

# Determinants of First Line Antiretroviral Treatment Failure among Patients on Highly Active Antiretroviral Therapy in selected Public Hospitals Jimma, Southwest Ethiopia a Case Control Study

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## Research article

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# Abstract

**Background:** Highly Active Antiretroviral Therapy (HAART) has substantially declined morbidity and mortality related to Human immunodeficiency virus/Acquired immunodeficiency syndrome (HIV/AIDS). Despite this fact, first-line ART failure has emerged as a growing concern. However, factors associated with first-line ART failure are not well empathized and studied. Hence, we aimed to identify the determinants of first-line ART failure among patients attending ART in Public Hospitals Jimma, Southwest Ethiopia. **Methods:** A case-control study was conducted in March 2018 on a sample of 384(288 controls and 96 cases) adult people living with HIV/AIDS (PLWHA). Cases were HIV patients aged 15 years or older who were on first-line ART regimens with documented therapeutic failure. Controls were HIV patients aged 15 years or older who were on first-line ART regimen but without evidence of therapeutic failure. Data were extracted from electronic databases and supplemented by data collected through interviewer-administered questionnaires. Bivariate and multivariate logistic regression analyses were used. Adjusted odds ratios and 95% confidence intervals were used to report independently associated factors at  $P\text{-value} < 0.05$ . **Results:** In this study, higher odds of first-line ART failure was experienced among urban residents (AOR:2.2;95%CI: 1.1, 3.6), smokers (AOR:5.9; 95%CI:3.2, 10.8), Khat users (AOR:2.2; 95%CI:1.3,3.7), poor treatment adherents (AOR:2.2; 95%CI: 1.1,4.5), tuberculosis coinfection (AOR:3.9; 95%CI:2.2, 6.8), prior exposure to ART (AOR:3.8; 95%CI:1.7, 8.1), zidovudine based regimen (AOR:4.8; 95%CI: 2.5,9.0) and longer duration on ART more than 73 months (AOR:1.9; 95%CI:1.2, 3.3). **Conclusions:** This study evidenced that being an urban resident, TB co-infection, poor treatment adherence, and zidovudine-based regiment were positively and independently associated with first-line ART failure. Thus, enhanced adherence counseling should be provided for those urban residents as well as substance users to improve adherence to ART; early screening and management of tuberculosis is highly recommended. Moreover, close follow up of adverse effects of ARVs must be strengthened. **Keywords :** determinants, first-line ART failure, HIV/AIDS, Jimma Zone, Public hospitals

## Background

Globally, it is estimated that 36.9 million people were living with HIV during 2017. Sub-Saharan Africa (SSA) remains significantly affected, accounting for 69.5% of the people living with HIV (PLWHA). Ethiopia is among the SSA countries most affected by HIV/AIDS with an estimated 710,000 people living with HIV in 2016 [1,2]. The introduction of highly active antiretroviral therapy (HAART) was a critical milestone in the history of HIV disease resulting in a dramatic reduction of morbidity and mortality, and improvement in the quality of life of PLWHA [3–5].

Despite the considerable reduction of morbidity and mortality due to HIV/AIDS after the start of HAART, a significant proportion of patients fail to attain the intended target of viral load suppression to therapy and many of them experience clinical deterioration attributable to ART failure. Treatment failure occurs when a combination of the ARV regimen fails to control HIV infection. This could be virologic, immunologic and/or clinical failure [6,7].

Virologic failure occurs when the plasma viral load is 1000 copies/ml and above in two consecutive measurements within the three-month interval with adherence support after at least six months of using ART. Immunologic failure occurs when CD4 cell count is lowered to 250 cells/mm<sup>3</sup> or below following clinical failure, or persistent CD4 cell level below 100 cells/mm<sup>3</sup> [8]. Clinical failure is the occurrence of new or recurrent WHO clinical stage four conditions [8]. Currently, the WHO recommends viral load testing as the preferred monitoring approach to diagnose and confirm ART treatment failure; however, targeted viral load monitoring or CD4 cell count and clinical monitoring should be used to diagnose treatment failure in settings where viral load test is not routinely available [5].

ART failure is a major challenge to HIV/AIDS management in resource-limited settings including Ethiopia where the diagnosis and management of ART failure is a key problem [9]. The documented findings showed that Virologic and Immunologic failure was 23% and 21.6% respectively among PLWHA who were on ART as reported from Vietnam and India [9,10]. In SSA countries, rates of first-line ART failure vary between 11.1% and 24% [11]. Studies showed that East Africa has faced a high prevalence of immunologic failure which ranges from 8% to 57%; studies from South Africa indicated that 19% of PLWHA had developed virologic and immunologic failure [12,13].

In Ethiopia, first-line ART treatment failure is 19.8% (immunologic 15%, clinical 6.3%, and virologic failure 1.3%) among adult PLWHA who are on ART according to the report from private health facilities in Addis Ababa [14]; Immunologic and clinical failure was 19.7 % and 19.5 % respectively as reported from Southwest Ethiopia [15]. Documented findings from the University of Gondar referral hospital, Debremarkos, St. Luke and Tulubolo hospitals showed that immunologic failures were 22.2%, 21%, and 6.8%, respectively [16–18].

Previous studies reported that various factors including being male gender [19], illiterate [20], widower [21], poor adherence and treatment interruption [22–25], WHO clinical stage III and/or IV [24–26], low CD4 cell at ART initiation [6,19,26,27], presence of opportunistic infections [6,24,25], low BMI [6,28], taking ARV regimen before ART initiation [22,24], taking Stavudine and Zidovudine (AZT) based regimen [29], TB co- infection [27,30,31], substance use [32–34] and longer duration on ART [3,20,26,35] were significantly associated with first line ART failure.

Currently, first-line ART failure is a major challenge on viral load suppression treatment targets and impairs quality life of PLWHA in resource-limited settings including Ethiopia [36]. Hence investigating and managing determinant factors of first-line ART treatment failure is very important to achieve the viral load suppression treatment target and sustain the quality of life PLWHA. However, there is limited evidence on the determinant factors of first-line antiretroviral treatment failure among PLWHA who are on first-line HAART in Ethiopia and the study area. Therefore, this study aimed to identify the determinant factors of first-line antiretroviral treatment failure among patients who were on first-line ART in public hospitals of Jimma Zone, Southwest Ethiopia.

## Methods

## 2.1. Study Design and Setting

A hospital-based case-control study was conducted from March 1 to 26/ 2018 in public hospitals of Jimma Zone, Southwest Ethiopia; namely Jimma University Specialized Hospital (JUSH), Shenen Gibe Hospital, Agaro Hospital, and Limu Genet Hospital. Jimma zone is one of the administrative zones in Oromia Regional State, located at 352 km from Addis Ababa. According to the zonal health department information, the zone had an estimated total population of 3,324,912 in the year 2017. The hospitals have been providing ART services for a long period and have maintained data of the patients in the electronic medical record database. There were 11,186 PLWHA taking HIV chronic care services during the data collection period. The study hospitals provide both first and second-line ART. However, viral load testing service for HIV care has been available only in JUSH since 2015.

## 2.2. Study Participants, Sample Size Determination and Sampling Technique

All PLWHA adults aged 15 years or older who had to follow up with HAART between January 2004 and December 2017 were considered to be the source population of the study. A Case was defined to be HIV patients aged 15 years or older who were on HAART between January 2004 to December 2017 and documented to have first-line ART treatment failure either virologic, immunologic or clinical in the study hospitals. Controls were patients aged 15 years or older who were on HAART between January 2004 to December 2017 but who did not fail first-line ART treatment failure. PLWHA who were stayed on HAART for less than six months and who had incomplete relevant clinical data were excluded from the study.

Epi Info™ 7 StatCalc was used to determine sample size by considering the significant determinant factor of first-line ART failure Proportion of controls and cases age <35 years exposure status of virologic failure were 47.7% and 64.7% respectively taken from a study finding from a previous study [35] using margin of error of 5% and power 80%. Therefore, the total sample size was estimated to be 384 (288 controls and 96 cases; considering three to one controls to case ratio). There were 102 documented PLWHA first-line ART treatment failure; however, six of them were excluded because of incomplete relevant clinical data from their medical record cards whereas all the remaining 96 were included in the study without sampling because of their relatively small number. The desired number of controls (n = 288) who fulfilled the inclusion criteria were randomly selected using computer-generated random numbers based on the unique ART identification number. Proportion to sample size allocation was used to allocate the sample for each hospital.

Table 1 Calculated sample size for study on determinants of first-line antiretroviral treatment failure among PLWHA on HAART, at Jimma Zone Public Hospitals, South West Ethiopia 2018

Variables	The ratio of Control to Cases	% of controls exposed	OR	% of cases exposed	Total sample size	Selected sample size
Age <35 years (35)	3	47.7	2.01	64.74	384(288:96)	Large sample
Unemployment (3)	3	30	2.48	51.5	228 (176:59)	
low base line BMI(3)	3	45	2.08	63	348 (261:87)	
Baseline CD4 count <200cells/mm <sup>3</sup> (35)	3	48.4	4.77	81.7	100(75:25)	
Poor adherence (35)	3	7.8	11.67	49.7	52(39:13)	

## 2.1. Data Collection Tools and Procedure

The sources of data for this study were both secondary and primary data. Secondary data were extracted from the electronic database using a structured checklist. Primary data was obtained using a structured interviewer-administered questionnaire. Data collection tools were prepared by adapting and contextualizing the WHO standard tool and Federal Ministry of Health of Ethiopia ART guideline as well as by reviewing related literature [37, 38]. Socio-demographic profiles, substance use, treatment support, HIV result disclosure status, wealth index status and missed follow-up appointment was included in structured interviewer-administered questionnaires whereas Body mass index (BMI), Haemoglobin level, opportunistic infection, TB coinfection, functional status, HIV test entry, and type of ARV drugs were included in the checklist.

Ten nurses (six data collectors and four supervisors) who have experience in HIV care were recruited for data collection. The primary data was collected on the day of scheduled clinic visits for all cases and randomly selected controls. Participants, who were not available at the time of scheduled clinic visits were traced using the phone number and home address available on the card and interviewed on the consecutive days of the study period. For the secondary data, data collectors from ART clinics were accessed and reviewed electronic databases and patient charts.

## 2.2. Study Variables

The dependent variable was the occurrence of first-line antiretroviral treatment failure. In this study, first-line antiretroviral treatment failure was defined as the fulfillment of either virologic, immunologic or clinical failure criteria set by WHO. This was determined by reviewing whether the patient was diagnosed with first-line ART failure or not on his/her medical record. The independent variables include: socio-

demographic and economic variables (age, residence, sex, religion, ethnicity, marital status, household relative wealth index, HIV disclosure status, missed clinic appointment, educational status, employment status), substance use (smoking, Khat chewing and alcohol use), adherence status (good, poor or fair), BMI, hematologic level, opportunistic infection, TB coinfection, functional status, HIV test entry, type of ARVs and treatment support history.

### **2.3. Operational Definitions**

Khat (*Catha edulis*) is a leaf cultivated in Kenya, Yemen, and Ethiopia. It has alkaloids cathine and cathinone which have amphetamine-like properties and has been used for centuries in many African countries for its euphoric effect and as a sanctioned cultural practice. Khat has been associated with various health effects in the long-term, including oesophagitis, gastritis, duodenal ulcer, hepatic cirrhosis, autoimmune hepatitis, migraine, cerebral hemorrhage, pulmonary edema, and myocardial infarction when it is used frequently [39].

### **2.4. Data Quality Assurance, Processing, and Statistical Analysis**

Data collectors and supervisors were trained on data collection tools before the commencement of data collection. Collected data entered into Epi Data version 3.1 and exported to SPSS version 23 for analysis. Simple frequencies were carried out to check data cleanness. Descriptive statistics including median and interquartile range (IQR) values and frequencies were used to summarize participant's characteristics in each group. Dimension reduction using factorial analysis by a method of principal components was employed to assess an individual's wealth index status. Assumptions of principal component analysis such as a measure of sampling adequacy (MSA) less than 0.5, overall Kaiser-Meyer-Olkin (KMO) value less than 0.5, communality value less than 0.5 and complex structure were checked for each variable. Variables with p-value < 0.25 at bivariate analysis were taken to multivariate logistic regression analysis. The multivariable model was fitted to identify the independent determinants of first-line ART failure using a backward stepwise removal method. The model fitness was checked by Hosmer-Lemeshow goodness of fit tests (chi-square at 6.57 and p-value=0.583). Finally, variables that had significant associations with first-line ART failure were identified and reported based on the adjusted odds ratio (AOR) with corresponding 95% CI at p-value <0.05.

## **Results**

### **Socio-demographic characteristics of the study participants**

In this study, a total of 36(9.4%), 31(8.1%) and 29(7.6%) participants developed virologic, immunologic and clinical failure respectively. The median age at the time of ART initiation for cases and controls was 28 (IQRs 25-32) and 27 (IQRs23-33), respectively. Female participants were 53 (55.2%) and 181 (62.8%) among cases and controls, respectively [*Table 2*].

Table 2 Sociodemographic Characteristics of PLWHA  $\geq 15$  years, who have had a follow-up at selected public hospitals of Jimma Zone, Southwest Ethiopia, 2004-2017

Variable	Categories	Cases n (%)	Controls n (%)
Age, years	Median	28(IQR 25-32)	27(IQR 23-33)
	< 28 years	41 (42.7)	149 (51.7)
	$\geq 28$ years	55 (57.3)	139 (48.3)
Sex	Male	43 (44.8)	107 (37.2)
	Female	53 (55.2)	181 (62.8)
Marital Status	Married	57 (59.4)	174 (60.4)
	Single	6 (6.3)	30 (10.4)
	Divorced	22 (22.9)	44 (15.3)
	Widowed	11 (11.5)	40 (13.9)
Occupation Status	Government employee	20 (20.8)	83 (28.8)
	Private business	52 (54.2)	116 (40.3)
	Student	4 (4.2)	8 (2.8)
	Unemployed	3 (3.1)	11 (3.8)
	Housewife	7 (7.3)	45 (15.6)
	Farmer	10 (10.4)	25 (8.7)
Wealth Index	First Quintile	16 (16.7)	44 (15.3)
	Second Quintile	27 (28.1)	67 (23.3)
	Third Quintile	14 (14.6)	64 (22.2)
	Fourth Quintile	19 (19.8)	56 (19.4)
	Fifth Quintile	20 (20.8)	57 (19.8)
HIV result disclosure Status	Yes	74 (77.1)	218 (75.7)
	No	22 (22.9)	70 (24.3)
Missed Appointment	Yes	52 (54.2)	126 (43.8)
	No	44 (45.8)	162 (56.2)
Religion	Christian	57 (59.3)	148 (51.4)
	Muslim	39 (40.6)	140 (48.6)
Ethnicity	Oromo	48 (50.0)	163 (56.6)
	Amhara	22 (22.9)	52 (18.1)
	Kaffa	15 (15.6)	29 (10.1)
	Other <sup>a</sup>	11(11.5)	34(15.2)

Variables	Categories	Cases n(%)	Controls n(%)
Educational status	No formal education	19 (19.8)	39 (13.5)
	Primary education	43 (44.8)	148 (51.4)
	Secondary education	19 (19.8)	59 (20.5)
	College and above	15 (15.6)	42 (14.6)
Residence	Urban	77 (80.2)	186 (64.6)
	Rural	19 (19.8)	102(35.4)

a: Gurage, Dawro, and Tigre

## Substance use characteristics

Among the study participants, 35(36.5%) cases and 52(18.1%) controls had history of smoking, 24 (25.0%) cases and 69 (24.0) controls had history of alcohol use whereas 44 (45.8%) of cases and 91 (31.6%) of controls had a history of Khat use [Table 3].

Table 3 Behavioral related information of PLWHA  $\geq$  15 years, who have had a follow-up at selected public hospitals Jimma: 2004-2017

Variable	Categories	Cases n (%)	Controls n (%)
Smoking status	Yes	35 (36.5)	52 (18.1)
	No	61 (63.5)	236 (81.9)
Alcohol use	Yes	24 (25.0)	69 (24.0)
	No	72 (75.0)	219 (76.0)
Khat use	Yes	44 (45.8)	91 (31.6)
	No	52 (54.2)	197 (68.4)
Frequency of using tobacco products	Never	61 (63.5)	236 (81.9)
	Daily	13 (13.5)	16 (5.6)
	Once/twice a Week	22 (22.9)	36 (12.5)
Frequency of using Alcoholic beverages	Never	72 (75.0)	220 (76.4)
	Daily	8 (8.3)	46 (16.0)
	Once/twice a Week	16 (16.7)	22 (7.6)
Frequency of using Khat	Never	52 (54.2)	197 (68.4)
	Daily	40 (41.7)	57 (19.8)
	Once/twice a Week	4 (4.1)	34 (11.8)

## Adherence and Antiretroviral drug-related characteristics

The study revealed that 70 (72.9%) and 261(90.6%) cases and controls had good baseline adherence to ARVs, respectively. Majority 90(93.8%) cases and 282(97.9%) controls have good current adherence to ARVs. Among the cases, 30 (31.3%) and 38 (39.6%) of them used TDF-3TC-EFV and AZT-3TC-NVP initial ARV regimen, respectively. Whereas 154(53.5%) and 35(12.2%) of controls used TDF-3TC-EFV and AZT-3TC-NVP initial ARV regimen, respectively. 61(63.5%) cases and 132(45.8%) of controls were on HAART for more than the median duration of 73 months [Table 4].

Table 4 Antiretroviral medication-related information of PLWHA  $\geq$  15 years, who have had a follow-up at selected public hospitals Jimma: 2004-2017

Variable	Categories	Cases n (%)	Controls n (%)
Baseline adherence to treatment	Good	70 (72.9)	261 (90.6)
	Fair/poor	26 (27.1)	27 (9.4)
Current adherence to treatment	Good	90 (93.8)	282 (97.9)
	Fair/poor	6 (6.3)	6 (2.1)
Prior ARV exposure	Yes	32 (33.3)	20 (6.9)
	No	64 (66.7)	268 (93.1)
Initial ARV regimen	TDF-3TC-EFV	30(31.3)	154(53.5)
	D4T-3TC-NVP	13(13.5)	52(18.1)
	AZT-3TC-NVP	38(39.6)	35(12.2)
	D4T-3TC-EFV	4(4.2)	21(7.3)
	AZT-3TC-EFV	7(7.3)	13(4.5)
	TDF-3TC-NVP	4(4.2)	13(4.5)
Duration on HAART	Median	84.5(60-103.8)	67.5(35-108)
	<73months	35(36.5)	156(54.2)
	≥73months	61(63.5)	132(45.8)

### Clinical Characteristics of the Study Participants

Regarding opportunistic infections, 52(54.2%) cases and 174(60.4%) controls had history of baseline opportunistic infections. 53(55.2%) of cases and 77(26.7%) of controls had TB coinfection at the time of ART initiation. Concerning BMI, 45(46.9%) of the cases had baseline median BMI < 19.3kg/m<sup>2</sup>, whereas 147 (51.0%) of controls had baseline median BMI < 19.3kg/m<sup>2</sup> [Table 5].

Table 5 Clinical related information of PLWHA ≥ 15 years, who have had a follow-up at selected public hospitals Jimma: 2004-2017

Variable	Categories	Cases n (%)	Controls n (%)
HIV testing entry	VCT	41 (42.7)	114 (39.6)
	PITC	19 (19.8)	62 (21.5)
	PMTCT	7 (7.3)	19 (6.6)
	Other <sup>b</sup>	29 (30.2)	93 (32.3)
Baseline opportunistic infection	Yes	52 (54.2)	174 (60.4)
	No	44 (45.8)	114 (39.6)
Current opportunistic infection	Yes	11 (11.5)	24 (8.3)
	No	85 (88.5)	264 (91.7)
TB coinfection at ART initiation	Yes	53 (55.2)	77 (26.7)
	No	43 (44.8)	211 (73.3)
Baseline functional status	Working	64 (66.6)	215 (74.7)
	Ambulatory	26 (27.1)	62 (21.5)
	Bed ridden	6 (6.3)	11 (3.8)
Current functional status	Working	92 (95.8)	278 (96.5)
	Ambulatory	3 (3.1)	9 (3.1)
	Bed ridden	1 (1.0)	1 (0.3)
Baseline BMI kg/m <sup>2</sup>	Median	18.9(IQR 16.0-21.5)	19.4(IQR 17.6-21.8)
	<19.3kg/m <sup>2</sup>	45(46.9%)	147(51.0%)
	≥19.3kg/m <sup>2</sup>	51(53.1%)	141(49.0%)
Current BMI kg/m <sup>2</sup>	Median	21.6(IQR18.7- 23.6)	21.4(IQR19.4- 24.0)
	<21.5kg/m <sup>2</sup>	51(53.1%)	142(49.3%)
	≥21.5kg/m <sup>2</sup>	45(46.9%)	146(50.7%)

Notes: <sup>b</sup> on campaign session

### Haemoglobin Profile of the Study Participants

In this study 41(42.7%) of cases and 91(31.6%) of controls had baseline median Hemoglobin level less than 12g/dl (IQR:11-12.8) and 12g/dl (IQR:11.2-13.1), respectively whereas 55 (57.3%) cases and 197 (68.4) had baseline median Hemoglobin level greater than or equal 12(IQR11-12.8) and 12(IQR11.2-13.1) respectively [Table 6].

Table 6 Haemoglobin Profile of PLWHA ≥ 15 years, who have had a follow-up at selected public hospitals Jimma: 2004-2017

Variable	Categories	Cases n (%)	Controls n (%)
Baseline hemoglobin status(median)	Median	12(IQR11-12.8)	12(IQR11.2-13.1)
	≥12g/dl	55 (57.3)	197 (68.4)
	<12g/dl	41 (42.7)	91 (31.6)
Current hemoglobin status (median)	Median	13(IQR 12.4-14.1)	13(IQR 12.5-14.1)
	≥13g/dl	56 (58.3)	200 (69.4)
	<13g/dl	40 (41.7)	88 (30.6)

## Treatment support Characteristics of Study Participants

Regarding treatment support, 47(49%) of cases and 182(63.2%) of controls had history of treatment support, of whom 21(21.9%) of cases and 80(27.8%) of controls had emotional support; 22(22.9%) of cases and 76(26.4%) of controls had physical support; 23(24.0%) of cases and 118(41.0%) of controls have got the supports from their family whereas 19(19.8%) of cases and 39 (13.5%) of controls obtained the supports from governmental organizations.

## Determinant Factors Associated with First-line ART Treatment failure

The bivariate logistic regression analysis indicated that age, sex, marital status, occupation status, missed follow up appointment, residence, smoking, Khat use, baseline, and current adherence status, prior exposure to ARV dose, AZT and EFV based medication, longer duration on HAART, baseline functional status, TB coinfection and baseline, and current hemoglobin level were associated with first-line ART failure. However, multivariate logistic regression analysis revealed that being urban resident, smoking, Khat use, poor baseline adherence status, TB coinfection at the time of ART initiation, prior exposure to ARV, taking AZT based first-line ARV regimen, median duration on HAART for  $\geq 73$  months were found to be significantly associated with first-line ART treatment failure. However: age, sex, marital status, occupational status, missed follow up appointment, current adherence status, EFV based medication, baseline, and current hemoglobin level were not significantly associated with first-line ART treatment failure.

ART users who resided urban were two times more likely to develop first-line ART failure than those reside rural (AOR:2.2; 95% CI:1.1, 3.6). ART users who had a smoking history were 5.9 times more likely to develop first-line ART failure than those who did not (AOR:5.9; 95% CI: 3.2,10.8). ART users who had history of Khat use were two times more likely to develop first-line ART failure than those who did not (AOR: 2.2; 95% CI:1.3, 3.7).

ART users with poor medication adherence were two times more likely to develop first-line ART failure than patients with good adherence (AOR:2.2;95%CI:1.1,4.5). ART users with baseline TB coinfection were 3.9 times as likely to develop first-line ART treatment failure as those not coinfecting (AOR: 3.9; 95% CI: 2.2, 6.8). ART users with prior exposure to ART were 3.8 times more likely to develop first-line ART failure than those non-exposed (AOR:3.8; 95% CI:1.7, 8.1). ART users with AZT based medication were 4.8 times as likely to develop first-line ART failure as ART users with TDF based medication (AOR:4.8; 95% CI: 2.5, 8.0). ART users stayed on ART for a median duration  $\geq 73$  months were two times more likely to develop first-line ART failure than those who took treatment for  $<73$  months (AOR:1.9; 95% CI: 1.2, 3.3) [Error!

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Table 7 Determinants of First-line ART failure among PLWHA > 15 years, who had a follow-up at selected public hospitals Jimma: 2004-2017

Variables	First-line ART Failure		Bivariate Analysis		Multivariate Analysis	
	Cases n (%)	Controls n (%)	P-value	COR (95%CI)	P-value	AOR (95%CI)
<b>Baseline Median Age</b>	<b>28(IQR 25-32)</b>	<b>27(IQR 23-33)</b>				
>=28 years	55 (57.3)	139 (48.3)	0.126	1.4(0.9,2.3)	-	-
<28 years	41 (42.7)	149 (51.7)	1	1	1	1
<b>Sex</b>						
Male	43 (44.8)	107 (37.2)	0.185	1.3 (0.9,2.2)	-	-
Female	53 (55.2)	181 (62.8)	1	1	1	1
<b>Marital status</b>						
Married	57(59.4)	174 (60.4)	1	1	1	1
Single	6 (6.3)	30 (10.4)	0.296	1.6 (0.2,1.5)	-	-
Divorced	22 (22.9)	44 (15.3)	0.162	0.7 (0.8,2.8)	-	-
Widowed	11 (11.5)	40 (13.9)	0.639	1.2 (0.4,1.7)	-	-
<b>Occupation status</b>						
Government employee	20 (20.8)	83 (28.8)	1	1	1	1
Private business	52 (54.2)	116 (40.3)	0.038	0.5(1.0,3.4)	-	-
Unemployed	24(25)	89(30.9)	0.358	0.9(0.3,1.6)	-	-
<b>Wealth Index status**</b>						
Fifth quintile	20 (20.8)	57 (19.8)	1	1	1	1
Fourth quintile	19 (19.8)	56 (19.4)	0.928	1.0(0.5,2.0)		
Third quintile	14 (14.6)	64 (22.2)	0.229	1.6(0.3,1.4)		
Second quintile	27 (28.1)	67 (23.3)	0.689	0.9(0.6,2.3)		
First quintile	16 (16.7)	44 (15.3)	0.927	1.0(0.5, 2.2)		
<b>HIV result disclosure Status**</b>						
Yes	74 (77.1)	218 (75.7)	1	1	1	1
No	22 (22.9)	70 (24.3)	0.783	1.1(0.6,1.9)		

Variables	First-line ART Failure		Bivariate Analysis		Multivariate Analysis	
	Cases n (%)	Controls n (%)	P-value	COR (95%CI)	P-value	AOR (95%CI)
<b>Missed follow up appointment</b>						
Yes	52 (54.2)	126 (43.8)	0.077	1.5(0.9, 2.4)	-	-
No	44 (45.8)	162 (56.2)	1	1	1	1
<b>Educational status**</b>						
No formal education	19 (19.8)	39 (13.5)	0.450	1.3(0.6,3.0)		
Primary education	43 (44.8)	148 (51.4)	0.552	0.8(0.4,1.6)		
Secondary education	19 (19.8)	59 (20.5)	0.796	0.9(0.4,1.0)		
College and above	15 (15.6)	42 (14.6)	1	1	1	1
<b>Residence*</b>						
Urban	77 (80.2)	186 (64.6)	0.004	2.2(1.3,3.9)	0.010	2.2 (1.1, 3.6)
Rural	19 (19.8)	102 (35.4)	1	1	1	1
<b>Smoking*</b>						
Yes	35 (36.5)	52 (18.1)	0.000	2.6(1.6,4.4)	0.000	5.9(3.2,10.8)
No	61 (63.5)	236 (81.9)	1	1	1	1
<b>Alcohol use**</b>						
Yes	24 (25.0)	69 (24.0)	0.837	1.1(0.6,1.8)	-	-
No	72 (75.0)	219 (76.0)	1	1	1	1
<b>Khat chewing*</b>						
Yes	44 (45.8)	91 (31.6)	0.011	1.8(1.1,2.9)	0.002	2.2(1.3,3.7)
No	52 (54.2)	197 (68.4)	1	1	1	1

Variables	First-line ART Failure		Bivariate Analysis		Multivariate Analysis	
	Cases n (%)	Controls n (%)	P-value	COR (95%CI)	P-value	AOR (95%CI)
<b>Baseline adherence status*</b>						
Fair/poor	26 (27.1)	27 (9.4)	0.000	3.6(1.0,6.5)	0.037	2.2(1.1,4.5)
Good	70 (72.9)	261 (90.6)	1	1	1	1
<b>Current adherence to treatment</b>						
Fair/poor	6 (6.3)	6 (2.1)	0.042	3.1(0.9,9.9)	-	-
Good	90 (93.8)	282 (97.9)	1	1	1	1
<b>Prior ARV exposure*</b>						
Yes	32 (33.3)	20 (6.9)	0.000	6.7(3.6,12.5)	0.001	3.8(1.7,8.1)
No	64 (66.7)	268 (93.1)				
<b>Initial first-line ARV regimen (TDF, D4T, AZT) based*</b>						
AZT based	45(46.9)	48(16.7)	0.000	4.6(2.7,7.0)	0.000	4.8(2.5,8.0)
D4T based	17(17.7)	73(25.3)	0.682	1.14(0.6,2.2)	0.793	0.9(0.4,1.9)
TDF based	34(35.4)	167(58)	1	1	1	1
<b>Initial first line ARV regimen (EFV, NVP) based</b>						
NVP based	55(57.3)	100(34.7)	0.000	2.5(1.6,4.0)	-	-
EFV based	41(42.7)	188(65.3)	1	1	1	1
<b>Duration on HAART (median)*</b>						
>=73 months	61(63.5)	132(45.8)	0.003	2.1(1.3,3.3)	0.009	1.9(1.2,3.3)
<73 months	35(36.5)	156(54.2)	1	1	1	1
<b>HIV test entry**</b>						
PITC	19 (19.8)	62 (21.5)	0.574	0.8(0.4,1.6)		
PMTCT	7 (7.3)	19 (6.6)	0.902	1.0(0.4,2.7)		
Other <sup>b</sup>	29 (30.2)	93 (32.3)	0.594	0.9(0.5,1.5)		
VCT	41 (42.7)	114 (39.6)	1	1	1	1

Variables	First-line ART Failure		Bivariate Analysis		Multivariate Analysis	
	Cases n (%)	Controls n (%)	P-value	COR (95%CI)	P-value	AOR (95%CI)
<b>Baseline functional status</b>						
Working	64 (66.6)	215 (74.7)	1	1	1	1
Ambulatory	26 (27.1)	62 (21.5)	0.189	1.4(0.8,2.5)	-	-
Bed ridden	6 (6.3)	11 (3.8)	0.338	1.7(0.5,5.3)	-	-
<b>Current functional status**</b>						
Working	92 (95.8)	278 (96.5)	1	1	1	1
Ambulatory	3 (3.1)	9 (3.1)	0.789	0.8(0.2,3.2)		
Bed ridden	1 (1.0)	1 (0.3)	0.665	1.9(0.1,38.1)		
<b>TB coinfection at baseline*</b>						
Yes	53 (55.2)	77 (26.7)	0.000	3.4(2.0,5.5)	0.000	3.9(2.2,6.8)
No	43 (44.8)	211 (73.3)	1	1	1	1
<b>Baseline opportunistic infection**</b>						
No	44 (45.8)	114 (39.6)	1	1	1	1
Yes	52 (54.2)	174 (60.4)	0.283	1.2(0.8, 2.1)		
<b>Current opportunistic infection**</b>						
Yes	11 (11.5)	24 (8.3)	0.358	1.4(0.7,3.0)		
No	85 (88.5)	264 (91.7)	1	1	1	1
<b>Baseline BMI kg/m<sup>2</sup> (median)**</b>						
<b>18.9(IQR 16.0-21.5)</b>	<b>19.4(IQR 17.6- 21.8)</b>					
$\geq 19.26\text{kg/m}^2$	51(53.1)	141(49.0)	1	1	1	1
$< 19.26\text{kg/m}^2$	45(46.9)	147(51.0)	0.480	1.1(0.7,1.9)	-	-
<b>Current BMI kg/m<sup>2</sup> (median)**</b>						
<b>21.6(IQR18.7-23.6)</b>	<b>21.4(IQR19.4-24.0)</b>					
$<21.5\text{kg/m}^2$	51(53.1%)	142(49.3%)	0.517	1.2(0.7,1.8)		
$\geq21.5\text{kg/m}^2$	45(46.9%)	146(50.7%)	1	1	1	1

Variables	First-line ART Failure		Bivariate Analysis		Multivariate Analysis	
	Cases n (%)	Controls n (%)	P-value	COR (95%CI)	P-value	AOR (95%CI)
<b>Baseline hemoglobin status (median)</b>	<b>12(IQR11-12.75)</b>	<b>12(IQR11.23-13.08)</b>				
>=12g/dl	55 (57.3)	197 (68.4)		1	1	1
<12g/dl	41 (42.7)	91 (31.6)	0.047	0.6(0.4, 1.0)	-	-
<b>Current haemoglobin status (median)</b>	<b>13(IQR 12.4-14.1)</b>	<b>13.1(IQR 12.5-14.1)</b>				
>=13.1g/dl	56 (58.3)	200 (69.4)	0.046	0.6(0.4, 1.0)	-	-
<13.1g/dl	40 (41.7)	88 (30.6)	1	1	1	1

**Notes:** \*Significant at a p-value of <0.05 \*\*variables which are not candidate by Bivariate logistic regression analysis **AOR:** adjusted odds ratio

## Discussion

This study was identified determinants of first-line ART treatment failure in public hospitals and disclosed that being urban resident, smoking, Khat use, poor adherence, TB co-infection, prior exposure to ART, AZT based medication use and longer duration on HAART enrollment were ascertained to have increased odds of first-line ART failure. In this study, ART users who resided urban appear to have higher risk of first-line ART failure than those reside rurally. Comparable with a study done in Cameroon which showed that first-line ART treatment failure was less likely to occur among patients residing far from the treatment centers as compared with near the treatment center [40]. This might be due to the good adherence status of patients residing in rural than urban as evidenced by our finding; other assumption could be urban inhabitants might face more HIV-related stigma and discrimination which resulted in poor adherence and failure to take their medication.

With regard to substances use, the present study showed that ART users with a history of smoking were 5.9 times increase the odds of developing first-line ART failure than those who did not; ART users with history of Khat use were two times more likely to develop first-line ART failure than those who did not. This finding was in tandem with the study findings from Ethiopia [33] and Vietnam [19]. This might be due to the fact that using ARV drugs and substances simultaneously, would prone to mental health problems resulted in poor adherence characterized by failure to take medication properly; moreover interrupting the medication which leads finally to first-line ART treatment failure [34].

ART users with poor medication adherence were two times higher risk of developing first-line ART failure than ART users with good adherence. In line with findings conducted in Ethiopia [8,14,35,41], South Africa [13], Tanzania[12], Rwanda [23]and Kenya [31]. Possibly this might be due to the reality that poor adherence can predispose patients to take medications improperly; moreover, interrupt the therapy and hence allow more viral replication which in turn increases infection of more CD4 cells and eventual

depletion of their number and hastening to the advanced stage of HIV finally resulted in first-line ART treatment failure.

ART users with TB co-infection appear to have 3.9 times increased risk of developing first-line ART failure than those who did not have TB. Comparable with findings reported from Ethiopia [30,41] and Nigeria [28]. This might be due to the fact that TB infection impairs cellular immune responses through Tuberculosis-induced apoptosis of CD4 cells which subsequently leads to depletion of CD4 cells and resulting in first-line ART treatment failure [16].

ART users with a history of exposure to any type of ARV regimen prior to ART initiation appear to have 3.8 times higher risk of developing first-line ART treatment failure than those who did not expose. In tandem with the findings from South Africa [13,22] and Peru [24]. This might be due to poor adherence to ARVs because of the drug's adverse effect [42]. Patients with AZT based medication users have 4.8 times increase the odds of developing first-line ART failure than those with TDF based medication users. Comparable with the study findings from Tanzania [29] and Kenya [31]. This might be due to the fact that AZT induces more adverse effects including severe anemia, nausea, and vomiting that might contribute to reduced treatment adherence [31].

ART users, who were on first-line ART for longer duration (more than median duration of 73 months) appear to have higher risk of developing first-line ART failure than those who stayed lower duration (less than median duration of 73 months). Comparable with study findings from Ethiopia [35] and Swaziland [26]. This might be due to the fact that being on HAART for longer duration increases the probability of experiencing poor adherence and drug interruption which might be resulted in treatment failure [35]. However, our finding contradicts with study finding from Woldia hospital Ethiopia, which revealed that first-line ART failure was less likely occurred among PLWHA who were on ART for a longer duration (mean duration on ART were 48.4 and 76.5 months for cases and controls, respectively) [3]. This might be due to the difference between baseline characteristics of the study participants.

A study conducted in Ethiopia revealed that age less than 35 years [35] and older age above 40 years [43] were significant factors for first-line ART failure however in our study age was not found to be significantly associated with first-line ART failure. The study finding from Ethiopia showed that ART users who are male were more likely experience first-line ART treatment failure as compared to females [8] similar study from Uganda identified that virologic suppression was more likely successful among female patients when compared to male patients [44]. However in our study sex was not found to be significantly associated with first-line ART failure. But our study was supported by findings from Ethiopia and Tanzania which concluded that the odds of first-line ART treatment failure were not associated with age and sex [3,11].

Being widowed marital status, unemployed occupational status, missed follow up appointment and hemoglobin level were significantly associated with first-line ART treatment failure as reported from Ethiopia [3], Uganda [44], Tanzania [29] and Australia [45]. However, in our study none of these factors were found to be significantly associated with first-line ART failure.

## Study limitations

The present study has some limitations; this study has made use of secondary data where measuring the adherence status of the patients is based on health care providers' assessment, which is inadequate to detect poor adherence even though this method is often in clinical practice in the Ethiopian context. Again, virologic, immunologic or clinical methods were used for the diagnosis of first-line ART treatment failure; however, measuring treatment failure with immunologic or clinical have poor sensitivity and specificity to detect first-line ART treatment failure. Finally, as a case-control study, this study might face recall bias regarding the information given by the study participants

## Conclusion

Finally, the study revealed that being urban resident, smoking, Khat chewing, poor baseline adherence, TB coinfection, exposed to any type of ARV prior to ART initiation, taking AZT based initial first-line ARV and 73 months and more duration on HAART were identified to be the independent determinant factors of first-line ART treatment failure.

Health workers need to dedicate time with every patient to provide enhanced adherence counseling to improve adherence of patients towards ARV medication particularly for PLWHA who are urban residents, smokers, Khat chewers and those who stayed on HAART for a longer duration. The focus should be given on early screening and management of tuberculosis and other opportunistic infection among PLWHA. Monitoring and follow up of adherence and ensuring proper use of ARVs is important to reduce failure of the first-line ART among the PLWHA who take ARVs for PEP. Physicians and other health workers should have strengthened monitoring and evaluating the adverse effects of ARVs and decide changing medications when it is mandatory. The findings of this study indicate the need for more dedication and effort from both health care providers and clients to act on the determinants so as to sustain the long-term efficacy of HAART and hence, achieving the ambitious target of 2030.

## Abbreviations

**ART:** Antiretroviral Therapy; **BMI:** Body Mass Index; **D4T:** Stavudine; **IQR:** Inter Quartile Range; **PLWHA:** People Living with HIV/AIDS; **PMTCT:** Prevention of Mother-to-Child Transmission **SSA:** Sub-Saharan Africa; **TB:** Tuberculosis; **3TC:** Lamivudine; **AIDS:** Acquired Immune Deficiency Syndrome; **AOR:** Adjusted Odds Ratio; **ARV:** Antiretroviral; **AZT/ZDV:** Zidovudine; **CI:** Confidence Interval; **EFV:** Efavirenz; **HAART:** Highly Active Antiretroviral Therapy; **HIV:** Human Immunodeficiency Virus; **NNRTI:** Non-Nucleoside Reverse-Transcriptase Inhibitor **NRTI:** Nucleoside Reverse-Transcriptase Inhibitor; **NVP:** Nevirapine **PEP:** Post-Exposure Prophylaxis; **TDF:** Tenofovir Disoproxil Fumarate; **UNAIDS:** Joint United Nations Program on HIV/AIDS; **WHO:** World Health Organization

## Declarations

## Ethics approval and consent to participate

Ethical approval was obtained from Jimma University Institute of Health Ethical Review Committee. Written informed consent was obtained from each study participant before conducting the interviews. The confidentiality of information obtained from each study participant was ensured through anonymity. The findings of the study are communicated in an aggregated form where individual information cannot be disclosed in any way.

## Consent for publication

Not applicable

## Availability of data and material

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

## Competing interests

The authors declare that they have no competing interests

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## Authors' contributions'

**ABA, ANT, LSD, and TS:** Involved in the inception, design, data acquisition, analysis, and interpretation, and wrote the manuscript. **EKG and TBL:** Participated in design, data acquisition and analysis, administrative matters and reviewing the manuscript. **MG and DA:** Participated in data acquisition, data management, and analysis as well as critically reviewing the manuscript.

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