

# Determinants of First Line Anti-Retroviral Treatment Failure Among Adult Human Immunodeficiency Virus Infected Patients in Western Oromia Public Hospitals, West Ethiopia

Fraol Jaleta<sup>1,\*</sup>, Alemayehu Getahun<sup>2</sup>, Getu Bayissa<sup>3</sup>

<sup>1</sup>Oromia Regional Health Bureau, Adama Public Health Research and Referral Laboratory Center, Adama, Ethiopia

<sup>2</sup>Department of Public Health, College of Medical and Health Science, Wollega University, Nekemte, Ethiopia

<sup>3</sup>Department of Pharmacy, College of Medical and Health Science, Wollega University, Nekemte, Ethiopia

## Email address:

firanoljako1387@gmail.com (F. Jaleta), alemayehugthn@gmail.com (A. Getahun), alemayehug@wollegauniversity.edu.et (A. Getahun), kiyabayisa@gmail.com (G. Bayissa)

\*Corresponding author

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**Abstract:** Back ground: First line antiretroviral treatment failure has led to increased HIV associated mortality especially in resource limited setting. A determinant of First line antiretroviral treatment failure is not well studied in Ethiopia. The objective of the study was to identify determinants of first line treatment failure among adults living with HIV in western Oromia public hospitals, West Ethiopia. Method: Unmatched case control study was conducted at public hospitals of West Oromia using medical record review. Cases were adult HIV patients on ART in selected hospitals who were switched to second line ART regimen because of first line treatment failure in the past ten years (2005-2015) and Controls were adult HIV patients on ART in selected hospitals who were on first line ART for greater or equal to six month in the same years (2005-2015). Data was collected by trained nurses (counselors) using checklists developed from Ministry of Health ART follow up form and entered to EPI data version 3.1 and transferred to SPSS version 20.0 for analysis. To identify determinants of first line anti-retroviral treatment failure, multivariate analysis with P-value <0.05 was done. Results: A total of 115 cases and 345 controls were included in the study. Baseline CD4 measure (AOR [95% CI] = 3.96 [1.84, 8.54]), regimen change due to drug stock out (AOR [95% CI] = 2.54 [1.38, 4.66]), treatment interruption (AOR [95% CI] = 5.09 [2.39, 10.82]), adverse effect of drug (AOR [95% CI] = 8.49 [1.87, 38.42]) and History of opportunistic infection (AOR [95% CI] = 2.15 [1.28, 3.64]) were independently associated with first line antiretroviral treatment failure. Conclusion: Intervention for First line antiretroviral treatment failure needs to emphasize on regimen change due to drug stock out, treatment interruption, history of opportunistic infection, adverse effect of drug and base line CD4 <50cell/ $\mu$ .

**Keywords:** Treatment Failure, Antiretroviral Therapy, Case Control

## 1. Introduction

Human immunodeficiency Virus (HIV) is a virus which causes Acquired Immunodeficiency syndrome (AIDS) by which a failure of human immune system leads life threatening opportunistic infection. Introduction of Highly Active Anti-Retroviral Therapy (HAART) has led to an increase in survival among HIV-infected patients [1, 2].

At the start of ART, first line regimen of two Nucleotides reverse transcriptase inhibitors backbone with one of non-nucleotide reverse transcriptase inhibitors is used. In case of first line treatment failure (anti HIV medication can't control the infection) there is a decision to start second line regimens which contain additional protease inhibitors. Treatment failure might happen in the form of virological failure, immunological failure and clinical progression. World Health Organization (WHO) defines treatment failure virologically

as viral load persistently (at least 2 results) above 1000 copies/ml. The success of antiretroviral treatment is defined more specifically by viral suppression [3-5].

Clinical failure is the combination of New or recurrent opportunistic infection (OI), malignancy, pulmonary Tuberculosis (TB) and severe bacterial infections whereas immunological failure includes fall of CD4 count to pre-therapy baseline or CD4 levels rise from the baseline after six months of treatment [6].

According to WHO report, about 36.9 million people were living with HIV /AIDS worldwide and around 1.2 million died at the end of 2014 and an estimated 2 million people were newly infected individuals [7, 8]. During 2014, Sub-Saharan Africa accounted more than two third of global AIDS related death which was felt by 48% of death in 2004 due to accesses of Anti-Retroviral Therapy. To the contrary, treatment failure has been shown to increase morbidity and mortality [9, 10].

The same report implies, about 6% of patients receiving first-line therapy in sub-Saharan Africa need to switch to second-line regimens in any given year due to first line ART failure [11, 12]. Ethiopia is one of the Sub-Saharan African countries most severely affected by HIV/AIDS. It has the fifth largest population of HIV infected individuals living in Africa, which accounts to approximately 4% of the world's HIV/AIDS cases. According to federal Ministry of Health (FMOH) report, there were 1.2 million people living with HIV, and 397,818 are estimated to be in need of antiretroviral treatment in 2011. Adult Prevalence was decreased from 1.5 in 2013 to 1.1% in 2015. But the number of patients on second line due to treatment failure and others remain low which is 1.7% of all of ART recipients [13, 14].

Patients with first line treatment failure due to inadequate drug adherence are at high risk of a subsequent treatment failure on second-line ART [4, 15] Factors that lead to ART treatment failure are not well studied in Ethiopia. Therefore, the aim of this study was to determine risk factors associated with first line antiretroviral treatment failure which was defined in this study as regimen changed to second line due to clinical failure with WHO stage III and IV and immunological failure considered as fall of CD4 count to pre-therapy baseline after six months on treatment. The study was also aimed to identify patient and health service related factor contributed for treatment failure. Particularly, this finding is an input for zonal and woreda health offices, partners and health care providers to design better strategies that ensure the effectiveness of HAART which minimizes the risk of drug resistance or increases the suppression of viral load. It also supports the patients to be aware of their drug intake as per scheduled.

## 2. Methods

### 2.1. Study Area and Period

Unmatched case control study was conducted from

January 20 to February 2, 2017 in four public hospitals (Nekemte, Ghimbi, Nedjo and Dembidolo) located in west Oromia which were selected purposively based on ART service initiation before ten years preceding the study. There were 4830 enrolled adult HIV/AIDS patients in the selected hospitals [16-19].

### 2.2. Study Population

The study population consisted of cases and controls. Cases were adult HIV patients on ART in Public hospitals who failed first line ART and switched to second line ART regimen in the past ten years (2005-2015) and Controls were adult HIV patients on ART in selected hospitals who were on first line ART for equal or greater than six months and had not failed first line treatment in the same years (2005-2015).

Patients with incomplete information and transfer in (TI) were not included in the study.

### 2.3. Sample Size and Sampling Procedure

Sample size was calculated using EPI Info version 7.1.4 by considering exposure to nevirapin based first line regimen as the main exposure. From the literature it is 41% and 27% in cases and controls respectively [20]. Power 80%, 95% CI, case to control ratio 1:3 (case to control) and a total of 460 were included in the study.

Sampling frame for case and control was prepared using unique identification number from medical records. Cases and controls were selected randomly and proportional to the size of the study population who started ART in the past ten years (January 2005- January 2015) from four selected public hospitals. Finally, 115 of the patients who were on second line drug regimen were selected as a case and 345 of those on first line drug regimen were selected as control.

### 2.4. Data Collection Methods and Tools

Data was collected from medical records using checklists developed from FMOH of Ethiopia ART follow up form and guideline. Patient related variables which includes levels adherence measured before cases switched to second line drug, history of treatment interruption before treatment failure, baseline CD4 count, WHO clinical stage, Duration on first line ART before failure, History of diarrhea, health service and drug related variables which includes distance from health facility type of initial first line regimen, regimen change due to drug stock out, history of adverse effect before switched to second line treatment and socio-demographic factors were extracted from medical record review. Eight ART nurses (counselors) were recruited from study hospitals and two days training was provided for data collectors which include practical tests to ensure their competency of filling checklist. There was a close supervision and daily based checkup for completeness of filled questionnaire during data collection.

### 2.5. Data Processing and Analysis

Data was first checked manually for completeness and

then entered into Epidata version 3.1. After data entry and cleaning, the data was transferred to SPSS version 20.0 for analysis. Bivariate analysis was performed using binary logistic regression. Variables which showed significant association in the bivariate analyses ( $P < 0.2$ ) were candidates for the multivariate logistic regression model. To control the effect of confounding variables, multivariate logistic regressions were done. Explanatory variables significantly associated with outcome variable with  $p$ -value  $< 0.05$  in multivariate logistic regression were determined as independent predictors of first line treatment failure. Finally, conclusion and recommendation were made based on the findings. Adjusted OR and 95% CI were used to interpret the findings.

The study was ethically approved by Ethical Review Committee of Wollega University. Formal letter from Wollega university department of public health was written and submitted to selected public hospitals and permission was obtained from each hospital. Identification of participant was done only through ART identification codes and name of the participant was not included in the checklist in order to ensure the confidentiality of the patient information.

### 3. Results

#### *Socio-demographic Characteristics*

A total of 460 (115 cases and 345 controls) HIV patients were included in the study. The mean age at which participants started ART was 33 (SD  $\pm 9$ ) and 34 (SD  $\pm 9$ ) years for the case and control respectively. 59 (51.3%) of cases and 207 (60.0%) of controls were females. Regarding to religion, 60 (52.2%) of cases and 145 (42%) of controls were protestant [Table 1].

The study also tried to assess adherence and depicted out 91 (79.0%) of cases and 331 (95.9%) of controls had good adherence to the drug. Concerning to Substance use only 17 (14.8%) of cases and 38 (19.4%) of controls used substance. The media duration on first line ART for case and controls were 72 and 53 months respectively.

Clinical diseases and other health related problems related variables. During initiation of HAART, 74 (64.3%) of case and 150 (43.5%) of controls were on WHO clinical stage III. Functional status of patients before ART initiation was assessed and 69 (60%) of cases and 287 (83.2%) of controls were at working status and the rest were ambulatory. 60 (52.2%) of cases and 88 (25.5%) of controls had history of opportunistic infection [Table 2].

#### *Health service and drug related variables of study population*

According to the result, 4 (55.7%) of cases and 201 (58.1%) of controls resides in  $< 10$  km from ART clinics. Initially, 49 (42.6%) of cases and 78 (22.6%) of controls were on initial regimen of d4T + 3TC + NVP. Adverse effect of drug used for ART was 37 (32.2%) for cases and 27 (7.8%) for controls. Regimen was changed for 50 (43.5%) of cases and 64 (18.6%) of controls due to drug stock out [Table 3].

#### *Determinants of first line anti-retroviral treatment failure*

In multivariate logistic regression six variables were independently associated with first line anti-retroviral treatment failure. HIV/AIDS patients with Baseline CD4  $< 50$  cell/microliter were around four times more likely to fail first line antiretroviral treatment when compared with those patients base line CD4  $> 150$  cell/microliter (AOR [95% CI] = 3.96 [1.84, 8.54]). Patients with regimen change due to drug stock out were more likely to develop first line treatment failure when compared with those whose regimen was not changed (AOR [95% CI] = 2.54 [1.38, 4.66]). Study participants with history of Adverse effect were around five times more likely to fail first line treatment than who had no (AOR [95% CI] = 5.33 [2.78, 10.24]). History of opportunistic infection had more likely to fail first line anti-retroviral treatment compared with no opportunistic infection (AOR [95% CI] = 2.15 [1.28, 3.64]). Patients interrupted treatment during ART Treatment were five times more likely to fail first line treatment when compared with not interrupted treatment (AOR [95% CI] = 5.09 [2.39, 10.82]) [Table 4].

**Table 1.** Socio-Demographic characteristics of adult HIV infected patients in public hospitals of Western Oromia, West Ethiopia, 2017.

Variables		Patient category	
		Cases (n=115)	Controls (n=345)
SEX	Male	56 (48.7)	138 (40%)
	Female	59 (51.3%)	207 (60%)
AGE	15-24 years	15 (13.1%)	28 (8.1%)
	25-34 years	48 (41.7%)	179 (51.9%)
	35-44 years	42 (36.5%)	108 (31.3%)
	45+ years	10 (8.7%)	30 (8.7%)
Religion	Protestant	60 (52%)	145 (42%)
	Orthodox	42 (36.5%)	159 (46.1%)
	Muslim	13 (11.3%)	37 (10.7%)
	Other		4 (1.2%) *
Marital status			

Variables		Patient category	
		Cases (n=115)	Controls (n=345)
Educational status	Single	24 (24%)	49 (14.2%)
	Married	66 (57.4%)	225 (65.2%)
	Divorced	4 (3.5%)	19 (5.5%)
	Widowed	13 (11.5%)	31 (9%)
	Separated	8 (7.1%)	21 (6.1%)
	None	28 (24.3%)	91 (26.4%)
	Primary	44 (38.3%)	129 (37.4%)
	Secondary	32 (27.8%)	95 (27%)
	Tertiary	11 (9.6%)	30 (8.7%)
Occupational status	Non-employed	92 (80%)	270 (78.3%)
	Full time employed	21 (18.3%)	71 (20.6%)
	Partial employed	2 (1.7%)	4 (1.2%)

\*Other: Adventist, Catholic and Jehovah

**Table 2.** Patient and clinical diseases related variables of adult HIV infected patients in public hospitals of western Oromia, West Ethiopia, 2107.

Variables		Patient category	
		Cases	Controls
Adherence	Good adhered	91 (79.1%)	331 (95.9%)
	Fairly adhered	18 (15.7%)	8 (2.3%)
	Poorly adhered	6 (5.2%)	6 (1.7%)
Treatment interruption	Yes	24 (20.9%)	19 (5.5%)
	No	91 (79.1%)	326 (94.5%)
Substance use	Yes	17 (14.8%)	67 (19.4%)
	No	98 (85.2%)	278 (80.6%)
Type of substance	Alcohol	16 (94.1%)	48 (71.6%)
	Tobacco	1 (5.9%)	13 (19.4%)
	Khat	0 (0%)	4 (5.9%)
	Soft or hard drug	0 (0%)	2 (2.9%)
Duration on first line ART	<24 month	98 (85.2%)	278 (80.6%)
	>24 month	7 (6.1%)	52 (15.1%)
WHO stages	WHO stage One	12 (10.4%)	93 (27%)
	WHO stage Two	22 (19.1%)	95 (27%)
	WHO stage Three	74 (64.3%)	150 (43.5%)
	WHO stage Four	7 (6.1%)	7 (2%)
Chronic diarrhoea	Yes	32 (27.8%)	98 (28.4)
	No	83 (72.2%)	247 (71.6%)
History of GI problem	Yes	53 (46.1%)	103 (29.9%)
	No	62 (53.9)	242 (70.1%)
Opportunistic Infection	Yes	60 (52.2%)	88 (25.5%)
	No	55 (47.8%)	261 (74.7%)
Type of opportunistic infection	Pneumocysticcarini pneumonia	4 (3.5%)	6 (1.7%)
	Bacterial pneumonia	16 (13.9%)	35 (10.1%)
	CNS Toxoplasmosis	1 (.9%)	1 (0.3%)
	Pulmonary TB	15 (13%)	18 (5.2%)
	Extra pulmonary TB	4 (3.5%)	9 (2.6%)
	Other	17 (14.8%)	15 (4.3%)

Abbreviation: CNS, central nerves system; TB, tuberculoses; GI, gastro intestinal; WHO, world health organization.

**Table 3.** Health service and drug related variables of adult HIV infected patients in selected hospitals of western Oromia, west Ethiopia, 2017.

Variables	Patient Category	
	Case (%)	Controls (%)
Distance in km		
<10km	64 (55.7%)	201 (58.1%)
>10km	51 (44.3%)	144 (41.7%)
Initial first line regimen		
D4T +3TC+NVP	49 (42.6%)	78 (22.6%)
D4T +3TC+EFV	12 (10.4%)	30 (8.7%)
ZDV+3TC+NVP	13 (11.3%)	48 (13.9%)
ZDV+3TC+EFV	9 (7.8%)	19 (5.5%)
TDF+3TC+EFV	25 (21.7%)	148 (42.9%)
TDF+3TC+NVP	7 (6.1%)	22 (6.4%)
EFV based		
Yes	48 (41.7%)	200 (58%)
No	67 (58.3%)	145 (42%)
NVP based		
Yes	67 (58.3%)	146 (42.3%)
No	48 (41.7%)	199 (57.7%)
Adverse effect		
Yes	37 (32.2%)	27 (7.8%)
No	78 (67.8%)	318 (92.2%)
Co-medication		
Yes	38 (33%)	94 (27.2%)
No	77 (67%)	251 (72.8%)
Regimen change due to drug stock out		
Yes	50 (43.5%)	64 (18.6%)
No	65 (56.5%)	281 (81.4%)

Abbreviations: KM, kilometre; D4T, stavudine; 3TC, lamivudine; NVP, Niverapine, EFV, efanfrenze; TDF, tenofovir.

**Table 4.** Multivariate analysis associated with first line anti-retroviral treatment failure among adult HIV infected patients in selected hospitals of western Oromia, west Ethiopia, 2017.

Variables	Patient Category		COR (95% CI)	AOR (95% CI)	P-value
	Case	Controls			
Baseline CD4					
<50 cell/microlitre	21 (18.3%)	35 (10.1%)	13.56 (6.87-26.74)	3.96 (1.84-8.54)	0.000
50-150 cell/microlitre	46 (40%)	97 (30.8%)	3.73 (1.88-7.41)	14.84 (6.86-32.08)	0.000
>150 cell/microlitre	48 (41.7%)	248 (78.7%)	1.00	1.00	
Regimen change due to drug stock out					
Yes	50 (43.5%)	64 (18.6%)	3.38 (2.14-5.34)	2.54 (1.38-4.66)	0.03
No	65 (56.5%)	281 (81.4%)	1.00	1.00	
Adverse effect					
Yes	37 (32.2%)	27 (7.8%)	5.59 (3.20-9.73)	5.33 (2.78-10.24)	0.000
No	78 (67.8%)	318 (92.2%)	1.00	1.00	
Treatment interruption					
Yes	24 (20.9%)	19 (5.5%)	4.53 (2.37-8.63)	5.09 (2.39-10.82)	0.002
No	91 (79.1%)	326 (94.5%)	1.00	1.00	
History of opportunistic OI					
Yes	57 (49.6%)	84 (24.3%)	3.19 (2.06-4.94)	2.15 (1.28-3.64)	0.004
No	58 (50.4%)	261 (75.7%)	1.00	1.00	

Abbreviations: CD4, cluster differentiation; OI, opportunistic infection; COR, crude odd ratio; AOR, adjusted odd ratio; CI, confidence interval.

## 4. Discussion

Treatment failure is one of the burning issues in clinical management of HIV patients follow up on ART now days. In this study, it was assessed based on clinical failure which was described by WHO clinical stages (III and IV) and immunological failure considering the decrease of CD4 count to

pre-therapy baseline or CD4 level that has not been raised from baseline count after six month start of ART. Long stay on a fail of first line treatment increases the risk of mortality and morbidity inciting treatment failure and development of drug resistance. In this study, several risk factors associated with treatment failure described by clinical and immunological failure were identified. From baseline laboratory Measures, this study identified that patients with baseline CD4 <50 cell/microliter

have 3.96 times more risk of a developing treatment failure than those with higher CD4 count. This study is also similar with the study conducted in Kenya that depicted patients with CD4 count below 50cell/ $\mu$ l increases the probability of treatment failure more than 5 folds. This study is also consistent with the study done in Addis Ababa in which patients with base line CD4 less than 50cell/ $\mu$ l failed 2.7 times than that of higher CD4 counts. This might be due to patient with low base line CD4 count have lesser immunity that can result in the risk of developing immunological failure and consequently become high risk for treatment failure [21, 22]. Patients whose regimen was changed due to drug stock out were failed 2.5 times more than that of whose regimen has not been changed due to drug stock out. This study is consistent with the study conducted in Zshivane district of Zimbabwe in which patients who faced drug stock out were 3.02 times more to have first line treatment failure than that of who have not faced. This might be due to the variability of potency and dosing of replaced drugs and the initial drug in first line ARV options. Frequent change of drug due to stock out might also increases the chance of acquiring adverse affect of drug and drug resistance.

However, this study is not supported with the study done in Harare central hospital of Zimbabwe in which regimen change was not associated significantly with first line treatment failure. The discrepancy might be treatment change in Harare central hospital of Zimbabwe was assessed due to some other factors unlike in this study which specifically focused on drug stock out. The other reason might be due to the difference in the study design and the sampling technique [23, 24].

The finding of this study indicates that adverse effect of the drug is another independent predictor of treatment failure. Patients who developed adverse effect were 5.33 times more likely in developing treatment failure than those who has not developed adverse effects. This study is supported with the study done in Harare Central hospital adult opportunistic clinics of Zimbabwe that showed patients with Severe depression due to side effect of ART drug was 3.7 times more likely at risk of developing first line antiretroviral treatment failure than that of without depression. The possible reason might be adverse effects which are probably caused by improper selection of drug or co morbidity conditions lead to regimen change and discontinuation which consequently increase the risk of treatment failure. However, this study is inconsistent with the study done in Zshivane district of Zimbabwe in which there was no association of drug side effect with first line antireviral treatment failure. The possible reason for the variation may be due to the difference in the method of data collection in which interview was conducted by semi structured questionnaire and checklist for medical record review in Zimbabwe. When conducting interview with patient there may be information or recall bias [23, 24]

Unplanned treatment interruption was strongly associated with first line anti retroviral treatment failure in this study. Patients who interrupted treatment were 5.08 times at risk of treatment failure when compared to patients who had not experienced treatment interruption. This study is supported

by the study done in public and private hospitals of Addis Ababa in which the odd of first line treatment failure among case was 5.36 times when compared to controls. This study is also comparable with the study done in Zimbabwe in which patient with discontinuation of treatment are 4.4 more likely failed first line treatments than those who haven't experienced discontinuation of treatment. Unplanned treatment interruption may lead to damage of immune system, an increase in the risk of opportunistic infection and development of drug resistance which may leads to the risk of treatment failure. However, this study is inconsistent with the study conducted in university of Gondar hospital North West Ethiopia, in which history of treatment interruption is not independently associated with first line treatment failure. The possible reason for discrepancy may be, the study conducted in Gondar was only in single health facility with low sample size which may affect the precision of the study and qualities of ART patients management might be differ from this study which included four health facilities [21, 23, 24].

History of opportunistic infection before failure of first line treatment was another independent risk factor for treatment failure. Patients with history of opportunistic infection failed 2.15 times more than those who had not developed opportunistic infection. This finding is consistent with the study done in hospitals of Bale zone in which the odd of treatment failure among case increased more than 5 folds. This might be due to initiation of antiretroviral therapy before treating opportunistic infection which decreases the effectiveness of immunological function decreasing CD4 count and proliferation of opportunistic infections. This might causes immunological failure which incites the risk of developing first line antiretroviral treatment failure and immune suppression in HIV infected patients. However, the study was not comparable with the study done in Uganda, Kampala which indicates that there was no association of opportunistic infection with treatment failure. This finding is not in line with the study conducted in university of Gondar teaching hospital [25-27].

## 5. Limitation of the Study

Viral load test which is one of the decision criteria for ART failure was not included in the study due to the absence of the test service in the study area

## 6. Conclusion

According to this study the determinants of first line ART treatment failure were: Baseline CD4, Regimen change due to drug stock out, treatment interruption, adverse effect and history of opportunistic infection. Health professionals should regularly follow the patients to avoid unplanned treatment interruption and they should also aware of patients with lower CD4 count for early initiation of ART. If there is an acute opportunistic infection, it should be addressed first since it suppresses patient immunity being life threatening if

left untreated. Health facilities should monitor supply management system by regular performance of inventory management to minimize regimen change due to drug stock out. Oromia Regional Health Bureau must support the health facilities to implement viral load test service which is the gold standard for decision of virological failure.

## List of Abbreviations and Acronyms

AIDS	Acquired Immune Deficiency Syndrome
AOR	Adjusted Odds Ratio
ART	Anti-Retroviral Therapy
CD4	Cluster Differentiation
CI	Confidence Interval
FMOH	Federal Ministry of Health
HAART	HighlyActiveAnti-RetroviralTherapy
HIV	HumanImmunodeficiencyVirus
OI	Opportunistic Infection
OR	Odds Ratio
SD	Standard Deviation
SPSS	Statistical Package for the Social Sciences
TB	Tuberculosis
TI	Transfer In
WHO	World Health Organization

## Declarations

### *Ethics Approval and Consent to Participate*

Ethical clearance was obtained from Wollega University ethical review committee. Formal letter from Wollega university department of public health was written and submitted to the four selected Hospitals. Name of the participant was not included. Permission was assured from respected hospitals. No consent since based on secondary data.

### *Consent for Publication*

Not applicable

### *Availability of Data and Materials*

The datasets generated and/or analyzed during the current study are not publicly available due to confidentiality and ethics for HIV/AIDS patients, But available from the corresponding author on reasonable request.

### *Competing Interests*

The authors declare that they have no competing interests

### *Funding*

Nekemte Public Health Research and Referral Laboratory center contributed financial support for data collection.

## Authors' Contributions

FJ conceived the study, involved in the data analysis and Report writing and drafted the manuscript. AG was involved

in the conception, design, data analysis and review. GB was involved in conception, design and data analysis. All authors read and approved the manuscript.

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