INCIDENCE AND PREDICTORS OF ART TREATMENT FAILURE AMONG ADULTS LIVING WITH HIV AIDS IN WEST ARSI ZONE SOUTH ETHIOPIA

A Research Paper

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Declaration of the Paper:

We affirm that this research paper is our work result and it was not addressed previously in the study area. For assurance, we confirm with our signature.

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Abstract

Background: Human Immunodefciency Virus (HIV) treatment failure has become highly prevalent in sub Saharan Africa (SSA). Despite the extensive scale-up of antiretroviral therapy (ART) treatment program, treatment failure has become an emerging problem in developing countries including Ethiopia

Objectives: To estimate the incidence of ART treatment failure and its predictors among HIV positive adult patients on antiretroviral Therapy (ART) in West Arsi zone South Ethiopia

Methods: A facility based retrospective cohort study was conducted among 428 HIV positive adult patients on ART for at least six months from January 1, 2014 to January 1, 2020. ART follow up form and patient charts were used as a source of data. Outcome of the study is treatment failure. Descriptive statistics was used to present socio-demographic and clinical characteristics. An incidence rate was computed using new cases of treatment failure as a numerator and person time of observations as a denominator. Both bivariable and multivariable Cox proportional hazards models was used to identify predictors of ART treatment failure. Variables which have a 95% confidence interval for hazard ratio (HR) without including one were considered as to be significant predictors of treatment failure.

Result: The mean age of the study participants is 33.7 (SD ± 9.3). The incidence of treatment failures was 8.9 per 1000 person years of retrospective follow up. The highest rate of treatment failure occurred between 12 and 24 months. Those patients who had fair and poor ART adherence were six times more likely to experience treatment failure as compared to patients with good adherence [AHR =6.05; 95%CI: (1.4 - 25.5)]. Additionally, TB co-infected patients at initiation of ART were 8.89 more likely to encounter treatment failure compared to their counterparts [AHR =8.89; 95%CI: (2.11 - 37.44)].

Conclusion: Incidence of treatment failure among adult HIV positive on ART in West Arsi zone is high. The highest rate of treatment failure occurred the early months of ART initiation. The

main factors contributing to high incidence of treatment failure in the study setting are being in a fair and poor adherence level and TB co-infection at ART initiation. Special attention should be given during the early months of ART initiation. Strengthening adherence support and early screening of all TB suspected patients for HIV should be given attention. ART care service providers should strengthen the adherence counselling and support for the clients.

Key words: Treatment, failure, incidence, HIV, adults, ART, West, Arsi

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Abbreviations/ Acronyms

AIDS	Acquired Immune Deficiency Syndrome
ART	Antiretroviral Therapy

ARV	Antiretroviral
EPHI	Ethiopian Public Health Institute
FHAPCO	Federal HIV/AIDS Prevention and Control Office
FMOH	Federal Ministry of Health
HIV	Human Immunodefciency Virus
HSTP	Health Sector Transformation Plan
NNRT	Non-nucleoside Reverse Transcriptase Inhibitor
NRT	Nucleoside Analogue Reverse Transcriptase Inhibitor
NVP	Nevirapine
OIs	Opportunistic Infections
PI	Protease Inhibitor
PLHIV	People living with HIV
SPSS	Statistical Package for Social Sciences
TB	Tuberculosis
TDF	Tenofovir
UNAIDS	The Joint United Nations Program on HIV/AIDS
VL	Viral Load
WHO	World Health Organization

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1. Introduction

1.1. background

The 2018 Federal Ministry of Health (FMOH) National Consolidated Guidelines for Comprehensive Human Immunodefciency Virus (HIV) Prevention, Care and Treatment defines virologic failure (VL) as viral load above 1000 copies/ml based on two consecutive viral load measurements in 3 months, with enhanced adherence support following the first viral load test (FMOH, 2018). CD4 count at or below 250 cells/mm3 following clinical failure or Persistent CD4 levels below 100 cells/mm3 indicates immunological failure. New or recurrent clinical event indicating severe immune defciency (WHO clinical stage 4 condition and certain WHO clinical stage 3 conditions (pulmonary Tuberculosis and severe bacterial infections) may also indicate treatment failure) after 6 months of effective treatment (FMOH, 2018).

World Health Organization (WHO) report indicated the effectiveness of Antiretroviral Therapy (ART) in reducing Human Immune Deficiency Virus (HIV) related morbidity and mortality worldwide. With more people living with HIV receiving ART and improved early detection of failure to suppress viral loads through monitoring in low- and middle-income countries, many people are anticipated to experience first line treatment failure and need to switch to second-line and subsequent ART regimens (WHO, 2018).

Antiretroviral treatment began in 2003 and free ART was launched in Ethiopia in 2005 (FMOH, 2017). An estimated 738,976 people are currently living with HIV and all of them require antiretroviral treatment (ART) however only 426,000 are currently taking Antiretroviral (ARV) (FMOH, 2017). In Ethiopia as of May 2018, 79 percent of People living with HIV (PLHIV) knew their status; 71 percent of eligible people living with HIV (PLHIV) are on ART (FHAPCO,2018).

According to Ethiopian Public Health institute (EPHI) HIV impact assessment report, prevalence of Viral Load Suppression among HIV-positive adults ages 15-64 years in urban Ethiopia is 70.1%: One of an ambitious treatment target to help end the AIDS epidemic is to achieve 90% of all people receiving ART will have viral suppression by 2020 (EPHI, 2018). To achieve this goal, data on clinical, immunological and virological treatment failure is timely required (Ayale et al.,2018).

Routine viral load testing is a more sensitive and early indicator of treatment failure. Viral load testing should be done after 6 &12 months of initiating ART and every 12 months then after in order to detect treatment failure timely (FMOH, 2018). In Ethiopia, viral load determination and

guiding ART treatment with the gold standard test (viral load) has started recently because of resource limitation (Ayale et al.,2018).

The available studies mainly focus only on clinical and immunological criteria to assess treatment failure. However, these criteria's may lead to misclassification bias due to low specificity and positive predictive value (FMOH, 2018). Therefore, the purpose of our study is to assess the incidence of the ART treatment failure and its associated factors among people living with HIV AIDS in West Arsi Zone South Ethiopia

1.2. Statement of the problem

HIV has continued to be a major public health problem and 32.0 million people have died from AIDS related illness since the start of the epidemic (UNAIDS, 2019). Globally, approximately 37.9 million people were living with HIV in 2018, and 23.3 million people living with HIV were accessing ART (UNAIDS, 2019). There are about 750,000 people living with HIV/AIDS in Ethiopia (HSTP, 2015), and more than a quarter of them 26% live in Oromia regional state (FHAPCO, 2018).

The number of patients at risk of treatment failure is increasing in sub-Saharan Africa (Estill et al.,2016). About 8·7 – 25·6 million people are expected to receive antiretroviral therapy in 2020. In 2030, the estimated range of patients receiving antiretroviral therapy will remain constant, but the number of patients with treatment failure and shifting to and receiving second-line antiretroviral therapy will increase to 0·8–4·6 million (6·6 –19·6%) (Estill et al., 2016).

HIV treatment failure has become highly prevalent in sub Saharan Africa (SSA) with alarming rates during the 12–18-month period of treatment start (Edessa D, Sisay M, Asefa F 2019). The study conducted in South Africa compared the cost of first line and second line ART and reported that second-line therapy was 2.4 times more expensive per year in care than first-line therapy (Long *et al*., 2010). There is a need to maximizing the duration of stay on the first-line regimen (Alene et al.,2019). Early identification and closer clinical follow up of patients at risk of failing on ART would also improve their outcome (Gunda et al., 2019).

Only a few studies were conducted on ART treatment failure in Ethiopia and majority of them were done in Northern part of Ethiopia. The study conducted in Amhara region involved 8 public hospitals and defined ART treatment failure based only on clinical and immunological failure (Alene et al..,2019).

The studies conducted in Africa identified medication non-adherence as one of the factors mainly associated with treatment failure (Ajose et al., 2012, Edessa D, Sisay M, Asefa F 2019, Levison et al.,2012). Other relevant variables identified were younger age, WHO stage III&IV at ART initiation, duration of exposure to previous drug regimens, high viral load, low CD4 count and type of ART (Nsanzimana et al.,2019, Ajose et al., 2012, Edessa D, Sisay M, Asefa F 2019, Levison et al.,2012, Gunda et al., 2019).

Although few studies have been conducted in other sub-Saharan countries, there is dearth of literature about ART treatment failure in Oromia in general and in West Arsi Zone in particular. The incidence of the ART treatment failure and its associated factors may also be different from one area to the other in Ethiopia, further representative institutional based researches are needed across all regions of Ethiopia (Ayale et al.,2018). Thus, we aimed to assess the incidence of treatment failure and its associated factors among adult PLHIV who are on ART for at least 6 months in West Arsi Zone South Ethiopia

1.3. Significance of the study

Access to treatment options beyond first-line remains limited and expensive, therefore, it is important to identify incidence of treatment failure and the main factors contributing to it. This helps to inform planners and policy makers to address all the factors that are going to be identified by the study. Identification of predictors of treatment failure also decrease the economic burden due to expense of ART drug. It also helps as a guide for health professionals and higher health officials to alleviate the problem and to develop strategies towards decreasing rate of treatment failure. The reduction of the risk of treatment failure decreases HIV transmission, increases productivity, and enables to maximize the duration on first-line treatment. This study is used to inform policy makers and planners about the current state of first-line ART users. It will also be used as a baseline data for researchers

1.4. Objectives

1.4.1. General objective

To estimate the incidence of treatment failure and its predictors among adult HIV positive patients on ART in West Arsi Zone South Ethiopia from January 1,2014 to January 1, 2020

1.4.2. Specific objectives

To estimate the incidence rate of treatment failure among adult HIV positive patients on ART in West Arsi Zone South Ethiopia from January 1,2014 to January 1, 2020

To determine predictors of treatment failure among adult HIV positive patients on ART in West Arsi Zone South Ethiopia from January 1,2014 to January 1, 2020

1.5. Scope of the study

This study is hospital based retrospective cohort study using retrospective record and chart review. Two hospitals and two health were included in the study. It addressed incidence rate of treatment failure and factors affecting it. It used the data from patient charts, treatment logbook and computer database. It included adult HIV Positive patients on ART for at least 6 months and aged 15 and above. Selected public Hospitals and health centers giving ART management according to the national guideline (FMOH, 2018) were included. The data from January1, 2014 to January 1, 2020 were used for analysis.

1.6. Operational definition

Clinical failure

New or recurrent clinical event indicating severe immune-deficiency (WHO clinical stage 4 condition and certain WHO clinical stage 3 conditions (pulmonary TB and severe bacterial infections) after 6 months of effective treatment (FMOH, 2018).

Immunological failure

CD4 count at or below 250 cells/mm3 following clinical failure or Persistent CD4 levels below 100 cells/mm3(at least two consecutive CD4 cell count in a row is less than 100 cells/mm3) (Alene et al.,2019, FMOH, 2018)

Virologic failure

Viral load above 1000 copies/ml based on two consecutive viral load measurements in 3 months, with enhanced adherence support following the first viral load test (FMOH, 2018)

Treatment failure: Treatment failure was classified retrospectively from what was recorded by clinicians in the patient's clinical charts based on the above three definitions (Haile et al.,2016).

Lost-to-follow-up refers clients stopped ART follow-up for 3 months or longer due to different reasons (Alene et al.,2019).

Censored

Patients on ART who were lost-to-follow-up, transferred-out, and died were considered as censored (Alene et al.,2019). Patients who didn't experience treatment failure criteria in the above-mentioned follow-up period were also considered as censored (Alene et al.,2019).

ART adherence was measured by considering patient's clinical compliance in scheduled visits. Patients adherence was classified as poor, fair, and good if their level of adherence was < 85, 85–95%, and > = 95% respectively (Alene et al.,2019).

Regimen modification will be considered when patients had regimen modification at least once in the follow-up period (Alene et al.,2019).

Adult and adolescents: those >= 15 years

Viral non-suppression: An elevated viral load (VL) Ribo Nuclic Acid (RNA) copies of >1000 copies/ml in plasma in a patient who has been on ART for at least six months **(**Desta et al.,2019).

2. Literature review

2.1. **Treatment failure rate**

The study conducted in minority area in China among 5157 PLWH showed that 2156 (41.81%) PLWH showed virological failure on ART (Yuan et al.,2020). HIV treatment failure has become highly prevalent in SSA with alarming rates during the 12–18-month period of treatment start (Edessa D, Sisay M, Asefa F 2019). However, the study conducted in South Africa reported moderate virological failure during the first 24 months of ART (Levison et al.,2012). In Ethiopia, the national routine viral load program data from Ethiopian Public Health Institute (EPHI) showed that 40 out of 198 (20%) patients had virologic failure i.e. viral load of >1000copies/ml (FMOH,2018).

According to the systematic review and meta-analysis study conducted in resource limited settings, the cumulative pooled proportion of adult patients failing virologically increased as the time of follow up increases sequentially and it was 21.8, 23.1, 26.7 and 38.0% at 6, 12, 24 and 36 months, respectively (Ajose et al., 2012). Another systematic review and meta-analysis study conducted in sub-Saharan Africa countries found that the pooled HIV treatment failure rate was 15.0 per 100 Person Years (95% CI: 13.0–18.0) (Edessa D, Sisay M, Asefa F 2019).

According to the retrospective follow up study conducted in Amhara Region, the median survival time of patients on ART was 92 months. This implies that half of patients didn't have treatment failure in the 92 months after starting treatment (Alene et al..,2019). However, the study conducted in South Africa identified that most individuals failed ART quickly within a mean of 10 months (Levison et al.,2012).

According to the study conducted in Amhara region (AR) the overall incidence of treatment failure was 9.86 per 100 person-years. It was high during the first and the last year of follow-up (Alene et al..,2019). About two-thirds (60.44%) of the ART clients started ART at CD4 cell count level of below 100 cells/mm3. Another similar study in North West Ethiopia reported that the probability of failure at the end of 12 and 24 months were 5.6% and 13.6%, respectively. It also reported incidence rate of failure of 61.7/1000 person years (Tsegaye AT, Wubshet M, Awoke T, et al., 2016).

A Cross-sectional study conducted using the database of Tigrai national regional state conducted among 19,525 study subjects showed that 26.39% of them had no viral suppression (Desta et al.,2019). A Retrospective cohort study which was conducted in four hospitals of Bale Zone among 4,809 adult ART clients reported the incidence rate of treatment failure to be 9.38 per 1000 person years (Haile et al.,2016).

2.1. Factors associated with treatment failure

The study conducted in China reported that variables like being males, drug injection and mother to child transmission routes, the clinical stage of AIDS, having used illicit drugs and shared the needles having ever replaced ART regimen, increased the risk of virological failure among PLWH, while higher education lever and ≥ 12 months on ART was associated with lower likelihood of virological failure (Yuan et al.,2020).

A national representative study conducted in Rwanda among 1688 patients reported the factors associated with virological failure as younger age, WHO stage III&IV at ART initiation, CD4 cell count ≤500 cells/mm3, regimen and receiving care at a health center compared to hospital settings (Nsanzimana et al.,2019)

A case control study conducted among 197 patients on ART in Tanzania has shown that those patients who failed shortly on first line ART regimen, those who were younger than 30 years were at risk of virological failure. Additionally, non-improving CD4 counts is also a potential marker of a subsequent virological failure in this subgroup of patients (Gunda et al., 2019).

According to the systematic review and meta-analysis conducted in resource limited settings, rates of virological failure are high in resource limited settings. The main factors associated with virological failure include duration of exposure to previous drug regimens and poor adherence (Ajose et al., 2012).

Another systematic review and meta-analysis study in sub-Saharan Africa identified high viral load; advanced clinical stage; and low CD4 counts, and suboptimal adherence to therapy as the factors associated with increased failure rates (Edessa D, Sisay M, Asefa F 2019).

The African Cohort Study which involved four countries and assessed the overall virologic failure indicated that being on second line treatment was one of the risk factors for virologic

failure. The findings also show that low CD4 count, missing any day of ART and history of fever in the past week remain important predictors of virologic failure (Kiweewa et al., 2019)

The study conducted in South Africa identified that medication non-adherence is an important cause of ART failure (Levison et al.,2012). The study indicated that time to virologic suppression was most rapid among patients with 91-100% adherence compared to patients with 80-90% and <80% adherence. The study also identified that most individuals failed ART quickly (e.g. within a mean of 10 months). Medication non-adherence is an important cause of ART failure (Levison et al.,2012). The study from China also reported similar relationship between medication adherence and viral suppression (Chen et al.,2018)

Retrospective cohort study which was conducted in Amhara region of Ethiopia identified that patients who didn't change regimens, who had poor ART adherence, and not taking INH had higher rate of treatment failure as compared to their counter group (Alene et al..,2019). The rate of treatment failure for patients who were under *WHO clinical stage III was also lower as compared to clients who were under WHO clinical stage I.* (Alene et al..,2019).

The study conducted in the university of Gondar referral hospital Northwest Ethiopia showed, only patients who had no formal education, primary level education and duration on ART < 6 years were a significant risk factor for treatment failure. However, initial adult regimen D4T +3TC+ EFV, AZT +3TC + NVP; AZT + 3TC +EFV and TDF +3TC +EFV were significantly protective for treatment failure (Ayale et al.,2018).

A retrospective follow-up study conducted in 2015 among 356 adult patients in North West Ethiopia reported the significant predictors of failure like: WHO clinical stage IV at switch; CD4 count <100 cells/ mm3 at switch; and weight change (Tsegaye AT, Wubshet M, Awoke T, et al., 2016).

Factors significantly associated with viral non-suppression were being male, 15–19 years of age, patients from primary hospital, WHO staging II, poor ART adherence level, fair ART adherence level, baseline CD-4 count of < 200 cells/micro liter, recent CD-4 count of < 200 cells/micro liter, regimen types: 1c (AZT-3TC-NVP), 2 h (TDF-3TC-ATV/R), and declined immunological responses after ART initiation (Desta et al.,2019). In addition to that, factors leading to viral non-suppression may vary across different settings and population groups and hence a context

specific data are critical to the implementation of corrective measures against viral non suppression (Desta et al.,2019). The retrospective cohort study conducted in bale zone in 2015 identified male ART clients, lower CD4 count (<100 m3/dl) at initiation of ART, bedridden and ambulatory patients and TB co-infected clients, patients who had developed TB after ART initiation, having other opportunistic infection during ART initiation and having fair and poor drug adherence as factors independently associated with treatment failure (Haile et al.,2016).

3. Methodology

3.1. Study area and period

A facility based retrospective cohort study was conducted using data from January 1, 2014 and January 1, 2020 in West Arsi zone South Ethiopia. Two hospitals namely, Malka Oda hospital, Shashemene referral hospital and two health centers namely Arsi Negelle and Abosto were included in this study. The selected hospitals and health centers give ART service for more than 70% of all the ART patients in the zone.

3.2. Population

3.2.1. Source population

All adult (i.e. >=15 years) people living with HIV/AIDS on ART treatment and those enrolled in selected Hospitals and health centers ART clinic were the source population

3.2.2. Study population

All adults aged 15 and above and started ART treatment between January 1, 2014 and January 1, 2020 were the study population

3.2.3. Inclusion criteria

All adults aged 15 and above who were on ART follow-up between January 1, 2014 and January 1, 2020 in the selected Public hospitals and health centers were included in the study

3.2.4. Exclusion criteria

The study excluded HIV positive individuals with incomplete baseline information of CD4 cell count and WHO clinical stage. HIV infected patients on ART for less than 6 months were also excluded.

3.3. Sample size determination

Sample size was calculated using Epi-Info STAT CALC version 7.0. The following assumption was made during the calculation: 95 % confidence interval, 80 % power, 39.7% of treatment failure among patients with good adherence, Adjusted Hazard Ratio =1.4 (Alene et al., 2019) and ratio of exposed to unexposed 1:1. By considering design effect of 1.25 for an error that may occur due to multi-center nature of the study and 10% for possibility of incompleteness, the final sample which can address both objectives were estimated to be 457 (Tab 1).

Table 1. Sample size determination for incidence of treatment failure and its associated among adult PLHIV in public hospitals of West Arsi Zone Oromia Ethiopia, 2019/20.

Factors	aHR	% of unexposed with Tx failure	Ratio	Baseline n	Design effect	Loss to follow up(incomplete info)	Final n	Reference
INH prophylaxis	1.68	27.4%	1	230	1.25	10	316	Alene et al., 2019
ART adherence	1.4	39.76	1	332	1.25	10	**457**	Alene et al., 2019

INH- Isoniazid ART- Antiretroviral Therapy AHR- adjusted hazard ratio Tx- Treatment

3.4. Sampling procedure

Two hospitals (Malka Oda and Shashemene referral) and two health centers (Abosto and Arsi Negelle) were purposively selected due to their respective large number of patient load. The number of adult patients on ART who fulfill the eligibility criteria were obtained from ART clinic of each health institution. The probability proportional to size was used to distribute the sample size to all selected hospitals and health centers based on their patient load. In such a way Shashemene Referral hospital (N=2250, n1=257), Malka Oda Hospital (N= 630, n2= 72), Arsi Negelle health center (N=545, n3 =63) and Abosto health center (N= 565, n4=65). Finally, the systematic random sampling method was used.

3.5. Data collection methods and tools

ART follow up form and patient charts were used as a source of data. Data were collected using extraction format that was developed using the Ethiopian treatment guideline format (FMOH, 2018). The format was prepared for the collection of both baseline and follow-up socio-demographic, clinical failure, immunological failure, virological failure, adherence and treatment outcome related information that are important for the assessment of treatment failure. Charts were retrieved using patient medical record numbers found in the database of health facilities. The data was collected by 8 data collectors who had training on the ART and they were recruited

from health workers working in the selected hospitals and health centers ART clinic in collaboration with ART focal persons.

3.6. Data quality management

Training was given for one day on the extraction format and objectives of the study. The extraction format was pre-tested using 20 patient charts in Adaba health center. Necessary modifications were made after pre-test. Daily supervision of data collection process was done by investigators.. Medical record number were used to access the patient charts.

3.7. Variables

3.7.1. Dependent variable

Outcome of our study is treatment failure. The study participants were managed using different treatment guidelines due to guideline updates over time. We used the already documented information by clinicians concerning the definition of treatment failure.

3.7.2. Independent variables

Socio-demographic variables (age, sex, educational status, and functional status at baseline), body mass index (BMI) at baseline, taking Isoniazid (INH) preventive therapy, opportunistic infections (OI), CD4 cell count at baseline, regimen modifications, WHO clinical stage (I-IV) at, ART adherence and type of ART regimen

3.8. Data processing and analysis

Extracted data were checked for completeness and entered into EPI-INFO version 7.0 and exported to SPSS version 21.0 software for further analysis. Descriptive statistics was used to present socio-demographic and clinical characteristics. An incidence rate was computed using new cases of treatment failure as a numerator and person time of observations as a denominator. Person-time is the sum of the amount of time contributed by study participants in the follow-up period (Alene et al.,2019). Person-time at risk was measured starting from the time of ART initiation until each patient ended the follow-up.

Both bivariate and multivariable Cox proportional hazards models was used to identify predictors of treatment failure. Hazard Ratios (HR) with 95% confidence intervals were computed and statistical significance was accepted at the 5% level ($p < 0.05$)

4. Dissemination plan

The final report will be presented to Shashemene campus and Madda Walabu University. Copies will be provided to all hospitals and health centers of West Arsi Zone. It will be disseminated through publication of the findings, in peer reviewed reputable journal and presentations on scientific conferences.

5. Ethical clearance

Ethical clearance was obtained from Madda walabu University Research Committee. Permission letter was obtained from medical directors of each hospital. Anonymity was maintained by using identity numbers of patients. All the data will be kept confidential and used only for research purpose.

6. Result

6.1. Sociodemographic characteristics

The current study included 428 adults ART clients from the hospitals and health centers of West Arsi Zone. The median age of the study participants is 32 (IQR = 27 - 40). Majority of the study participants 344 (80.4%) live in urban areas and 367(85.7%) were unemployed. About one in five of the study participants 90 (21%) had no education. Around half 212 (49.5%) of the study participants were Orthodox in religion followed by Muslim 117(27.3%). Two hundred ten (49.1%) of the study participants were married followed by 76(17.8) divorced.

Table 2. Sociodemographic characteristics of HIV positive patients on ART in West Arsi Zone, 2019/20

Variable	Frequency	Percent
Age in years		
15-24	65	15.2
25 - 34	175	40.9
35-44	121	28.3
>=45	67	15.7
Sex		
Male	178	41.6
Female	250	58.4
Marital status		
Single	71	16.6
Married	210	49.1
Divorced	76	17.8
Widowed	71	16.6
Residence		
Urban	344	80.4
Rural	84	19.6
Occupation		
Employed	61	14.3
Unemployed	367	85.7

Religion		
Muslim	117	27.3
Orthodox	212	49.5
Protestant	91	21.3
Others*	8	1.9
Educational status		
Not educated	90	21
Primary education	207	48.4
Secondary and above	89	20.8
Tertiary	42	9.8
Family size		
<=2	227	53
>2	201	47

6.2. Clinical and behavioral characteristics of adult HIV patients on ART in West Arsi Zone 2019/20

Concerning baseline functional status, 397(92.8%) of the study participants are working. More than half, 225(52.6%) are in WHO stage I, whereas 126(29.5%) of them are categorized in WHO stage III and IV. The body mass index of the study participants indicates that, 305(71.3%) are underweight and only 13(3%) of are overweight and obese. One in three adults 144(33.6%) had history of opportunistic infections (OIs). The major OIs recorded were Pulmonary Tuberculosis 59(13.8%), herpes zoster, diarrhea and other skin infections all equal 23(5.4%). Sixty-five (15.2%) and 14 (3.3%) had TB co-infection at initiation of ART and developed TB after ART initiation, respectively. Three hundred fifty-two (82.2%) disclosed their HIV status. Eighty- four (19.6%) had history of addiction.

Table 3.Clinical and behavioral characteristics of adult HIV patients on ART in West Arsi Zone 2019/20

Variable	Frequency	Percent
Baseline functional status		
Working	397	92.8

Ambulatory	28	6.5
Bedridden	3	.7
Baseline WHO stage		
WHO stage I	225	52.6
WHO stage II	77	18
WHO stage III	115	26.9
WHO stage IV	11	2.6
Baseline body mass index		
<18.5	305	71.3
18.5-24.99	110	25.7
>=25	13	3
History of OIs		
No	284	66.4
Yes	144	33.6
TB Co-infection at initiation of ART		
No	363	84.8
Yes	65	15.2
Developed TB after ART initiation		
No	414	96.7
Yes	14	3.3
Disclosure status		
No	76	17.8
Yes	352	82.2
History of addiction		
No	344	80.4
Yes	84	19.6

6.3. Drug related characteristics of HIV positive patients on ART in West Arsi Zone, 2019/20

About one third 142 (33.2%) of the study participants had taken both CPT and INH. Majority 354(82.7%) of the patients were on 1e drug regimen. Slightly less than two third 275 (64.3%) had history of drug regimen change. The major reasons for drug regimen change were new drug 182 (42.5%) and drug stock out 88 (20.6%). History of ART drug side effect was recorded in 14(3.3%). Baseline adherence level was good for 391(91.4%) of the patients.

Table 4.Drug related characteristics of HIV positive patients on ART in West Arsi Zone 2019/20

Variable	**Frequency**	**Percent**
Prophylaxis given		
CPT	**77**	18
INH	199	46.5
Both	142	33.2
Not recorded	10	2.3
ARV drug regimen		
1c	20	4.7
1d	13	3.0
1e	354	82.7
1f	3	.7
1j	38	8.9
History of drug regimen change		
Yes	275	64.3
No	153	35.7
History ART drug side effect		
Yes	14	3.3
No	414	96.7
Baseline adherence level		
Good	391	91.4

Fair	12	2.8
Poor	25	5.8

6.4. Treatment failure

Four twenty-eight (428) study participants were followed for different periods in five years produced 1011 person years of observation. During the follow up period, 9 new treatment failure cases were observed. Thus, there were 9 treatment failures per 1011 person years of observation. This means, 8.9 treatment failures per 1000 person years of retrospective follow up. All of the treatment failures occurred early after ART initiation.The highest rate of treatment failure occurred between 12 and 24 months (Fig 1.)

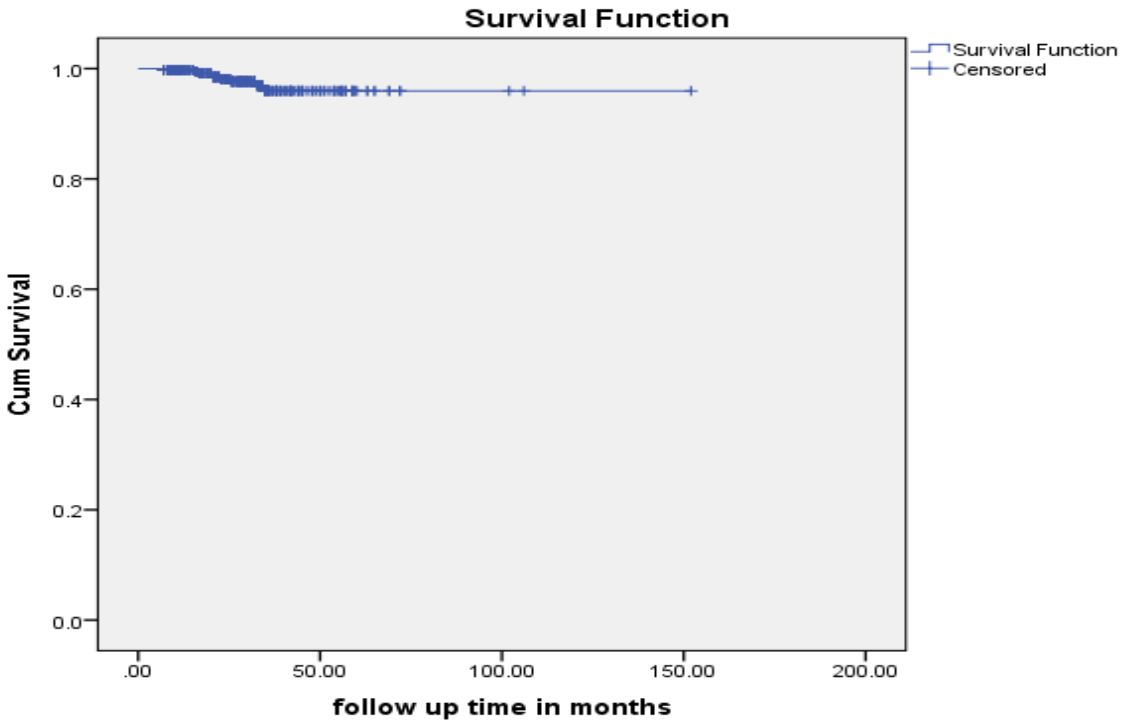

Figure 1. Kaplain meier survival estimate ART patients without treatment failure, West Arsi Oromia Ethiopia

6.5. Predictors of treatment failure

Twenty variables (20) were checked for crude association with treatment failure in bi-variable cox regression analysis and eight of them showed an association with treatment failure at p-value of 0.25. They include baseline WHO clinical stage [HR =2.56;95%CI: (1.03 – 6.37)], baseline

adherence level [HR= 7.1;95% CI: (1.69 – 29.8)], sex [HR = 2.5; 95%CI: (.59-10.5)], history of opportunistic infections [HR= 5.39; 95%CI: (1.1-26.7)], TB co-infection at initiation of ART [HR = 9.77; 95%CI: (2.33-40.9)], developed TB after ART initiation [HR =4.97; 95%CI:(.61 – 40.4)], history of ART drug side effect [HR =4.0; 95%CI:(.49- 32.5)] and baseline body mass index(undernutrition), [HR =7.3; 95%CI:(1.48 – 36.3)].

The multivariable cox regression analysis was conducted using the above eight variables and baseline functional status as a suspected confounder. Baseline functional status is found to be associated with treatment failure from previous studies. The model was done using forward stepwise (Likelihood ratio) method and showed that baseline adherence level and history of TB co-infection at initiation of ART were independently associated with treatment failure. Those patients who had fair and poor ART adherence were six times more likely to experience treatment failure as compared to patients with good adherence [AHR =6.05; 95%CI: (1.4 - 25.5)] (Figure 2).

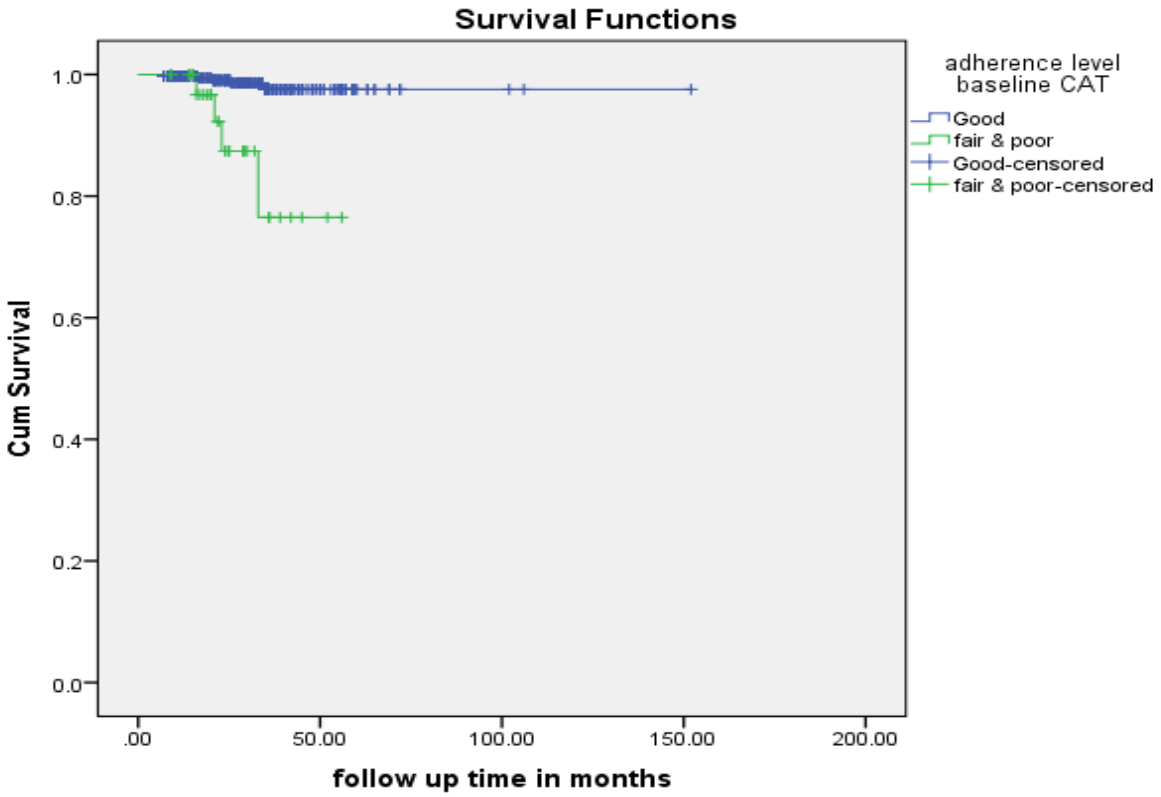

Figure 2.Kaplain Meier estimate of treatment failure based on adherence level of ART patients, West Arsi Oromia Ethiopia

TB co-infected patients at initiation of ART were 8.89 more likely to encounter treatment failure compared to their counterparts [AHR =8.89; 95%CI: (2.11 - 37.44)] (Table 5).

Table 5.Factors associated with treatment failure among patients on ART in West Arsi Zone, 2019/20

Variable	Treatment failure	
	Unadjusted HR (95% CI)	Adjusted HR (95% CI)
Sex		
Male	2.5(.59 - 10.5)	-
Female	Reference	
Baseline WHO stage		
WHO stage I & II	Reference	
WHO stage III & IV	2.56 (1.03 – 6.37)	-
History of OIs		
Yes	5.39 (1.1 - 26.7)	
No	Reference	
Adherence level		
Good	Reference	
Fair and poor	7.1 (1.69 – 29.8)	6.05 (1.4 - 25.5)
TB co-infection at ART initiation		
Yes	9.77 (2.33 - 40.9)	8.89 (2.11 - 37.44)
No	Reference	
Developed TB after ART initiation		
Yes	4.97(.61 – 40.4)	
No	Reference	
History of ART drug side effect		
Yes	4.0 (.49- 32.5)	
No	Reference	
Baseline body mass index (BMI)		
18.5 – 24.99	Reference	
<18.5	7.3 (1.48 – 36.3)	-
>=25	-	

7. Discussion

The current study aimed to assess the incidence of treatment failure and its predictors among adult HIV positive patients on ART in West Arsi Zone. The incidence of treatment failure was found to be 8.9 per 1000 person years of follow up. The main predictors of treatment failure identified were adherence level of the patients and TB co-infection at ART initiation. This study revealed that the incidence of treatment failure is high in the study area and needs serious attention. Additionally, strengthening adherence support and early screening of all TB suspected patients for HIV should be given attention.

The current study reported incidence rate of treatment failure to 8.9 per 1000 person years of follow up. This finding is similar to the retrospective cohort study which was conducted in Bale zone health facilities and reported the incidence rate of treatment failure to be 9.38 (95% CI: 7.79–11.30) per 1000 person years (Haile et al.,2016). The study conducted in Amhara region (AR) the overall incidence of treatment failure was 9.86 per 100 person-years up (Alene et al..,2019). The study conducted in Amhara reported low incidence compared to our study and the one conducted in Bale zone. The justification could be the geographical difference, time difference and criteria use to define treatment failure. Another cross-sectional study conducted using the database of Tigrai national regional state among 19,525 study subjects showed that 26.39% of them had no viral suppression **(**Desta et al.,2019).

The main factors found to be associated with treatment failure are adherence level of the patients and presence of TB co-infection at initiation of ART. Those ART patients with fair and poor drug adherence were more likely to encounter treatment failure as compared to those patients with good drug adherence. Similar findings were reported in Ethiopia and in Africa (Haile et al.,2016, Desta et al.,2019 & Levison et al.,2012). The study conducted in Tigrai identified poor ART adherence level and fair ART adherence level as factors significantly associated with viral non-suppression (Desta et al.,2019). Similarly, having fair and poor drug adherence level were identified as main predictors of treatment failure in Bale zone of Southeast Ethiopia (Haile et al.,2016).

Presence of TB co-infection at ART initiation was another factor which is independently associated with treatment failure in our study. the retrospective cohort study conducted in Bale zone also reported that TB co-infection is one of the consistent predictors of treatment among

ART patients (Haile et al.,2016). Similar finding was reported from the retrospective cohort study conducted in Debremarkos hospital of North West Ethiopia (Melsew et al., 2013).

Limitations of the study

Incompleteness of the data on the important variables like CD4 count and viral load which are used to determine treatment failure. Using secondary data for analysis also limited the scope of the study due to difficult of controlling for extraneous variables that not available in the patient chart Small sample could also be one of the limitations of this study. We were unable to detect the difference for variables which are found to be associated with treatment failure in other studies and other confounders due to small sample size.

8. Conclusion

Incidence of treatment failure among adult HIV positive on ART in West Arsi zone is high. The highest rate of treatment failure occurred the early months of ART initiation. The main factors contributing to high incidence of treatment failure in the study setting are being in a fair and poor adherence level and TB co-infection at ART initiation.

9. **Recommendation**

We recommend the West Arsi Zone health office to give training on national ART guideline for both ART and TB care service providers. The linkage between all the service points in the health facility and ART clinic should be strengthened. Integration of ART and TB service provision must be given due attention in order to curb the high incidence of treatment failure among TB co-infected patients at ART initiation. ART care service providers should adhere to the national guideline and strengthen the adherence counselling and support for the clients.

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10.Annexes

10.1. Annex one :Questionnaire in English version

Questionnaire to assess incidence of treatment failure and its associated factors among adults living with HIV AIDS in West Arsi Zone, Ethiopia 2019/2020

Tab 1: Sociodemographic and baseline characteristics

Sno	Question	Response	SKIP
	Patient card number	_____	
01	Age of patient	_____in years	
02	Sex of patient	1. Male 2. Female	
03	Marital status	1. Single 2. Married 3. Divorced 4. Widowed	
04	Residence	1.urban 2. Rural	
05	Occupation	1. Employed 2. Unemployed	
06	Education level of the patient	1. No education 2. Primary (1-8) 3. Secondary (9-12) 4. Tertiary(college &above)	
07	Religion	1. Muslim 2. Orthodox 3. Protestant 4. Others __	
08	Family size	_____ number	
09	Baseline Functional status	1. Working 2. Ambulatory 3. Bedridden	
10	Date confirmed HIV positive	___/____/_____(dd/mm/yyyy)	
11	Disclosure status	1. disclosed 2. not disclosed	
12	History of addiction?	1. yes 2. No →	Tab 2
13	If **Yes** to **Q12**, the patient is addicted to? **More than one answer possible**	1.alcohol 2. Cigarette smoking 3. Khat chewing 4. other specify _____	

Tab 2. Characteristics during baseline and first-line treatment

sno	Question	Response	Skip
14	Baseline WHO clinical stage	1. WHO stage I 2.WHO stage II 3.WHO stage III 4. WHO stage IV	

15	Baseline CD4 count	_____cells/mm^3	
16	Weight at start of treatment	_____ kg	
17	Height at start of treatment	_____cm	
18	BMI (Kg/m^2) at start of treatment	1. normal (18.5 – 24.99kg/m2) 2. mild (17-18.49 kg/m2) 3. moderate (16-16.99kg/m2 4. severe malnutrition(<16kg/m2) 5. overweight(25 – 29.99kg/m2)	
19	History of loss to follow up	1. yes 2. No 3. Not recorded	
20	History of OIs at start of treatment	1. yes 2. No →	23
21	If **yes** to **Q 20**, what is/are OIs at start of treatment? **More than one answer possible**	1. Pulmonary Tuberculosis (PTB) 2.Extra polmunary tuberculosis (EPTB) 3. Pneumocystis carnii pneumonia (PCP) 3. Thrush oral 4. Esophageal candidiasis 5. CNS toxoplasmosis 6. Cryptococcal meningitis 7. Nonhodkings lymphoma 8. Kaposi sarcoma 9. Cervical cancer 10. Herpes zoster 11. Diarrhea (acute/chronic) 12.others specify ___	
22	What prophylaxis was given?	1. CPT 2. INH 3. Both 4. Not recorded	
23	What was the regimen at initiation of first line ART?	1) 1c 2)1d 3)1e 4)1f 5)1g 6) 1h 7) 1j 8)1k 9)1i other specify_____	
24	History of regimen modification?	1. YES 2.No →	26
25	If **yes** TO **Q** '24', what was the **reason** of regimen modification?	1. drug toxicity 2. TB Comorbidity 3. treatment failure 4. non-adherence 5. drug shortage 6. others specify _____	
26	Adherence level at first line treatment ?	1.Good 2. Fair 3. Poor	
27	History of ART drug side effect?	1. yes 2. No	
28	TB co-infection at initiation of ART	.yes 2.no	
29	Developed TB **after initiation of ART?**	1.yes 2.no	

30	**Initial viral load** at first line treatment?	_____copies/ml	

Table 3. History of the patient after at least 6 month of treatment

31	**Viral load** after 6 month of first line treatment?	_____copies/ml	If<1000 Go to'**33'**
32	If >**1000** copies/ml to **Q 31**, **follow up viral load** within 3 months	_____copies/ml	
33	**CD4 count after 6 month** of first line treatment?	_____ cells/mm3	
34	Adherence level **after 6 month** of first line treatment??	1.Good 2. Fair 3. Poor	
35	History of OI after **6 month** of first line treatment??	1.yes 2.no	
36	**Weight after 6 month** of first line treatment??	_____kg	
37	BMI (Kg/m^2) **after 6 month** of first line treatment??	1. normal (18.5 – 24.99kg/m2) 2. mild (17-18.49 kg/m2) 3. moderate (16- 16.99kg/m2 4. severe malnutrition(<16kg/m2) 5. overweight(25 – 29.99kg/m2)	
38	**Treatment stage after 6 month** at first line treatment??	1. tx stage I 2. tx stage II 3.tx stage III 4. Tx stage IV	
39	History of first line ***treatment failure***	1. yes 2.NO →	42
40	If "**yes" to Q 39, date** treatment failure confirmed	___/_____/_____(dd/mm/yyyy)	
41	If "**yes" to Q 39,** date switched to second line ART?	___/_____/_____(dd/mm/yyyy)	
42	Current status of the patient	1. On first line ART 2. On second line ART 3. Died 4. Loss to follow up 5. Transferred out 4. others specify _____	
43	**Hgb (hemoglobin)**	_____g/dl	