ART (AOR = 16.3) (48).

Some studies in our country Ethiopia has also explained that ART failure is increasing from time to time (49,50). A multicenter retrospective follow-up study among adolescents and adults in northern Ethiopia showed that, out of 227 HIV patients who are on second line ART 67 developed treatment

failure. Of this 1.4% are virological failures. Patients who started second-line ART at age >45 years were 3.3 times (AHR = 3.33, 95% CI = 1.33–8.31) more likely to develop treatment failure than patients in the age group of 15–29 years, being at WHO HIV stage IV when started second-line ART had 3.6 times (AHR = 3.63, 95% CI = 1.72–7.67) higher likelihood of treatment failure compared to patients who started second-line ART at early WHO HIV stages (stage I or II), patients with CD4 count below 100 cells/mm^3 at the start of second-line ART had 3.8 times (AHR = 3.79, 95% CI = 1.61–8.91) likelihood of second-line ART failure than patients who started second-line ART at CD4 count of 100 cells/mm^3 or above, TB co-morbidity had 3.4 times (AHR = 3.39, 95% CI = 1.91–6.01) higher likelihood of treatment failure compared to patients without TB and Patients with poor adherence level at start of second-line ART were 3.6 times (AHR = 3.63, 95% CI = 1.89–6.96) more likely to develop treatment failure than patients who had good/fair adherence level (25).

Another retrospective observational cohort study conducted among children and adolescents taking second line anti-retroviral treatment at Tikur Anbessa Specialized Hospital, Addis Ababa, the prevalence of second line ART virological failure was 18.4%. Virologic failure was significantly associated with the age of the child or adolescent (AOR= 0.00 CI: 0.000-0.039)(24).

A multi-centered retrospective follow-up study undertaken in Amhara region; North West Ethiopia to assess the Incidence and predictors of second-line Antiretroviral Treatment Failure among adults living with HIV reported that among 1011 participants 254 have had a virological treatment failure. Patients who didn't modify the second-line drug regimens, had poor ART adherence, being at WHO clinical stages I and not taking INH types of second-line drug regimen were 1.55, 1.4, 0.32, 1.68 times more likely to experience treatment failure than their counter groups respectively. Being on second-line regimen "TDF-3TC-LPV/r" were 1.55 times more risky to experience treatment failure than patients who were under second-line regimen "ABC-ddI-LPV/r" and also using "AZT-3TC-LPV/r", type of second-line regimen was 3 times more likely to experience treatment failure than "ABC-ddI-LPV/r" types of regimens (5).

A case control study conducted in Wollo, Amhara Regional State, Northeast Ethiopia identified the following predictors for second line ART virological failure; poor adherence (AOR=6.060; 95% CI=2.837-12.944), not disclosing their HIV status (AOR=4.178; 95% CI=1.431-12.198), OI (AOR=4.1), CD4 count < 100 cells/mm3 (AOR=3.497; 95% CI=1.233-9.923) and 100– 350 cells/mm3 (AOR=5.442; 95% CI=2.191-13.513), low BMI < 16 kg/m2 (AOR=7.223; 95% CI=2.218-23.520) and young age 15– 29 years (AOR=2.898; 95% CI=1.171-7.170) (51).

CHAPTER THREE: CONCEPTUAL FRAME WORK

Different risk factors for second line ART virological failure were reported by various researches. This factors can be categorized in to Socio demographic factors, behavioral factors/patient related/, Biological and clinical factors, drug related factors and Program/service/ related factors. The association between dependent variable and second line ART vivrological failure has shown below (*Figure 1*).

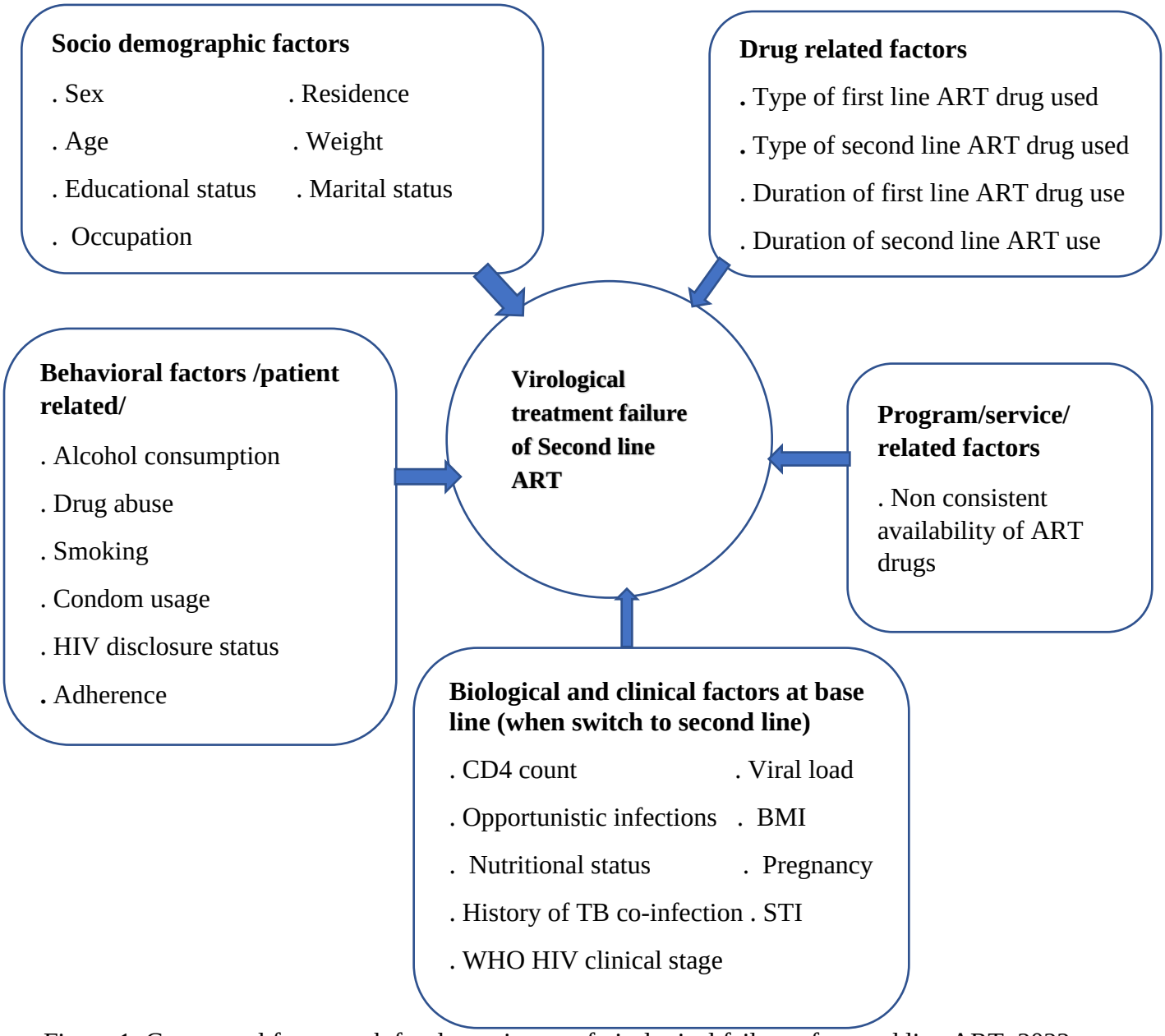

Figure 1: Conceptual framework for determinants of virological failure of second line ART, 2022.

Source: Adapted from different literatures (50, 51, 1, 17, 21, 8, 10, and 47).

CHAPTER FOUR: OBJECTIVE

Objective

The main objective of this study was to identify the predictors of second line antiretroviral treatment failure at Felege Hiwot and University of Gondar Comprehensive Specialized Hospitals, North West Ethiopia, 2021.

CHAPTER FIVE: METHODS AND MATERIALS

5.1 Study settings and period

The study was carried out from September first 2021 to December last 2021 at FHCSH and UGCSH which are found in Amhara regional state, North West Ethiopia. FHCSH is found in Bahir Dar city, the capital city of Amhara Regional state. It is located 561km away from Addis Abeba. Geographical coordinates of Bahir Dar city are 11° 36' 0" North, 37° 23' 0" East and an Elevation of 1,800 m (5,900 ft.) above sea level (52,53). According to the Amhara National Regional State Plan Commission Bureau 2021 data, Bahir Dar city administration had an estimated total population of 406,433 (192,041 male and 214,393 female) dwellers. Of which 85% live in the urban and 15% in the peri-urban and rural areas of the city. Based on Amhara Regional health bureau 2021 report, 14 Health posts, 10 Health centers 2 general hospitals and 2 referral hospitals are governmental health institutions found in the city. There are also 10 basic clinics, 28 Medium clinics, 10 higher clinics and 5 general hospitals among private health institutions. Only one governmental specialized referral hospital (Felege Hiwot) has provide third line ART treatment service in Bahir Dar. There were 740 and 31 ART patients who were on second-line and third-line regimens respectively at FHCSH by the end of August 2021.

The city of Gondar is situated in North-western parts of Ethiopia, Amhara Regional State. It far 725 km from Addis Ababa, 175 km from Bahir Dar and 120km from the Simien Mountains. It founds at 12° 36′ 0″ N, latitude 37° 28′ 0″ E longitude coordinates and an elevation of 2133 m above sea level. (54,55). The Regional Plan Commission Bureau also reported that, the metro area population of Gondar city in 2021 was 454,445 (218,378 male and 236,068 female). UGCSH is used as the referral center for more than 7 million catchment population (56). Based on reports obtained from this hospital, there were 5513 patients on ART until September 1st 2021. Out of these 520 were second-line ART users and 29 were on third-line regimens.

5.2 Study design

Institutional based unmatched case control study design was conducted

5.3 Source population

All HIV patients at FHCSH and UGCSH who were on second line and third line ART regimens.

5.4. Study population

All HIV patients who were on second line and third line ART regimens and took second line ART at least for six months at FHCSH and UGCSH during the study period.

5.5 Inclusion and exclusion criteria

5.5.1 Inclusion criteria

All HIV patients who were on second line and third line ART regimens at FHCSH and UGCSH ART clinics during the study period were included in the study.

5.5.2 Exclusion criteria

All HIV patients who had not taken second line ART regimen for more than six months at FHCSH and UGCSH ART clinics during the study period were excluded in this study.

5.5 Sample size determination and sampling techniques

5.5.1 Sample size determination

Based on a study conducted in Wollo, Amhara Regional State, Northeast Ethiopia, the following significant predictors were found (51) for minimum sample size calculation using EPIINFO .

Table 3. Sample size calculation based on significant predictors found from previous study (using EPIINFO).Bahir Dar, Northwest Ethiopia; 2021.

no	Variables	P value	No (%) of cases among exposed	N (%) of control among exposed	Possible total sample size
1	Age 15 – 29 years	<0.05	40(46)	53(19.2)	35ca + 103co = 138
2	Poor adherence	<0.001	46(52.9)	36(13)	16ca + 47co = 63
3	Have no disclosure status	<0.01	32(36.8)	16(5.8)	19ca + 57co = 76
4	BMI < 16 k.g/m^2	<0.01	24(27.6)	12(4.3)	27ca + 80co = 107
5	CD4 count < 100cells/mm^3	<0.001	26(29.9)	22(7.9)	35ca + 104co = 139
6	CD4 count 100 – 350 cells/mm^3	<0.01	27(31)	31(11.2)	**47ca + 140 co = 187**
7	Having opportunistic infections	<0.01	42(48.3)	33(12)	18ca + 54co = 72
Total sample size including 10% non-respondent rate					52ca + 154co = 206

Note: ca = cases, co = controls

Based on the above predictors as a reference and taking the following assumptions in to consideration, sample size was calculated using EPIINFO version 7.2.4 (using a two population proportion formula).

n= sample size (number of participants), 95% confidence level) Z α/2=1.96 (for 0.05 significance level), for 80% power, Z_β= 0.84, r = 1/3 (the ratio of cases to controls), p1= 31% (% of cases among exposed), p2= 11.2% (% of cases among non-exposed), the minimum sample size, including 10% non-respondent rate for this study was 206 participants (52 cases and 154 controls). But we recruited 216 patients (all the cases 60) and 156 controls.

5.5.2 Sampling techniques

Case selection; All HIV patients who had taken a second line ART for at least six months and had developed a virological failure were selected and listed from the patients registration book at FHCSH and UGCSH during the study period.

There were 31 patients at FHCSH and 29 patients at UGCSH who were failed for second line ART.

Control selection; All HIV patients who had taken a second line ART regime at least for six months and didn't developed virological ART failure were selected and listed from the patients registration book at FHCSH and UGCSH during the study period. Participants were recruited by a simple random sampling technique (generated using a computer excel).

By considering proportional allocation method,

Let nf = number of control participants and Nf = total number of control from FHCSH and ng = number of control participants and Ng = total number of control from UGCSH,

In this study N for controls = 740 + 520

$$N = 1260$$

$$n = 140$$

$$nf = \frac{740}{1260}\ x\ 140$$

$$nf = 83$$

$$ng = \frac{520}{1260}\ x\ 140$$

$$ng = 58$$

∴ 94 patients from FHCSH and 62 patients from UGCSH who were taking second-line ART were included in this study.

5.6. Definition of terms

Stable on ART- HIV Patients on ART for at least 1 year, no current illnesses or pregnancy, good understanding of lifelong adherence and evidence of treatment success (two consecutive viral load measurements below 1000 copies/mL) and absence of adverse drug reactions requiring regular monitoring (57).

Adherence- Refers to the whole process from starting HIV treatment, keeping all medical appointments and taking HIV medicines every day and exactly as prescribed. Or it is the degree to which the person's behavior, taking medication, following a diet and/or changing lifestyle corresponds with the agreed recommendations from a health care provider (33).

Good Adherence; drug adherence of ≥95% or if <2 doses of 30 doses or <3 doss of 60 doses is missed as documented by ART healthcare provider (33).

Fair/medium/ adherence. Drug adherence of 85–94% or 3–5 missed drug doses out of 30 doses or 4–9 missed drug doses out of 60 doses (33).

Poor adherence; If drug adherence is <85% or ≥6 doses of missed ART drug doses out of 30 doses or >9 doses of missed ART drug doses out of 60 as documented by the ART healthcare provider (33).

Adherence index = $$\frac{\text{Total number of drugs taken}}{\text{Total number of drugs prescribed}} \times 100$$

Suboptimal adherence; a report of ≥1 reason for missing ART ≥5 times within the past month (58).

Opportunistic Infections (OI); Infections that develop as a result of HIV-inflicted damage to the immune system (TB, PCP, gastrointestinal OI, herpes simplex, herpes zoster, fungal infection) and other national ART guidelines define opportunistic infection (59)

Virological failure; refers to a persistently detectable viral load exceeding 1000 copies/mL (two consecutive viral load measurements within a 3-month interval with adherence support between measurements) after at least 6 months of using ART (8)

Non-Disclosure; patients who did not disclose about their HIV status for anyone except their couples and health care providers.

5.7 Variables

5.7.1 Independent variables

Independent variables included the socio demographic, behavioral, clinical and immunological characteristics of the patient. Of these; sex, age, weight, residence, marital status, educational status, job, alcohol intake, drug abuse, smoking, disclosure status, number of sexual partners, condom use, adherence, body mass index (BMI) at switch, opportunistic infections (OI), TB coinfection, nutritional status, WHO HIV clinical staging at switch to second line, CD4 count (CD4 count at 2nd line ART initiation), viral load, type of first and second line treatment (being on a protease inhibitor plus 2 nucleoside analogues(NRTIs) or not), duration in second line ART and duration in first line ART.

5.7.2 Dependent variable

The dependent variable (outcome of interest) was second line ART virological failure.

5.8 Data collection tools and techniques

The data were collected by using structured questionnaires and checklist prepared by the principal investigator. The tools were adapted from different literatures, WHO guidelines, institutional checklists and some of it were developed by the investigator. This tools includes socio demographic, behavioral, clinical and immunological related data.

Personal interview and patient registration book/ card/ review was performed using data collection tools to gather the required information.

5.9 Data quality managements

To maintain the data quality, different techniques were employed to address major source of errors. The questionnaires were translated to local language (Amharic). Health professionals who were participated in the data collection were got on sight training before the data collection. Each day the collected data were crosschecked for its completeness (the extent to which data are of sufficient breadth, depth, and scope for the task at hand or whether there are any gaps in the data from what was expected to be collected and what was actually collected), accuracy (whether the data values interred were the correct values), clarity (clearly fulfilled without ambiguous), consistency (data across all systems reflected the same information) and missed values and missed variables carefully. Necessary modifications were made based on the gaps identified. All collected data were entered into EPI-data version 3.1 after being coded. Then it was transferred to Statistical Package for Social Science (SPSS) version 26 for analysis.

5.10 Data processing and analysis

The collected data were entered and analyzed by using SPSS version 26 for windows. Descriptive statistics was used to present and summarize the findings. Bivariate and multivariate binary logistic regression model was employed to identify determinates of second line ART virological failure. Odds ratios with its 95% confidence intervals and two-tailed P-value was calculated. Variables with P-value ≤ 0.25 in the bivariate analysis were included in the multivariate logistic regression mode and variables which had P value ≤ 0.05 in the multivariate analysis were consider as statistically significant.

5.11 Ethical clearance

Ethical clearance was obtained from Bahir Dar University, College of Medicine and Health Sciences Institutional Review Board (IRB). Official letter of co-operations was provided to FHCSH and UGCSH prior to data collection. Assent from children and verbal informed consent from adults were obtained after explaining the purpose and objective of the study. Confidentiality of the data had been maintained.

CHAPTER SIX: RESULTS

6.1. Socio-demographic and Behavioral characteristics

Out of the total of 216 patients on second and third line ART (60 cases and 156 controls) recruited, 212 (59 cases and 153 controls) were participated in this study. This accounts for a response rate of 98.2%. The mean age of the participants were 40.7 years. Among the participants, 117 (55.2%) were males and 187 (88.2%) respondents were urban residents. 208 (98.1%) of the respondents had age > 24 years and 4 (1.9%) were 24 years or below. 102 (48.1%) were married participants and 73 (34.4%) had elementary level of education (Table 4).

Table 4: Socio demographic characteristics of patients on second and third line ART regimen at FHCSH and UGCSH; Amhara Region, North West Ethiopia from September to December 2021.

General variables	Variables category	Frequency of Virological failure. No. (%)		Total No. (%)
		Cases (N=59) No. (%)	Controls (N=153) No. (%)	N = 212
Sex	Male	33(55.9)	84(54.9)	117(55.2)
	Female	26(44.1)	69(45.1)	95(44.8)
Age (in year)	< 14	3(5.1)	1 (0.7)	4(1.9)
	14 – 24	4(6.8)	13(8.5)	17(8.1)
	>24 – 64	51(86.4)	136(88.9)	187(88.2)
	>64	1(1.8)	3(2)	4(1.9)
Residence	Urban	51(86.4)	136(88.9)	187(88.2)
	Rural	8(13.6)	17(11.1)	25(11.8)
Educational status	Illiterate	14(23.7)	43(28.1)	57(26.9)
	Elementary level	21(35.6)	52(34)	73(34.4)
	Secondary level	12(20.3)	21(13.7)	33(15.6)
	Preparatory level	11(18.6)	20(13.1)	31(14.6)
	College and above	1(1.7)	17(10)	16(7.5)
Marital status	Single	16(27.1)	48(31.4)	64(30.2)
	Married	34(57.6)	68(44.4)	102(48.1)
	Divorced	7(11.9)	25(16.3)	32(15.1)
	Widowed	2(3.4)	12(7.8)	14(6.6)

From the study participants, 33 (55.9%) of the cases and 3(2%) of the controls had poor adherence to ART treatments. Similarly, 46 (78%) of the cases and 66 (43.1%) of the controls did not disclose their HIV status during taking ART. Likewise, 9 (15.3%) of the cases and 26 (17%) of the controls had a history of alcohol use. Most of the cases 53 (89.8%) and the controls 94 (61.4%) did not used condom (Table 5).

Table 5: Behavioral characteristics of patients on second and third line ART regimen at FHCSH and UGCSH; Amhara Region, North West Ethiopia from September to December 2021.

General variables	Variables category	Frequency of Virological failure. No. (%)		Total No. (%)
		Cases (N=59) No. (%)	Controls (N=153) No. (%)	212
Alcohol consumption	Yes	9(15.3)	26(17)	35(16.5)
	No	50(84.7)	127(83)	177(83.5)
Using condom	Yes	6(10.2)	59(38.6)	65(30.7)
	No	53(89.8)	94(61.4)	147(69.374.5)
Disclosure status	Disclosed	13(22)	87(56.9)	100(47.2)
	Not disclosed	46(78)	66(43.1)	112(52.8)
Smoking cigarettes	Yes	5(8.5)	1(0.7)	6(2.8)
	No	54(91.5)	152(99.3)	206(97.2)
Level of Adherence	Good	13(22)	91(59.5)	104(49)
	Medium	13(22)	39(25.5)	36(17)
	Poor	33(55.9)	3(2)	72(34)

6.2. Clinical and immunological characteristics

Among the participants recruited, 86(40.6%) had a CD4 count <200 (cells/mm3). 8(13.6%) of the cases and 7(4.6%) of the controls were severely malnourished. Viral load when switched to second line ART is ≥1000(copes/ml) for 71(33.5) patients. Most of the participants were at WHO HIV clinical stage I (Table 6).

Table 6: Clinical and immunological characteristics of patients on second and third line ART regimen at FHCSH and UGCSH; Amhara Region, North West Ethiopia from September to December 2021.

General variables	Variables category	Frequency of Virological failure. No. (%)		Total No. (%) N = 212
		Cases (N=59) No. (%)	Controls (N=153) No. (%)	
Body mass index (BMI)	<18.5	20(33.9)	25(16.3)	45(21.2)
	18.5 – 25	36(61)	106(69.3)	142(67)
	>25 – 30	2(3.4)	21(13.7)	23(10.8)
	>30	1(1.7)	1(0.7)	2(0.9)
CD4 count (cells/mm3)	<200	24(40.7)	62(40.5)	86(40.6)
	200 – 350	21(35.6)	53(34.6)	74(34.9)
	350.01 - 500	9(15.3)	29(19)	38(17.9)
	>500	5(8.5)	9(5.9)	14(6.6)
Nutritional status	Normal	33(55.9)	104(68)	137(64.6)
	MAM (Moderately)	10(16.9)	25(16.3)	35(16.5)
	SAM (severely)	8(13.6)	7(4.6)	15(7.1)
	Over weight	8(13.6)	17(11.1)	25(11.8)
Co-trimoxazole started	Yes	28(47.5)	74(48.4)	102(48.1)
	No	31(52.5)	79(51.6)	110(51.9)
Fluconazole started	Yes	3(5.1)	22(14.4)	25(11.8)
	No	56(94.9)	131(85.6)	187(88.2)
Viral load when switched to second line ART (copes/ml)	<150	18(30.5)	104(68)	122(57.5)
	150 – 999.999	11(18.6)	8(5.2)	19(9)
	≥1000	30(50.8)	41(26.8)	71(33.5)
WHO HIV clinical stage	stage I	49(83.1)	151(98.7)	200(94.3)
	stage II	1(1.7)	1(0.7)	2(0.9)
	stage III	9(15.3)	1(0.7)	10(4.7)
Duration in first line ART /in years/	<2 years	6(10.2)	26(17)	32(15.1)
	2 -5 years	16(27.1)	58(37.9)	74(34.9)
	5.01 – 10 years	30(50.8)	60(39.2)	90(42.5)
	> 10 years	7(11.9)	9(5.9)	16(7.5)

6.3 Factors associated to second line ART virological failure

In bi-variable logistic regression from a total of 36 variables the following: Not using condom, Non-disclosure about HIV status, poor Level of Adherence, severely malnutrition nutritional status and Viral load ≥1000 copes/ml when switched to second line ART were significantly associated with second line virological ART failure (P-value<0.25). These factors were also selected for further multivariable binary logistic regression analysis (Table 7).

Table 7: Factors related to second line ART Virological failure among HIV Patients at FHCSH and UGCSH; Amhara Region, North West Ethiopia from September first 2021 to December last 2021.

General variables	Variables category	Virological failure		COR (95% CL)	AOR (95% CL)
		Yes	No		
Using condom	Yes	6	59	1	
	No	53	94	5.54 (2.3 - 13.7)****	4.5(1.63 – 12)***
Disclosure status	Disclosed	13	87	1	
	Not disclosed	46	66	4.6(2.33 – 9.34)****	3.4(1.5 – 7.8)***
Level of Adherence	Good	13	91	1	
	Medium (faire)	13	23	3.95(1.6 - 9.7)***	3.7(1.3 - 10.7)*
	Poor	33	39	5.9(2.8 – 12.4)****	5.3(2.2 – 12.5)****
Nutritional status	Normal	33	104	1	
	Moderately malnourished	10	25	1.26(0.55 – 2.9)	1.2(0.4 – 3)
	Severely malnourished	8	7	3.6(1.2 – 10.7)*	3.56(1 – 14.4)
	Over weight	8	17	1.48(0.59 – 3.8)*	1.6 (0.4 – 5)
Viral load when switched to second line ART (copes/ml)	<150	18	104	1	
	150 – 999.9	11	8	7.9(2.8 – 22)****	5.4(1.5 – 19)**
	≥1000	30	41	4.2(2.13 – 8.4)****	3.56(1.5 - 8)***

Note; P value < 0.05 = *, P value < 0.01 = **, P value < 0.005 = ***, P value < 0.001 = ****

In the multivariable binary logistic regression analysis; Not using condom, non-disclosure about HIV status, poor level of adherence and viral load ≥1000 copes/ml when switched to second line ART had a significant impact on second line ART outcomes. Peoples who did not disclosed their HIV status were 3 times (AOR=3.4, 95% CI: 1.52 – 7.79) more likely to develop second line ART virological failure as compared to those patients who disclosed their HIV status. Among the respondents those patients who had poor level of adherence were 5 times (AOR= 5.27, 95% CI=2.2 – 12.5) more likely to develop second line ART virological failure as compared to those who had a good adherence (Table 7).

Moreover, the likely hood of developing second line virologic failure among patients with Viral load ≥1000 copes/ml when switched to second line ART medication were 3.5 times (AOR=3.56, 95% CI: 1.5 - 8) more likely as compared to those patients who had Viral load result <1000 copes/ml (Table 7).

6.4 Discussion

This study was aimed to assess the predictors of virological failure among second-line ART users. Poor adherence to ART, non-disclosure of HIV status, not using condom and having Viral load ≥1000 copes/ml when switched to second line ART were the factors which increased the odds of second line ART virological failure.

Patients who had poor ART adherence were 5 times more likely to develop second line ART virological failure as compared to patients who had good treatment adherence. Similar findings was reported in Wollo, Amhara Regional State Northeast Ethiopia (50) and Northern Ethiopia (25) where the odds of developing second line ART virologic failure was strongly associated with poor ART adherence. This finding is supported by a study conducted in Johannesburg, South Africa (26), Southwestern Nigeria (47), sub-Saharan Africa (44) and Asia (42) which showed that poor adherence was a strong predictor of second-line ART failure. Another investigation done in Cambodia (Southeast Asian) also confirmed that, patients on second line ART with good adherence were significantly associated with viral suppression (43).

ART adherence is generally regarded as an important factor in achieving optimal treatment outcomes. High levels of treatment adherence to ART results to effective viral suppression outcomes. Poor adherence to ART is the most frequent cause of treatment failure and the subsequent development of drug resistant strains of HIV. If the patients do not always take their

meds on schedule as prescribed the virus will replicate and develop new resistance mutations over time. Missing doses can lead to low drug levels in the body, which allows the virus to resume replication and accumulate resistance mutations as it multiplies. This results less effective viral suppression and a rise in plasma viral load. Inadequate suppression of viral replication has a continued destruction of CD4 cells, progressive decline in immune function and disease progression, Limited future treatment options and higher costs to the individual and ARV program. Even though these risks the immediate health of the patient, it is also an important reason for the emergence of viral resistance to one or more antiretroviral medications (61–63).

The study found that, not using condom was one of the factor for second line ART virological failure. Patients who didn't used condom were 4 times more likely to develop ART failure than those who used.

Inconsistent use of a condom by people living with HIV/AIDS on ART has led to further risk of new HIV infection and the development of reinfection with new drug-resistant viral strains. Using condom prevents from acquiring and transmitting drug resistant HIV infection. Patients on ART may also acquire transmitted drug resistant HIV virus if they do not use condoms. This type of HIV infection results treatment failure among ARV drug–naive people with no history of ARV drug exposure (34,64). Not using Condom also exposed for many sexually transmitted infections (STIs) that leads to further worsening the HIV infection by dipping the immune system. So that ART may not be effective and new drug resistant viral strains may occurred (65).

The study also identified that patients who had a high viral load ($\geq$1000 copes/ml) when switched to second line ART were 3.5 times more likely to develop second line ART virological failure than those patients who had suppressed viral load (<1000 copes/ml). This outcome is supported by a studies conducted in Sub-Saharan Africa (26) and Johannesburg, South Africa (44) in which they presented that high viral load was a significant predictor for second line ART virological failure.

Different literature stated that a high viral load can lead to a low CD4 cell count which in turn increases the risk of developing an illness or infection. Circulating high viral particles in blood results high destruction of the immune system (CD4 cell) which in turn aggravates disease progression. Finally it will lead to the emergence of resistant viral strains. This indicates the treatment is not working well. The higher the viral load, the more risk developing treatment failure (66).

In addition, our investigation identified that the odds of developing second line virological ART failure was increased by 3 folds for patients who did not disclosed their HIV status as compared to their counter parts.

Previous studies conducted in Wollo, Amhara Regional State, Northeast Ethiopia and Johannesburg, South Africa also reported that not disclosing HIV status was the main risk factors for virological ART failure (50,67).

Different scholars had agreed that disclosure play a significant roles in good ART outcomes (68). It is regarded as a double-edged sword in terms of ART adherence and patient retention in care. People who achieved full disclosure about their HIV status had lower viral load (improved viral suppression), increased ART adherence and allowed for better self-care and treatment. Patients who disclosed about their HIV status have good adherence to ART compared with those who did not. Studies have found that patients who disclosed their sero-status had better social support; stronger family and relationship cohesion; reductions in anxiety and depression; improvements in physical health, emotional support, and financial support; and were better able to take their ART freely. These helps to improve their ART adherence and having lower risk of developing ART failure. Patients who did not disclosed their HIV status were at high risk of developing Virological failure.(69–71).

6.5 conclusions and recommendations

6.5.1 Conclusions

The study identified that poor adherence to ART medication, not disclosed about HIV status, not using condom and high viral load ≥1000 copes/ml were significantly associated with second line ART virological failure.

6.5.1 Recommendations

For Patients;

Patients on ART should not miss their medication for any reasons and use their full efforts in order to have good ART adherence. Disclosing their HIV status and using condom will have an incredible benefit in terms of social supports and to get early ART treatment.

For Healthcare Providers;

Early identification of patients who had poor adherence, non- disclosed and high viral load will be an important task to reduce ART failure.

Such patients will need closer clinical follow-up in order to minimize the risk of treatment failure.

For Researchers;

Further investigation is needed to explore factors associated with poor adherence and not disclosing HIV status.

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ANNEXES

Annex I. Information sheet and consent form

Deep greetings, my name is …….

I temporarily represent Bahir Dar University, College of Medicine and Health Science, School of Public health

Department of Health System Management and Health Economics. Here the mission justified below why I am here.

Title of the research project: Magnitude and predictors of virological treatment failure of second line ART among on ART patients at Felege Hiwot specialized Referal hospital Bahir Dar, North West Ethiopia.

Name of Investigator: Getahun Ayenew Wobetu

Name of the Organizations: Bahir Dar University

Purpose of the study: To determine the magnitude of virological ART failure and to describe its associated factors among ART patients who are on secondline ART regime at Felege Hiwot specialized Referal hospital. The study will provide base line information for concerned bodies and for further research.

Procedure: To perform this study, you are being one of the invited persons as you are fulfilled the criteria. If you are willing to participate, you need to understand the purpose of the study and give your consent. Socio-demographic and socio-economic information will be collected from the study participants using structured questionnaires by face to face interview. You are kindly asked to genuinely answer the prepared questionnaires. The other required clinical pattern will be collected from the registry using a data collection format.

Potential risk factors: the study has no any risk for both the participants the community. During sample collection there will not cause any illness or injury.

Benefits of the study: this study will give some clues about the factors that contributes for virological ART failure and to work against.

Compensation for participation: You will not receive any payment for your participation in this study.

Confidentiality of your information- All information gathered from the study participant will remain confidential. If you do not need the result, your participation in this study can be anonymous. Personal information will be treated confidentially and under no circumstances will it be transmitted to any person or organization.

Right to Refusal or Withdraw: participating in this study is absolutely depend on your willingness. You have a full right to refuse from participation as well as to cancel after you start at any course of the study. You can refuse to respond any or all the questionnaires and this will not affect the service you get from.

Person to Contacts: If you want to know more information about this study, you can contact the following organization and individuals at any time.

Organization - Bahir Dar University, Department of Department of Health System Management and Health Economics.

P.Box 79, Bahir Dar, Ethiopia

Individuals - Getahun Ayenew Wobetu

Phone no. - 0918512275

E-mail - Getahun.ayenew@yahoo.coom

Final participant decision: - Agree to participate ☐

Not Agree to participate/refuse/ ☐

Annex II Consent form

Name of health institution----------Code of the Participant --------- Date-------

I the undersigned study participant have been well informed about the objective of the study entitled on Magnitude and predictors of virological treatment failure of second line ART among on ART patients at Felege Hiwot specialized Referal hospital Bahir Dar, North West Ethiopia. And I am clear on this.

I clearly know that, all the information obtained at any course of the study will be kept confidential. I also well informed of my right to keep hold of, decline to cooperate and drop out of the study if I don't want and none of my actions will have any bearing at all on the service I get.

I agreed voluntarily to answer the provided questionnaires.

Name and signature of study participant ……Date…….

Name and signature of investigator /data collector/ ……..……Date…….

Annex III Data collection tools

Questionnaires:

Name of data collector ……

Participant code …….. Date ……

I. Participant socio demographic characteristics		
S.no	Questions (Variables)	Answers
1	Sex	1. Male 2. Female
2	Age (in years)	…..
3	Residence	1. Urban 2. Rural
4	Weight	…...
5	Body Mass Index (BMI) (kg/m^2)	…….
6	Educational status	1. Has no any educational level/ illiterate 2. Elementary level 3. High school level 4. Preparatory level 5. College level 6. University level or above
7	Marital status	1. Single 2. Married 3. Divorced 4. Widowed
8	Job	1. House wife 2. Merchant 3. Government worker 4. Student 5. Sex worker 6. Private employee 7. Daily laborer 8. Mention if any……...
9	Family income (birr/month)	……
10	Duration in first line ART /in years/	
11	Duration in second line ART /in years/	

II. Participant behavioral characteristics		
12	Did you drink alcohol?	1. Yes 2. No
13	Adherence level	1. Good 2. Medium 3. Poor
14	Do you have one fixed sexual partner? /if not married/	1. Yes 2. No
15	Do you use condom?	1. Yes 2. No
16	If yes for Ques.No13, how often?	1. Always 2. Sometimes
17	Do you had disclosed yourself for others regarding taking ART?	1. Yes 2. No
18	Do you practice drug abuse?	1. Yes 2. No
19	Do you smoke cigarettes?	1. Yes 2. No
20	If yes for Que. No 17, how many pieces /day?	…..
III. Clinical and immunological characteristics		
21	CD4 count at time when switched to second line ART regime	……..
22	Nutritional status	1. Normal 2. Moderately malnourished 3. Severely malnourished
23	Pregnancy status /for women/	1. Yes 2. No
24	Co-trimoxazole started	1. Yes 2. No
25	Fluconazole started	1. Yes 2. No
26	Having STI	1. Yes 2. No
27	Chronic disease other than TB	Mention it …
28	Viral load result when switched to second line ART regime	…….
29	Presence of opportunistic infections (OI) during taking second line ART	1. Yes 2. No
30	If yes for que. No 21 above, what	

	type of OI there were?	.....	
31	WHO HIV clinical stage at the time switched to second line ART regime	1. Stage one 3. Stage three	2. Stage two 4. Stage four
32	Presence of TB coinfection	1. Yes	2. No
33	Presence of Anemia	1. Yes	2. No
IV. Program / service related characteristics			
34	Consistent availability of ART drugs	1. Yes	2. No
V. Drug related characteristics			
35	Type of first line ART drug used	……	
36	Type of second line ART drug used (based on WHO 2016 treatment guideline)	…..	