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Prevalence of Virologic Failure and Determinants Among Adults on First-Line Antiretroviral Therapy at Debre Tabor Comprehensive Specialized Hospital in Northwest Ethiopia

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Abstract: *Introduction:* Even though first-line antiretroviral therapy (ART) has led to a profound reduction in the incidence of opportunistic infections (OIs) and AIDS related deaths, it is challenged by virologic failure, which predisposes patients to a new or recurrent clinical condition and, as a result, affects their quality of life and increases HIV-associated mortality. Therefore, understanding the burden of virologic failure and its determinants helps with early prevention and improvement of the quality of life. However, the prevalence of virologic failure and its associated factors among adult patients on first-line ART at Debre Tabor Comprehensive Specialized Hospital is not well understood. *Objective:* This study was aimed at determining the prevalence of virologic failure and identifying its contributing factors among HIV-positive adults receiving first-line ART at Debre Tabor Comprehensive Specialized Hospital in Northwest Ethiopia. *Methods:* An institutional-based cross-sectional study was conducted on 376 adults who had started ART from February 8, 2017, to February 7, 2022. After selecting a computer-generated simple random sampling technique, data on patients' socio-demographic, behavioral, clinical, and ART-related factors were collected through a review of medical charts. A binary logistic regression model was used to identify associated factors with virologic failure, and an AOR with a 95% CI at P less than or equal to 0.05 was used to declare the association. *Results:* The prevalence of virologic failure was 13.6% (95% CI: 10.4%- 17.2%). Significant associated factors for virological failure were smoking cigarettes (AOR 4.76, 95% CI: 1.06-21.38), HIV non-disclosure (AOR 4.56, 95% CI: 1.6-2.46), presence of stigma and discrimination (AOR 2.91, 95% CI: 1.14-7.39), having baseline OIs (AOR 6.66, 95% CI: 1.94-22.90), not taking CPT (AOR 3.21, 95% CI: 1.12-9.18), treatment interruption (AOR 2.97, 95% CI: 1.11-7.94), loss to follow-up (AOR 9.03, 95% CI: 3.08-26.47), fair or poor adherence status for ART (AOR 3.409, 95% CI: 1.26-9.24). *Conclusion and recommendation:* The prevalence of virologic failure was in line with the national prevalence. Smoking cigarettes, HIV non-disclosure, baseline OIs, suboptimal adherence, loss to follow-up, treatment interruption, not taking CPT, and taking additional medication were significantly associated with virological failure. Therefore, special attention should be given to those individuals who have the above factors to minimize and prevent virologic failure.

Keywords: Prevalence, First-Line Antiretroviral Therapy, Virological Failure, Adults, Northwest Ethiopia

1. Introduction

At the end of 2021, the human immunodeficiency virus (HIV) was still a major global public health problem, with an estimated 38.4 million people living with HIV (PLHIV) worldwide [1], with more than two-thirds (25.4 million) in

the WHO African Region [2], and 20.6 million in eastern and southern Africa [1]. HIV is a viral infection that has no cure and targets cells of the immune system and replicates, damages, and destroys the cells [1]. However, the effective use of highly active antiretroviral treatment (HAART) achieves long-term durable suppression of HIV replication, which gives immunologic and clinical benefits and, in turn, leads to a reduction in HIV-associated morbidity and mortality, ultimately improving the quality of life and minimizing the risk of HIV transmission through heterosexual relationships [2]. However, the effective goals of first-line HAART are affected by drug resistance and treatment failure, which are major bottlenecks for effective viral suppression in resource-limited countries like Ethiopia [3].

Antiretroviral treatment failure continues to be a major global public health issue. Of the total PLHI, more than 46% failed for first-line drugs [4]. According to the World Health Organization (WHO) recommendation, viral load is the preferred monitoring approach to diagnose and confirm treatment failure [5, 6]. Viral load monitoring was affected by the COVID 19 pandemic mainly because laboratory skilled staff members were shifted from molecular testing for HIV to testing for SARS-CoV-2, using the same equipment for SARS-CoV-2 and HIV viral load testing and treatment follow-up restriction [7]. Virological failure is the overgrowing levels of detectable HIV, which is associated with multiple nucleoside or nucleotide resistance mutations [8]. Of the three 90 targets by the UNAIDS for 2020 goals, only an estimated, 28.7 million (75%) PLHIV had accessed ART and only 68% were being virally suppressed, globally at the end of 2021 [9] and drug resistance and subsequent ART failure [10] could be one of the factors for under-achievement of the third "90%" (viral suppression) [11]. Several developments have occurred for HIV globally since 2016; these include the introduction of a treat all strategy, the introduction of a new drug (dolutegravir), self-testing, scaling up of viral load, infant testing, and new options for TB preventive therapy (TPT) and post-exposure prophylaxis [5, 12]. However, antiretroviral therapy failure has been recognized as a persistent challenge in the world.

Despite the improved utilization of ART, the issue of drug resistance and subsequent treatment failure is a continuous and challenging public health problem in middle-income and low-income countries [13–15]. The Sub-Saharan region has the world's highest HIV prevalence, with 60% of new infections [16] that is being challenged by high ART drug resistance and treatment failure [17]. The prevalence of tenofovir resistance was highest (57%); 83% had cytosine analog resistance; 78% had major NNRTI resistance; and 65% had both [4]. The identification of drug resistance and management of first-line ART failure is a key challenge for HIV programs in resource-limited settings like Ethiopia.

In Ethiopia, even though the country has a high scale-up of ART coverage currently, the three 90 goals were not achieved and it was mainly affected by the COVID-19 pandemic and major conflict across the country [18]. This was mainly because of a limited number of viral load machines for monitoring in the country. Amhara regional state contributed 30% of the national PLHIV at the end of 2020 [18] that was challenged by viral load monitoring and patient retention in care due to the COVID-19 pandemic and the current neighborhood conflict which, could impact patient adherence and facilitate treatment failure.

Patients who developed first-line antiretroviral treatment had many health and health-related complications. Patients who had failed for first-line ART were 46% more likely to fail again for the second-line drugs, which are attributed to the higher number of side effects and have a greater likelihood of experiencing drug resistance and treatment fatigue as a result of being on treatment longer [19, 20]. Staying on a failing first-line therapy is associated with an increased risk of developing HIV/AIDS-related morbidity and mortality. Delayed detection of treatment failure may increase drug toxicity and the accumulation of drug resistance-associated mutations and may result in increased HIV-associated morbidity and mortality [21].

According to previous studies, age groups, being divorced, having no formal education and primary education, low baseline CD4 count, prolonged ART usage, having drug toxicities, poor adherence, recent CD4 count of less than 200 cells/mm3, presence of OIs, and ART discontinuation were associated with virological ART failure.

An early understanding of the burden and determinants of virologic failure helps for prevention and control as well as for an early switch to second-line ART. Anti-retroviral treatment failure can be prevented through the implementation of globally recommended strategies including improving ART adherence, taking medication based on the appropriate prescription, preventing drug-drug interactions, increasing knowledge and attitudes of patients towards HAART, timely initiation of ART, prevention and control of opportunistic infections, and implementation of effective food and nutrition policies [19, 22, 23]. The joint United Nations Program on HIV/AIDS has set the three 95 (95-95-95) targets to control HIV infection by 2030. However, antiretroviral drug resistance and virological failure are the main problems in achieving viral suppression.

Therefore, understanding the burden and the mechanism of virologic failure helps with health care planning and prevention as well as supports achieving the third 95 target. Despite improved ART coverage in Debre Tabor Comprehensive Specialized Hospital, ART failure has not been studied after the introduction of the treat all strategy and DTG as well as after the COVID-19 pandemic. Therefore, this study was intended to determine the prevalence of virologic failure and its associated factors among HIV-infected adults on first-line ART at Debre Tabor Comprehensive Specialized Hospital in Northwest Ethiopia from February 8, 2017 to February 7, 2022.

2. Methods and Materials

2.1. Study Setting

This study was conducted at Debre Tabor Comprehensive Specialized Hospital, Northwest Ethiopia. The hospital is located in Debre Tabor town, which is the capital of South Gondar Zone, in the Amhara regional state, about 100 kilometers from Bahir Dar and 666 kilometers from Addis Ababa, Ethiopia. It is also located at 11°51′N 38°1′E, with an elevation of 2,706 meters above sea level.

The hospital serves both outpatient and inpatient services to more than five million people. In the hospital, the ART Clinic was established in 2005, and since then, a total of 2,430 HIV-infected clients have started ART. Currently, there are 2,149 active patients on ART. Of the total, there were about 1,127 total HIV-infected adults enrolled for ART between February 2017 and February 2022 in the clinic.

2.2. Study Design and Period

An institutional based cross-sectional study was conducted to determine virological failure and its associated factors among adult HIV patients on first-line ART at Debre Tabor Compressive Specialized Hospital in Northwest Ethiopia between February 8, 2017 and February 7, 2022.

2.3. Population

The source population for this study were all HIV positive adults aged 18 years and above who were living in the South Gondar zone, Northwest Ethiopia between February 8, 2017 and February 7, 2022, while all adult HIV-positive patients whose age was 18 years or more at the time of ART initiation and who had started ART between February 8, 2017 and February 7, 2022 in the hospital and who had been taking ART for more than 6 months in the facilities were the study population.

2.4. Eligibility Criteria

All records of adult HIV-positive patients whose age was 18 years or older at the time of ART initiation and who had started ART in the hospital and had been taking ART for more than 6 months in the facilities were included in this study, whereas death, TO, LTFU, and incomplete charts with a major variable (viral load) were excluded from this study.

2.5. Sample Size Determination

The sample size was determined by using a single population proportion formula based on the following assumptions: the proportion (P) (33.42%) from the previous study [24], 95% CI, and margin of error (d) (5%). Therefore, the sample size calculated was 342 by using single population proportion formula, and after adding 10% for incomplete charts, the total sample size was 376.

Sample Size for Associated Factors Was Considered and It Was Described as Follow:

Table 1. *Sample size calculation for second objectives (factors).*

Sr.No.	Variables selected	Parameters	Sample size	After adding 10%
1	Duration of ART ≤ 6 years (2)	Two-sided 95% CI Power=80% %Outcome in exposed group=38.3% %Outcome in unexposed group=61.7%	160	176
2	No formal education (2)	Two-sided 95% CI Power=80% Ratio (unexposed: exposed) = 0.36 %Outcome in unexposed group=7% OR=3.65 %Outcome in unexposed group=61.7%	280	308
3	Initial ART regimen: TDF + 3TC + EFV (2)	Two-sided 95% CI Power=80% Ratio (unexposed: exposed) = 0.7 %Outcome in unexposed group=30% Odds ratio=0.05	66	72

2.6. Sampling Techniques

About 1,127 HIV-infected adults aged 18 years and above on first-line ART were enrolled between February 8, 2017 and February 7, 2022 in Debre Tabor Comprehensive Specialized Hospital Northwest Ethiopia. Those participants who had taken first-line ART for less than 6 months were not part of this study. First, we exclude TO, loss to follow-up, and death from study population. Then, among 1076 eligible participants, we used computer-generated SRS to select a sample size of 376. Of these, 2 medical charts were excluded due to incomplete data (absence of viral load measurement). Therefore, 374 study participants were included in this analysis (Figure 1).

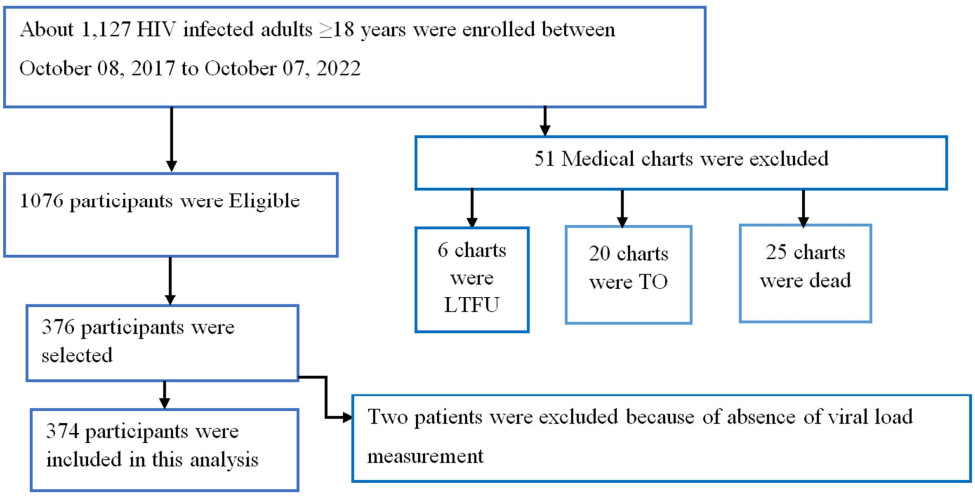

Figure 1. *Flow chart showing a selection of HIV infected adults aged ≥ 18 years on the first line ART in Debre tabor comprehensive specialized hospital between October 08, 2017 and October 07, 2022.*

2.7. Study Variables

The dependent variable is first-line antiretroviral therapy virologic-failure. Virological failure is defined as a viral load greater than 1000 copies/mL based on two consecutive viral load measurements taken three months apart, with enhanced adherence support following the first viral load test, as documented by the health provider [6]. Independent variables are described as follows: *Sociodemographic factors* (age, sex, educational status, marital status, occupation, residence, distance from health facility, religion); *personal factors* (smoking, alcohol abuse, stigma and discrimination, HIV disclosure status, absence of treatment supporter, and having unsafe sex during ART); *clinical factors* (nutritional status, baseline WHO stage, current WHO stage, TB/HIV co-infection. mental illness, initial viral load, baseline CD4 count, baseline functional status, comorbidity, base line OIs, and OIs in the past 6 months); *factors related to ART* (adherence status, loss to follow-up, TB preventive therapy, Baseline ART regimen, cotrimoxazole preventive therapy, duration of ART taken, taking other medications, ART interruption). *Loss to follow-up (LTFU)* is defined as a patient who has not been seen at the clinic for at least 90 days (three months) after the last missed appointment, but not TO or dead" [6].

2.8. Data Collection Technique and Instruments

Four trained BSc professional nurses working in an ART clinic collected socio-demographic, personal characteristics, clinical, and ART-related factors by reviewing the patient's medical charts and database. Data collection tools or checklists were adapted from the WHO standard and/or EFMOH ART intake-form.

2.9. Data Quality Control

Two days of training were given for data collectors and a supervisor to maintain data quality. A pretest was done before data collection. Each item of data was checked for its completeness by the principal investigator and a supervisor during the data collection period every day.

2.10. Data Management and Analysis

Data were entered into Epi-Info 7 and exported to SPSS version 22 for cleaning, recoding, and analysis.

Both descriptive and analytic methods were used for data analysis. The median value with interquartile range for continuous variables and frequencies with percentages for participant categorical variables were summarized and described using text and tables in the descriptive analysis.

Binary logistic regression was used to identify associated factors with virologic factors. A bivariable analysis was carried out for all independent variables with an outcome variable, and variables with a P-value less than 0.2 were entered into a multivariable logistic regression model to identify the independent determinants of treatment failure. We used a backward stepwise method to enter variables for multivariable analysis. Overall model fitness was done by using the Hosmer and Lemeshow goodness of fit test, and a non-significant test result indicated a good model for the study. Finally, the adjusted odds ratio and 95% CI were determined, and variables with a P-value less than 0.05 were reported as significant for virological failure.

3. Results

3.1. Socio-Demographic and Personal/Behavioral Characteristics

Of a total sample size of 376, 374 study participants were included in the analysis. The participants' median age was 37 years (IQR: 30-45). More than half, 216 (58%), of the study participants were females. The majority of them, 270 (72%), came from urban areas. Of the total participants, 344 (92%) were orthodox Christians. More than half, 228 (61%), were married. One hundred thirty-eight (37%) were either government or NGO employees. More than half, 192 (51%), of the participants disclosed their HIV status to others, and

half of them, 188 (50%), had treatment supporters. Eighteen percent, 69 (18%), of study participants had a history of unsafe sex after ART initiation (Table 2).

Table 2. *Baseline socio-demographic and personal/behavioral characteristics of adult HIV patients on first-line ART in Debre tabor comprehensive specialized hospital, Northwest Ethiopia from February 2017 to February 2022 (N = 374).*

Variables	Categories	Frequency (n)	Percent (%)
Age in years	18-24	39	10.4
	25-34	119	31.8
	35-44	122	32.6
	≥45	94	25.1
Sex	Male	158	42.2
	Female	216	57.8
Religion	Orthodox	344	92.0
	Muslim	18	4.8
	Others	12	3.2
place of residence	Urban	270	72.2
	Rural	104	27.8
Marital status	Married	228	61.0
	never married	30	8.0
	Divorced	61	16.3
	widowed/separated	55	14.7
Educational status	not formally educated	110	29.4
	Primary	127	34.0
	Secondary	74	19.8
	college and higher	63	16.8
Occupation status	Government/NGO employee	138	36.9
	Farmer	40	10.7
	house wife	90	24.1
	Daily laborer	73	19.5
	Jobless	33	8.8
Cigarette Smoking status	Yes	26	7.0
	No	348	93.0
Alcohol dependence	Yes	49	13.1
	No	325	86.9
History of unsafe sex after ART initiated	Yes	69	18.4
	No	305	81.6
HIV disclosure status	Yes	192	51.3
	No	182	48.7
Presence of treatment supporter	Yes	188	50.3
	No	186	49.7
Presence of stigma and discrimination	Yes	83	22.2
	No	291	77.8
Distance from the hospital (Kms)	≤ 5	219	58.6
	> 5	155	41.4

3.2. Clinical and Antiretroviral Medication-Related Characteristics

The participants' median weight was 56 kg (IQR: 50-60) and most of them, 323 (86%), had a 18.5 or above BMI. The majority of participants, 83 (78%), had baseline ambulatory functional status. More than half, 194 (52%), had baseline opportunistic infections and the majority, 315 (84%), were in baseline WHO clinical stage I and II. The median baseline CD4 count was 230.50 cells/ul (IQR: 119.00- 387.25). Eighty-six (23%) had TB/HIV coinfection after ART. The median initial viral load was 414.00 copies/ml (IQR: 89.00-1234.00).

The majority, 314 (84%), had good adherence status for ART and the median duration of ART was 36 months (IQR: 25- 51.00). Fort-two (11%) had a history of loss to follow-up in the past. The majority of the participants, 347 (92%), took TPT (Table 3).

Table 3. *Clinical and antiretroviral medication-related factors among HIV infected adults on first-line ART in Debre tabor comprehensive specialized hospital between February 2017 and February 2022.*

Variables	Categories	Frequency (n)	Percent (%)
baseline functional status	Working	291	77.8
	ambulatory or bedridden	83	22.2
Baseline nutritional status	Under nutrition	51	13.6
	Normal/over weight	323	86.4
Presence of comorbidity	Yes	59	15.8
	No	315	84.2

Variables	Categories	Frequency (n)	Percent (%)
Baseline opportunistic infections	Yes	194	51.9
	No	180	48.1
opportunistic infections in the past six months after ART	Yes	86	23.0
	No	288	77.0
Baseline WHO stage category	WHO stage I & II	315	84.2
	WHO stage III & IV	59	15.8
TB/HIV coinfection	Yes	86	23.0
	No	288	77.0
Mental illness	Yes	28	7.5
	No	346	92.5
Base line CD4 count (cells/ml)	<200	153	40.9
	200-350	112	29.9
	351-500	61	16.3
	>500	48	12.8
Initial viral load status	<=1000 copies/ml	261	69.8
	>1000 copies/ml	113	30.2
ART adherence status	Good	313	83.7
	fair/poor	61	16.3
History of ART interruption in the past	Yes	72	19.3
	No	302	80.7
Loss to follow up status in the past	Yes	42	11.2
	No	332	88.8
Duration of ART in months	6-11	27	7.2
	12-23	55	14.7
	24-35	98	26.2
	36-48	74	19.8
	>48	120	32.1
Drugs taking now other than ART	Yes	51	13.6
	No	323	86.4
Cotrimoxazole preventive therapy (CPT)	Yes	211	56.4
	No	163	43.6
Tuberculosis preventive therapy (TPT)	Yes	347	92.8
	No	27	7.2

3.3. The Prevalence of Virological Failure and Its Associated Factors

This study showed that the prevalence of virological failure was found to be 13.6% (95% CI: 10.4% -17.2%). The overall model goodness of fit test was done with the Hosmer and Lemeshow Test and it was reported to be a good model with a chi-square significance level of 0.518. Logistic regression assumptions of multicollinearity and outliers were checked.

In the bi-variable logistic regression, independent variables with a "P-value" of less than 0.2 were candidates for multivariable logistic regression analysis to identify the effect of confounding.

In multivariable logistic regression analysis, we used a stepwise backward selection procedure to identify associated factors at a "P-value" less than 0.05 with AORs and 95% CIs to obtain the association with virologic failure. Cigarette smokers were 4.76 times more likely than nonsmokers to develop virological failure (AOR 4.76, 95% CI: 1.06-21.38). In this study, those HIV patients who did not disclose their HIV status to somebody who may have supported them were 4.56 times higher to develop virological failure compared with those who disclosed their status (AOR, 4.56; 95% CI: 1.67-12.46). According to our study, those study participants with a history of having stigma and discrimination after ART initiation were 2.91 times more likely to develop treatment failure (AOR, 2.91; 95% CI: 1.14-7.39) (Table 4).

Participants who had a history of baseline opportunistic infection were 6.66 times more likely to develop subsequent virologic treatment failure (AOR, 6.66; 95% CI: 1.94- 22.90). Similarly, those study subjects who did not take cotrimoxazole preventive therapy with ART were 3.21 times more likely to develop antiretroviral treatment failure (AOR, 3.21; 95% CI: 1.12-9.18). Those HIV clients having a history of treatment interruption for ART were 2.97 times higher for the development of virologic treatment failure compared with those consistently taking their medication (AOR, 2.97; 95% CI: 1.11-7.94). Similarly, participants with one or more episode of loss to follow-up for their antiretroviral medication were 9 times more likely to have virologic failure compared with their counter-parts (AOR, 9.03; 95% CI: 3.08-26.47). The odds of developing treatment failure among the study participants with either fair or poor adherence status to their antiretroviral medication were 3.41 times higher than those with good adherence status (AOR, 3.409; 95% CI: 1.26-9.24). The likelihood of developing antiretroviral treatment failure among HIV patients taking additional medication other than ART was 3.64 times higher compared with their counter parts (AOR, 3.64; 95% CI: 1.33- 9.97) (Table 5).

Table 4. *Sociodemographic and personal factors associated with first-line ART virologic failure among HIV infected adults on ART at Debre tabor comprehensive specialized hospital, Northwest Ethiopia between February 2017 and February 2022.*

Variables	Categories	Virologic failure, n (%)		OR (95% CI)	
		No	Yes	COR (95% CI)	AOR (95% CI)
Sex	Male	127 (39.3%)	31 (60.8%)	2.39 (1.31-4.38)	0.91 (0.319-2.57)
	Female	196 (60.7%)	20 (39.2%)	1.00	1.00
Marital status	Married	207 (64.1%)	21 (41.2%)	1.00	1.00
	never married	21 (6.5%)	9 (17.6%)	4.22 (1.72 - 10.40)	3.25 (0.57-18.37)
	Divorced	51 (15.8%)	10 (19.6%)	1.93 (0.86 - 4.36)	1.45 (0.39-5.41)
	widowed/separated	44 (13.6%)	11 (21.6%)	2.46 (1.11 - 5.48)	1.45 (0.32-6.60)
Occupation status	Government/NGO employee	123 (38.1%)	15 (29.4%)	1.00	1.00
	Farmer	32 (9.9%)	8 (15.7%)	2.05 (0.80 - 5.26)	1.22 (0.20-7.57)
	house wife	82 (25.4%)	8 (15.7%)	0.80 (0.32 - 1.97)	1.72 (0.28-10.65)
	Daily laborer	57 (17.6%)	16 (31.4%)	2.30 (1.06 - 4.98)	1.72 (0.41-7.17)
	Jobless	29 (9.0%)	4 (7.8%)	1.13 (0.35 - 3.66)	0.81 (0.08-8.30)
Distance from the hospital	≤ 5 Kms	203 (62.8%)	16 (31.4%)	1.00	1.00
	> 5 Kms	120 (37.2%)	35 (68.6%)	3.70 (1.97-6.97)	1.54 (0.59-5.20)
Cigarette Smoking status	Yes	14 (4.3%)	12 (23.5%)	6.79 (2.93 -15.73)	4.76 (1.06 - 21.38) *
	No	309 (95.7%)	39 (76.5%)	1.00	1.00
Alcohol abuse	Yes	30 (9.3%)	19 (37.3%)	5.80 (2.94 - 11.46)	0.82 (0.17-4.07)
	No	293 (90.7%)	32 (62.7%)	1.00	1.00
History of unsafe sex after ART initiated	Yes	43 (13.3%)	26 (51.0%)	6.77 (3.59 - 12.79)	1.67 (0.53-5.23)
	No	280 (86.7%)	25 (49.0%)	1.00	1.00
HIV disclosure status	Disclosed	182 (56.3%)	10 (19.6%)	1.00	1.00
	Not disclosed	141 (43.7%)	41 (80.4%)	5.29 (2.56 - 10.93)	4.56 (1.67 - 12.46) **
Absence of treatment supporter	Yes	148 (45.8%)	40 (78.4%)	4.30 (2.13 - 8.68)	1.17 (0.35-3.88)
	No	175 (54.2%)	11 (21.6%)	1.00	1.00
Presence of stigma and discrimination	Yes	55 (17.0%)	28 (54.9%)	5.93 (3.18 - 11.06)	2.91 (1.14 - 7.39) *
	No	268 (83.0%)	23 (45.1%)	1.00	1.00

Keys: 1. *** = "P-value" < 0.001 2 ** = "P-value" < 0.01 3. * = "P-value" < 0.05

Table 5. *Clinical and antiretroviral medication-related factors associated with first-line ART virologic failure among HIV infected adults on first-line ART in Debre tabor comprehensive specialized hospital between February 2017 and February 2022.*

Variables	Categories	Virologic failure, n (%)		OR (95% CI)	
		Yes	Yes	Crude OR (95% CI)	Adjusted OR (95% CI)
baseline functional status	Working	270 (83.6%)	21 (41.2%)	1.00	1.00
	Ambulatory/ bedridden	53 (16.4%)	30 (58.8%)	7.28 (3.87 - 13.67)	2.16 (0.85-5.50)
Baseline nutritional status	Under nutrition	39 (12.1%)	12 (23.5%)	2.24 (1.08-4.64)	1.13 (0.27-4.79)
	Normal/over weight	284 (87.9%)	39 (76.5%)	1.00	1.00
Presence of comorbidity	Yes	35 (10.8%)	24 (47.1%)	7.31 (3.81 - 14.04)	0.53 (0.11-2.53)
	No	288 (89.2%)	27 (52.9%)	1.00	1.00
Baseline opportunistic infections	Yes	148 (45.8%)	46 (90.2%)	10.88 (4.21- 28.09)	6.66 (1.94 - 22.90) **
	No	175 (54.2%)	5 (9.8%)	1.00	1.00
OI in the past six months after ART	Yes	55 (17.0%)	31 (60.8%)	7.55 (4.01 - 14.22)	2.19 (0.86-5.56)
	No	268 (83.0%)	20 (39.2%)	1.00	1.00
Baseline WHO staging	WHO stage I & II	148 (45.8%)	46 (90.2%)	1.00	1.00
	WHO stage III & IV	175 (54.2%)	5 (9.8%)	8.17 (4.25 - 15.72)	0.70 (0.18-2.76)
Recent WHO staging	T-stage I	319 (98.8%)	46 (90.2%)	1.00	1.00
	T-stage II to IV	4 (1.2%)	5 (9.8%)	8.67 (2.25 - 33.46)	0.81 (0.32-20.44)
TB/HIV coinfection	Yes	57 (17.6%)	29 (56.9%)	6.15 (3.30 - 11.48)	0.87 (0.24-2.2)
	No	266 (82.4%)	22 (43.1%)	1.00	1.00
Mental illness	Yes	14 (4.3%)	14 (27.5%)	8.35 (3.70 - 18.88)	1.55 (0.25-9.77)
	No	309 (95.7%)	37 (72.5%)	1.00	1.00
Base line CD4 count (cells/ul)	<200	117 (36.2%)	36 (70.6%)	3.39 (1.14 - 10.06)	0.22 (0.04-1.24)
	200-350	104 (32.2%)	8 (15.7%)	0.85 (0.242- 2.96)	0.14 (0.02-0.89)
	351-500	58 (18.0%)	3 (5.9%)	0.57 (0.12 - 2.67)	0.10 (0.01-1.16)
	>500	44 (13.6%)	4 (7.8%)	1.00	1.00
Initial viral load status	<=1000 copies/ml	245 (75.9%)	16 (31.4%)	1.00	1.00
	>1000 copies/ml	78 (24.1%)	35 (68.6%)	6.87 (3.61 - 13.08)	1.68 (0.58-4.82)
ART adherence status	Good	288 (89.2%)	25 (49.0%)	1.00	1.00
	fair/poor	35 (10.8%)	26 (51.0%)	8.56 (4.46 - 16.42)	3.41 (1.26 - 9.24) *
History of ART interruption in	Yes	47 (14.6%)	25 49.0% ()	5.65 (3.01 - 10.60)	2.97 (1.11 - 7.94) *
	No	276 (85.4%)	26 (51.0%)	1.00	1.00
Loss to follow-up status in the past	Yes	20 (6.2%)	22 (43.1%)	11.49 (5.62 -23.50)	9.03 (3.08 - 26.47) ***
	No	303 (93.8%)	29 (56.9%)	1.00	1.00

Variables	Categories	Virologic failure, n (%)		OR (95% CI)	
		Yes	Yes	Crude OR (95% CI)	Adjusted OR (95% CI)
Other drugs taking other than ART	Yes	24 (7.4%)	27 (52.9%)	14.02 (7.03 - 27.93)	3.64 (1.33 - 9.97) *
	No	299 (92.6%)	24 (47.1%)	1.00	1.00
Cotrimoxazole preventive therapy (CPT)	Yes	170 (52.6%)	41 (80.4%)	1.00	1.00
	No	153 (47.4%)	10 (19.6%)	3.69 (1.79 - 7.62)	3.21 (1.12 - 9.18) *

Keys: 1. *** = "P-value" < 0.001 2 ** = "P-value" < 0.01 3. * = "P-value" < 0.05

4. Discussion

First-line ART failure is the continued challenge for HIV programs in low- and middle-income countries. Understanding the magnitude of first-line ART failure is crucial for early prevention as well as for planning and monitoring services in resource-limited countries. This study was aimed at determining the prevalence of first-line ART virologic failure and its associated factors among HIV-infected adults on ART in Debre Tabor Comprehensive Specialized Hospital in Northwest Ethiopia.

Accordingly, our study showed that the prevalence of first-line ART failure was 13.6% (95% CI: 10.4% -17.2%), which was consistent with previous studies done in Northwest Ethiopia (14.9% and 15.1%) [2, 25], a nationally representative study in Ethiopia (11%) [26], and Northeast Ethiopia (16.6% and 15.9%) [27, 28], and India (15.40) [29].

However, this study was lower than studies conducted in Southwest Ethiopia (29.3%) [30] and Southwest Shewa, central Ethiopia (33.42%) [24]. This variation could be since there might be variations in sociodemographic factors like age greater or equal to18 years vs age greater or equal to 15 years, male to female ratio, female 58% vs 41%) and also relatively using a larger sample size in this study. Moreover, there might be variations in personal or behavioral activities and the quality of the healthcare delivery system. This study was also higher than the systematic review and meta-analysis in Ethiopia (5.8%) [31], the studies from Northern Ethiopia (4.70%) [32], and the studies done in Eastern African countries and Nigeria (9%) [33], and Bangkok, Thailand (5.34%) [34]. The possible explanation for this difference could be a difference in improved care and being closely monitored. It might also be the sample size variation, because these studies used relatively larger sample sizes, and the variation within the study population could be another reason.

Virologic failure was influenced by a variety of sociodemographic, clinical, and therapeutic-related factors. In this study, sociodemographic factors were not associated with virologic failure (VF); however, in similar previous studies, some of these factors were associated with VF. Accordingly, different scholars reported that participants aged older than 35 years in northern Ethiopia [22], age greater than 42 years in Southwestern Ethiopia [30], and 45-54 years in Eastern Ethiopia were significantly associated with virological failure (VF). In contrast to the above, similar studies showed that age less than 35 years in northeast Ethiopia [35] and 15-24 years in central Ethiopia [8] were significantly associated factors with VF. Similarly, being an adolescent was associated with VF in Myanmar [21]. From previous studies, being male [19], being rural resident [26, 30, 32], being divorced [4, 27, 30], having no formal education or primary education [2] and distance from health facilities [24] were significantly associated with virological factors. The possible justification for why these factors were not associated in the current study might be because of differences in personal and behavioral activities in society and variations in clinical conditions.

In this study, participants who smoked cigarettes were 4.76 times more likely to develop virological failure compared with non-smokers. This might be due to the fact that cigarette smoking lowers the immune system and facilitates the occurrence of different OIs. Moreover, being abducted increases the possibility of poor adherence and being lost from care and treatment. Previous research in Ethiopia [26, 36] supported it.

This study also identified that HIV patients who did not disclose their status were 4.56 times more likely to have antiretroviral treatment failure compared with those who disclosed themselves. This may be because of some Known HIV patients do not volunteer to disclose their status to anyone who helps them because they fear stigma and disclosure. Therefore, they might interrupt their medication and close follow-up. A systematic review and meta-analysis in Ethiopia [31], and a study in central Ethiopia [36] backed it up.

The findings of this study also stated that participants who had a history of stigma and discrimination in their lives were 2.91 times higher than their counterparts to have a virologic failure. This is due to the fact that the presence of stigma and discrimination affects their adherence, and they may be unable to follow-up on care and treatment. This increases subsequent drug resistance and the possibility of VF.

In the current study, the odds of having virologic failure were 6.66 times higher among HIV patients with baseline opportunistic infections (OIs) compared with those without OIs. This may be due to the fact that the presence of different OIs not only lowers their immunity but also increases viral replication in thousands of copies, which results in mutant virions and may cause long-term development of drug resistance and treatment failure. On the other hand, patients with OIs took many drugs other than ART, and it could have drug-drug interactions and possible adverse drug effects that affected their adherence status. This study was supported by Mulisa et al. in 2019 and 2020 in central Ethiopia [24, 37].

This study showed that adult HIV clients with sub-optimal adherence (fair/poor) to their antiretroviral medication were 3.41 times higher than those with good adherence status to develop virological treatment failure. This is because sub-optimal

adherence to their antiretroviral treatment leads to the gradual occurrence of possible drug resistance due to low serum levels for exposed drugs. Additionally, they may have an increased number of viral replication and, as a result, they have a low CD4 count to fight different OIs. This was supported by a systematic review and meta-analysis in Ethiopia [31], and various studies in Ethiopia [22, 25, 32, 35, 36, 38].

Similarly, this study showed that those HIV patients with a history of having ART interruptions in the past were 2.97 times more likely to develop virological failure than those who regularly took their medications. This might be justified by the presence of ART interruption, which might facilitate viral replication and gradual increment of drug-resistant mutants. It was supported by Bezabih et al., 2019 and D. G. Demsie et al., 2020 [32, 39].

In this study, HIV patients with a history of one or more episodes of loss to follow-up for their care and treatment were 9 times more likely to have virologic failure compared with those who were retained in care. This might be due to the fact that when HIV patients are lost from taking antiretroviral medication for prolonged periods, there is a possibility of increasing HIV viral replication, including drug-resistant mutants. This may finally cause virologic failure. This was supported by a study done in Myanmar [21].

From the current study, those study participants who did not take cotrimoxazole preventive therapy as indicated were 3.21 times more likely to develop antiretroviral treatment failure compared with their counterparts. This is because taking cotrimoxazole prophylaxis may help HIV clients prevent different OIs and, as a result, improve their immune status and subsequent viral load reduction. This study was supported by Age nehu et al., 2020, which sated that cotrimoxazole preventive therapy decreases the incidence of virologic failure by 45% [38].

The findings of this study also showed that the odds of developing antiretroviral treatment failure among HIV patients taking additional medication other than ART were 3.64 times higher compared with their counterparts. This might be because of having drug-drug interactions which decrease serum levels of antiretroviral drugs; taking many drugs may result in the development of adverse drug reactions (ADRs); and pill burden that affects adherence and, as a result, leads to loss to follow-up.

Strength and limitation of the study: This study provides an important input which could be helpful in HIV programs for health managers and different stakeholders. Since it is a cross-sectional study based on secondary data, a prospective multicenter analytical design with mixed research is recommended to identify the incidence and associated risk factors for first-line virologic failure.

5. Conclusion and Recommendation

The prevalence of virologic failure from this study is consistent with a national one. The findings of this study showed that smoking, non-disclosure status, having stigma and discrimination, presence of baseline opportunistic infections, not taking cotrimoxazole preventive therapy, past history of treatment interruption for ART, one or more episodes of loss to follow up, having fair or poor adherence status, and taking additional medication other than ART were significantly associated with virologic failure.

Therefore, HIV program stakeholders should give emphasis to an enhanced adherence counseling to improve HIV disclosure status, how to minimize and avoid stigma and discrimination, how to improve poor adherence, and how to reduce or minimize smoking among PLHIV. Moreover, special attention should be given to early diagnosis and management of OIs; CPT based on indication; enhanced adherence counseling and early tracing of interrupters and lost patients; and special concern should also be given for those taking additional medications (drug-drug interaction, side-effects, and pill burden).

List of Abbreviations

AIDS-Acquired Immunodeficiency Syndrome; AOR-Adjusted Odds Ratio; ART-Antiretroviral therapy; CI-Confidence Interval; COR-Crude Odds Ratio; CPT-Cotrimoxazole Preventive Therapy; EFMOH-Ethiopian Federal Ministry of Health; EID-Early Infant Diagnosis; EPHI-Ethiopian Public Health Institute; HAART-Highly Active Antiretroviral Therapy; HIV-Human Immunodeficiency Virus; IRBs-Institutional Review Boards; IQR-Inter-Quartile Rang; LTFU-Loss to Follow-Up; MDGs-Millennium Development Goals; NATs-Nucleic Acid Tests; OI-Opportunistic Infections; PLHIV-People Living with HIV; SDGs-Sustainable Development Goals; SRS-Simple Random Sampling; TB-Tuberculosis; TO-Transfer Out; TPT-Tuberculosis Preventive Treatment; UNAIDS United-Nations Program on HIV and AIDS; VF-Virologic Failure; VL-viral Load; VS-Viral Suppression; WHO-World Health Organization.

Declarations

Ethical Approval and Consent to Participate

The ethical approval was obtained from the University of Gondar Institutional Review Boards (IRBs) (Ref. No. SOM/1850/14). Then a permission letter was written from the department of internal medicine to Debre Tabor comprehensive specialized hospital. The data were kept confidential and secret, and no personal identifiers were used.

Consent for Publication

It is not applicable for this study because it is the secondary data analysis.

Availability of Data and Materials

Data for this study were collected for secondary use from medical charts already routinely collected medical services in ART clinic.

Author's Contribution

HAM: conceived and designed the study; extracted data; wrote the first draft and reviewed it; conducted analysis and interpretation; wrote the report; and did the final editing. TY: designed and conceptualized the study; assisted with data analysis, interpretation, validation, and visualization. FM conceptualized and designed the study, as well as assisted in data analysis, interpretation, validation, and visualization. NMD helped with data analysis, interpretation, validation, and visualization, as well as reviewing and editing the manuscript. All of the authors read and approved the final version of the manuscript.

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References

[1] WHO. https://www.who.int/news-room/questions-and answers/item/HIV-AIDS: Q&A 30 November 2020

[2] Ayele G, Tessema B, Amsalu A, Ferede G, Yismaw G. Prevalence and associated factors of treatment failure among HIV/AIDS patients on HAART attending University of Gondar Referral Hospital Northwest Ethiopia. BMC Immunology. 2018; 19 (1): 37. doi: 10.1186/s12865-018-02784.

[3] Ethiopian Federal Minestry of Health. National consolidated guidelines for comprehensive HIV prevention, care and treatment. guidline. Addis Ababa: EFMOH; 2018.

[4] Gregson J, Tang M, Ndembi N, Hamers RL, Rhee S-Y, Marconi VC, et al. Global epidemiology of drug resistance after failure of WHO recommended first-line regimens for adult HIV-1 infection: a multicentre retrospective cohort study. The Lancet Infectious Diseases. 2016; 16 (5): 565-75. doi: 10.1016/s1473-3099(15)00536-8.

[5] World Health Organization. Consolidated Guidelines on the Use of Antiretroviral Drugs for Treating and Preventing HIV Infection: Recommendations for a Public Health Approach, 2nd edition. Geneva, Switzerland: World Health Organization; 2016.

[6] World Health Organization. Consolidated guidelines on HIV prevention, testing, treatment, service delivery and monitoring: recommendations for a public health approach. Geneva: WHO; 2021.

[7] Lecher SL, Naluguza M, Mwangi C, al. e. Notes from the Field: Impact of the COVID-19 Response on Scale-Up of HIV Viral Load Testing — PEPFAR-Supported Countries, January–June 2020. MMWR Morb Mortal Wkly 2021; 70: 94–795. doi: http://dx.doi.org/10.15585/mmwr.mm7021a3.

[8] Tamrat Endebu *, Alem Deksisa, Tibka Moges, Teresa Kisi, Temesgen Ensermu. Incidence of Virological Failure and Associated Factors among Adult HIV-Positive Patients on First Line Antiretroviral Therapy Regimen, Central Ethiopia. International Journal of HIV/AIDS Prevention, Education and Behavioural Science 2018; 4 (2): 4451. doi: 11648/j.ijhpebs.20180402.13.

[9] UNAIDS. Global HIV & AIDS statistics: Fact sheet. 2021.

[10] WHO. HIV drug resistance report 2021. Geneva: World Health Organization; 2021.

[11] UNAIDS. Global AIDS update 2021. 2021.

[12] Dorward J, Lessells R, Drain PK, Naidoo K, de Oliveira T, Pillay Y, et al. Dolutegravir for first-line antiretroviral therapy in low-income and middle-income countries: uncertainties and opportunities for implementation and research. 2018; 5 (7): e400-e4.

[13] Gupta RK, Gregson J, Parkin N, Haile-Selassie H, Tanuri A, Forero LA, et al. HIV-1 drug resistance before initiation or re-initiation of first-line antiretroviral therapy in low-income and middle-income countries: a systematic review and meta-regression analysis. J The Lancet infectious diseases. 2018; 18 (3): 346-55.

[14] Wallis CL, Godfrey C, Fitzgibbon JE, Mellors JWJTJoid. Key factors influencing the emergence of human immunodeficiency virus drug resistance in low-and middle-income countries. 2017; 216 (suppl_9): S851-S6.

[15] Nachega JB, Sam-Agudu NA, Mofenson LM, Schechter M, Mellors JW. Achieving viral suppression in 90% of people living with human immunodeficiency virus on antiretroviral therapy in low-and middle-income countries: progress, challenges, and opportunities. J Clinical Infectious Diseases. 2018; 66 (10): 1487-91.

[16] UNAIDS. joint United Nations Program on HIV/AIDS. Geneva Switzerland: 2021 Contract No.: Licence: CC BY-NC-SA 3.0 IGO.

[17] Hauser A, Goldstein F, Reichmuth ML, Kouyos RD, Wandeler G, Egger M, et al. Acquired HIV drug resistance mutations on first-line antiretroviral therapy in Southern Africa: Systematic review and Bayesian evidence synthesis. Journal of clinical epidemiology. 2022; 148: 135-45. Epub 2022/02/23. doi: 10.1016/j.jclinepi.2022.02.005. PubMed PMID: 35192922; PubMed Central PMCID: PMCPMC9388696.

[18] PEPFAR-Ethiopia. Ethiopia Country Operational Plan COP 2021 Strategic Direction Summary Final May 26, 2021. 2021.

[19] Marconi VC, Wu B, Hampton J, Ordóñez CE, Johnson BA, Singh D, et al. Early Warning Indicators for First-Line Virologic Failure Independent of Adherence Measures in a South African Urban Clinic. AIDS Patient Care and STDs. 2013; 27 (12): 657-68. doi: 10.1089/apc.2013.0263.

[20] Bereda G. Rationale of Antiretroviral Treatment Failure-Hence Forth Implication of Clinical Management and Hospital Practice, 2021. J J Clin Med Img. 2021; 5 (16): 1-8.

[21] Kyaw NT, Harries AD, Kumar AM, Oo MM, Kyaw KW, Win T, et al. High rate of virological failure and low rate of switching to second-line treatment among adolescents and adults living with HIV on first-line ART in Myanmar, 2005-2015. PloS one. 2017; 12 (2): e0171780. doi: 10.1371/journal.pone.0171780. PubMed PMID: 28182786; PubMed Central PMCID: PMC5300167.

[22] Emagnu A, Abay Z, Bulti AB, Animut Y. Determinants of Virologic Failure among Adult HIV Patients on First-Line Antiretroviral Therapy at Waghimra Zone, Northern Ethiopia: A Case-Control Study. Advances in Public Health. 2020; 2020: 1-8. doi: 10.1155/2020/1929436.

[23] Shanmukhappa SC, Abraham RR, Huilgol P, Godbole R, Anand AK, Prasad R, et al. What influences adherence among HIV patients presenting with first-line antiretroviral therapy failure (ART failure)? A retrospective, cross-sectional study from a private clinic in Nagpur, India. Journal of family medicine and primary care. 2020; 9 (12): 6217-23. doi: 10.4103/jfmpc.jfmpc_1155_20. PubMed PMID: 33681067; PubMed Central PMCID: PMC7928081.

[24] Mulisa D, Tolossa T, Wakuma B, Etafa W, Yadesa G. Magnitude of first line antiretroviral therapy treatment failure and associated factors among adult patients on ART in South West Shoa, Central Ethiopia. PloS one. 2020; 15. doi: 10.1371/journal.pone.0241768.

[25] Genet A, Mekonnen Z, Yizengaw E, Mekonnen D. First line antiretroviral treatment failure and associated factors among people living with HIV in northwest Ethiopia. African Health Sciences. 2021; 21 (1): 263-72.

[26] Getaneh Y, Egziabhier AG, Zealiyas K, Tilahun R, Girma M, Deressa T, et al. HIV-1 treatment failure among population taking antiretroviral therapy in Ethiopia. 2019; 1 (2): 46-57.

[27] Teklehaimanot Fentie Wendie, Birhanu Demeke Workneh. Prevalence-and predictors-of-virological-failure among-adult living with HIV in south wollo, northeast Ethiopia, retrosective cohort study. HIV AIDS - Research and palliative care. 2020; 12: 393-402. doi: 10.2147/HIV.S266460.

[28] Nega J, Taye S, Million Y, Rodrigo C, Eshetie S. Antiretroviral treatment failure and associated factors among HIV patients on first-line antiretroviral treatment in Sekota, northeast Ethiopia. J AIDS Research. 2020; 17 (1): 1-9.

[29] Aishah Khan, Unnikrishnan, BA, Vaman Kulkarni, Ramesh Holla, John T. Ramapuram a, et al. Long-Term Impact of First-Line Anti-Retroviral Therapy on HiV-1 Positive Patients: A Retrospective Study in Karnataka, India. The Open AIDS Journal. 2022; 16. doi: 10.2174/18746136-v16-e2112200.

[30] Bereda G, Bereda G. Prevalence of, and Factors Influencing First Line Antiretroviral Treatment Failure among Adult HIV Patients at Antiretroviral Treatment Clinic of Mettu Karl Referral Hospital, South Western, Ethiopia: A Prospective Cross-Sectional Study, 2021. J Int J Virol AIDS. 2021; 8: 075.

[31] Assemie MA, Alene M, Ketema DB, Mulatu S, policy. Treatment failure and associated factors among first line patients on highly active antiretroviral therapy in Ethiopia: a systematic review and meta-analysis. Global health research. 2019; 4 (1): 1-10.

[32] Demsie DG, Bantie AT, Allene MD, Alema NM, Gebrie D. Antiretroviral treatment failure among HIV-positive adults taking first-line therapy and associated risk factors at Adigrat General hospital, Adigart, Ethiopia 2019: A cross sectional study. International Journal of Surgery Open. 2020; 26: 16-21.

[33] Kiweewa F, Esber A, Musingye E, Reed D, Crowell TA, Cham F, et al. HIV virologic failure and its predictors among HIV-infected adults on antiretroviral therapy in the African Cohort Study. J PLoS One. 2019; 14 (2): e0211344.

[34] Nasomsong W, Phokaphol K, Changpradub D. First-Line Antiretroviral Regimen Failure and Determinants in an Urban HIV Clinic at Phramongkutklao Hospital, Bangkok, Thailand: 20 Years Experience. HIV AIDS (Auckl). 2021; 13: 261-9. Epub 20210304. doi: 10.2147/HIV.S295512. PubMed PMID: 33692637; PubMed Central PMCID: PMCPMC7939509.

[35] Fentaw Z, Molla A, Wedajo S, Mebratu W. Determinants of Virological Failure Among Adult Clients on First-Line Antiretroviral Therapy in Amhara Regional State, Northeast Ethiopia. A Case -Control Study. HIV AIDS (Auckl). 2020; 12: 749-56. Epub 2020/11/27. doi: 10.2147/hiv. S267629. PubMed PMID: 33239920; PubMed Central PMCID: PMCPMC7680783.

[36] Abdullahi IJ, Deybasso HA, Adlo AM. Determinants of virological failure among patients on first-line antiretroviral therapy in central Oromia, Ethiopia: a case–control study. HIV/AIDS. 2020; 12: 931.

[37] Mulisa D, Tesfa M, Mullu Kassa G, Tolossa T. Determinants of first line antiretroviral therapy treatment failure among adult patients on ART at central Ethiopia: un-matched case control study. BMC Infectious Diseases 2012. 2019; 19 (1): 1-13.

[38] Agegnehu CD, Merid MW, Yenit MK. Incidence and predictors of virological failure among adult HIV patients on first-line antiretroviral therapy in Amhara regional referral hospitals; Ethiopia: a retrospective follow-up study. BMC Infectious Diseases 2012. 2020; 20 (1): 1-14.

[39] Bezabih YM, Beyene F, Bezabhe WM. Factors associated with first-line antiretroviral treatment failure in adult HIV-positive patients: a case-control study from Ethiopia. BMC Infectious Diseases 2012. 2019; 19 (1): 1-8.