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RESEARCH ARTICLE

# Cotrimoxazole prophylaxis, poor drug adherence, nutritional and educational status are key predictors of first-line antiretroviral therapy (ART) treatment failure among adults in Southern Ethiopia

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## Abstract

**Background**: The advent of antiretroviral therapy (ART) for HIV-infected patients has led to a significant decline in HIV-related morbidity and mortality conditions, globally. However, drug resistance with subsequent treatment failure becomes a great challenge.

**Objective**: This study aimed to determine the incidence and key factors associated with treatment failure of first-line ART therapy among adults living with HIV in Gedeo Zone of the southern Ethiopia region.

**Methods**: A facility-based retrospective follow-up study involving 509 patients who were 15 years and above old who started first-line ART between 2010 and 2017 was conducted at health facilities in Gedeo zone of southern Ethiopia. Data were collected from Dilla university referral hospital and Yirgachefe hospitals between March to April 2018. Systematic random sampling was used to select the study participants. Data were collected by five trained nurses. Survival analysis with a Cox proportional hazard model was fitted to determine factors associated with ART treatment failure. Variables with a $p$-value of $\leq 0.05$ in multivariable cox regression were considered statistically significant determinant factors.

**Result**: For a total of 3157 person-years follow-up or 509 adult HIV-infected patients on first-line ART at both hospitals, the cumulative treatment failure rate was found to be three per 100 person-years or nearly one in five 94 (18.5%). Using the cox hazard analysis at multivariate level, cotrimoxazole prophylaxis (AHR 2.96; 95% CI 1.35 to 6.47), poor adherence to ART (AHR 1.31; 95% CI 1.12 to 1.72), being malnourished (AHR 1.78; 95% CI 1.03 to 3.12), and lack of formal education (AHR 2.25; 95% CI 1.24 to 4.08) were independent predictors of treatment failure.

**Conclusion**: The cumulative rate of treatment failure in the study area is high. Poor treatment adherence, cotrimoxazole prophylaxis, and educational and nutritional status were found to be key predictors of treatment failure. Therefore, health system strengthening and nutrition interventions are essential to improve the rate of treatment failure.

**Keywords**: Adults, First-line Antiretroviral Therapy, HIV, Predictors, Treatment Failure

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## Background

Worldwide Human Immunodeficiency Virus (HIV) continues to be a major public health problem, approximately 37.9 million people were living with HIV at the end of 2018 [1]. From the global burden,the majority of the HIV-infected people were living in sub-Saharan Africa [2] and in Ethiopia, according to the 2016 Ethiopia Demographic Health Survey (EDHS) report the prevalence of HIV among adults was 0.9 percent and the magnitude is seven times higher in urban areas than in rural areas [3].

In the world,because of the starting of highly active antiretroviral therapy (HAART), morbidity and mortality have considerably reduced [4].The WHO report shows that in low- and middle-income countries, 62% of adults living with HIV were getting lifetime antiretroviral therapy in 2018 [1].

A combination of two nucleoside/nucleotide reverse transcriptase inhibitors (NRTI) with one non-nucleoside reverse transcriptase inhibitor (NNRTI) is a standard first-line regimen and the majority of the patients start their treatment with this ART regimen. First-line treatment failure after initiation of HAART can be assessed by clinical (the appearance of new opportunistic infections, ongoing weight loss, *etc.*), immunologic (a decline in CD4 count), or virologic (a viral rebound above a set of the threshold of 200 copies/ml) criteria [5]. A combination of clinical and immunologic monitoring or clinical monitoring alone is used to assess the response to ART and to determine treatment failure in settings in which there is no access to viral load testing [6].

According to a study done in India,the first-line ART treatment failure prevalence was 12.4% [7], Studies in East Africa have shown that immunologic failure ranges from 8% to 57% [8]. The failure rate in Ethiopia was found to be high. The study conducted at Debremarkos Hospital showed that 21% of the HIV patients had developed immunological failure with a failure rate of eight per 100 patient-years of follow-up [9],and in the University of Gondar referral hospital, northwest Ethiopia, the prevalence was (4.1%) [10]. In a study done in southern Ethiopia, 17.6% of the patients were found to have immunological treatment failure [11].

The factors associated with treatment failure from different kinds of literature include; old age group and educational status [12], urban areas,negative change in absolute lymphocyte count, a negative change in hemoglobin concentration, a negative change in body weight, and previous history of anti-tuberculosis treatment [7], Having WHO Stage III/IV [11], and low baseline CD4 count [12, 13, 14], zidovudine-based ART, and poor adherence [13], and cotrimoxazole prophylaxis (CPT) had a protective effect on peoples living with HIV/AIDS [15].

Delayed detection of treatment failure may increase drug toxicity/and may result in increased morbidity and mortality. Since second-line treatments are the next, most expensive, and the only options after failure of first-line ART as per the Ethiopian ART treatment guideline, it is crucial and timely to know the rate of failure and its predictors. Therefore, this study aimed to determine the incidence of first-line ART treatment failure and to identify the risk factors that contribute to treatment failure among adult HIV patients who were on ART follow-up in the Gedeo zone by using the three WHO criteria. It will help as a guide for health professionals and higher officials to alleviate the problem and to develop strategies to decrease the rate of treatment failure, and also inform the respective stakeholders about the current state of first-line ART users.**Ethical Consideration**

Ethical clearance was obtained from the Institutional review board of Dilla University, College of Health and Medical science. After that support letter was obtained from the Gedeo Zone health office and Permission was also obtained from the directors of each of the hospitals from whose HIV clinics data were used for this study. Informed consent was not obtained since there was no interaction with human subjects as the data were collected from patient charts and log-

books. Names of patients were not included during data collection. The collected data were kept confidential and used only for the study.

## Methods and Materials

### Study design

A facility-based retrospective follow-up study was conducted in the Gedeo zone of the southern region of Ethiopia between March and April/2018. Study area: This study was conducted in two selected hospitals in Gedeo zone. The zonal capital, Dilla town is located 360km south of Addis Ababa. Gedeo has six woredas or districts and two city administrations with an estimated total population of 1,086,768 (532,516 (49%) male and 554,225 (51%) female). The total land of Gedeo is estimated to be above 1,210.89 square kilometers. There are a total of 276 health facilities from this one referral hospital, three district hospitals, 38 health centers, and 146 health posts. ART services are available in seven health centers and four hospitals in the Gedeo zone.

### Participants

The source population for this study includes all HIV-positive adults age15 years and above who started first-line ART in Gedeo zone hospitals, SNNPR, Ethiopia between February 2010 and 2017. All HIV-positive adults age15 years and above who started first-line ART at Dilla university referral hospital and Yirgachefe primary hospital and followed at least 6 months between February 2010 and 2017 were included. Patients who had incomplete information about the outcome variable were excluded. The sample size was determined by using two population calculations formula. By using confidence level=95%, Power=80%, $t$ sample size=539

### Variables

**Dependent variable**: Treatment failure of first-line ART and its time of occurrence

**Explanatory variables**:

**Socio-demographic characteristics**: Age, sex, educational status, marital status Clinical characteristics: WHO clinical staging, Functional status, CD4 count at the shift of ART, change in weight, presence of OI, calendar year of starting first-line ART, Presence of active TB, and TB treatment.

**Treatment-related**. Drug regimen, OI prophylaxis, CPT, INH prophylaxis, history of first-line modification, treatment duration, number of changed NRTIs, and drug side effects.

### Operational definition

**Treatment failure**: is considered a composite outcome of immunological failure, clinical failure, and virological failure. If a patient had one of the three outcomes, he/she is considered as having treatment failure.

**Clinical failure**: New or recurrent clinical event indicating severe immunodeficiency. WHO clinical stage 4 conditions and certain WHO clinical stage 3 conditions (such as pulmonary TB and severe bacterial infections) after 6 months of effective treatment.

**Immunological failure**: Failure is defined if at least one of the criteria below is fulfilled: follow-up CD4 count fall to or below baseline values, a 50% fall from on treatment peak value, or persistent CD4 levels below 100 cells/mm3.

**Virological failure**: a viral rebound above a set of a threshold of 200 copies/ml) criteria.

### Data collection technique

The data were collecte dfrom patients' charts, computer databases, and logbooks by using A standardized data extraction checklist prepared by the investigators. Five BSC nurses who have experience of working at the ART clinic participated in the data collection process after one day of training is given and supervised by 4 supervisors.

### Data quality assurance

Training on the objective of the study and how to review the documents as per the data extraction format was given to data collectors and the supervisor for one day before data collection. The data extraction checklist was pre-tested for consistency of understanding the review tools and completeness of data items, and the necessary adjustments made to the final data extraction format. The filled formats were checked for completeness by the principal investigator and/or the supervisors daily.

### Data processing and analysis

The data was entered into EPI info version 7 and transferred to STATA version 12.0 for analysis. Descriptive and summary statistics were carried out. The rate of failure of the composite outcome (treatment failure) was measured for each of the outcomes separately. Person time at risk was measured starting from the time of starting the treatment until each patient ends the follow-up. Survival analysis with a Cox proportional hazard model was used to identify determinant factors of treatment failure. Schoenfeld residuals test (both global and scaled) and -Ln(-ln) graphs were used to check the Cox proportional hazard assumption. Both bivariable and multivariable Cox proportional hazards models were used to identify predictor variables. Variables having $p$-value 0.2 or less in the bi-variable analysis were fitted into the multivariable model. A ninety-five percent confidence interval of hazard ratio (HR) was computed and variables having a $p$-value less than 0.05 in the multivariable Cox proportional hazards model were considered as significantly associated with treatment failure.

### Ethical Consideration

Ethical clearance was obtained from the Institutional review board of Dilla University, College of Health and Medical science. After that support letter was obtained from the Gedeo Zone health office and Permission was also obtained from the directors of each of the hospitals from whose HIV clinics data were used for this study. Informed consent was not obtained since there was no interaction with human subjects as the data were collected from patient charts and logbooks. Names of patients were not included during data collection. The collected data were kept confidential and used only for the study.

## Results

### Baseline socio-demographic characteristics

In this study, a total of 539 charts of adult HIV-infected patients on first-line ART were reviewed, then 30 samples were excluded because of the incompleteness, and 509 collected samples were included in the analysis. The median age of the patients at the start of antiretroviral treatment was 32 years with an Inter-quartile range (IQR of 12 years). The majority of the participants, 289 (57%), 360 (70.7%), and 274 (54.4%) were female by gender, with no formal occupation and under 32 years by age,respectively. Close to two in every five or 161 (38.33%), had a primary educational status and some 120 (28.57) had no formal education (Table 1).

### Clinical and immunological characteristics

About two-third or3 40 (66.80%) of the study participant had a working functional status and 293 (57.792%) were in WHO clinical stages III & IV. About four in five or 399 (78.51%) of the patients had poor adherence levels, and close to a quarter or 96 (22.9%) were malnourished. About six in five 433 (87.12%) and slightly above half 261 (53.37%) were given cotrimoxazole and Isoniazid (INH) preventive therapies, respectively. Among the study participants, only one in ten, or 51 (10.2%) had a CD4 count of $\leq 50$ cells/mm$^3$ (Table 2).

**Table 1** Socio-demographic characteristics of adult HIV patients on first-line ART in Gedeo zone, SNNPR, Ethiopia, 2018

| Variable | Category | Frequency | Percent (%) |
|---|---|---|---|
| **Gender** | Female | 289 | 57 |
| | Male | 220 | 43 |
| **Occupation** | Employed | 149 | 29.3 |
| | unemployed | 360 | 70.7 |
| **Age** | <32 years | 274 | 54 |
| | 32-40 years | 148 | 29.2 |
| | >40 years | 85 | 16.8 |
| **Educational status** | Lack of formal education | 120 | 28.57 |
| | Primary | 161 | 38.33 |
| | Secondary | 94 | 22.38 |
| | Tertiary | 44 | 10.48 |

**Table 2** Clinical and immunological characteristics of adult HIV patients on first-line ART in Gedeo zone, SNNPR, Ethiopia, 2018

| Variable | Category | Frequency | Percent (%) |
|---|---|---|---|
| Re occurrence OI | Yes | 57 | 12.72 |
| | No | 390 | 87.28 |
| Past TB Rx | Yes | 117 | 23.17 |
| | No | 387 | 76.63 |
| CD4 (cells/mm$^3$) | ≤50 | 51 | 10 |
| | 51-200 | 187 | 37.4 |
| | >200 | 262 | 52.4 |
| Functional status | Working | 340 | 66.80 |
| | Ambulatory | 145 | 28.49 |
| | Bedridden | 23 | 4.52 |
| WHO stage | Stage 1 | 122 | 24.06 |
| | Stage 2 | 91 | 17.95 |
| | Stage 3 | 265 | 52.27 |
| | Stage 4 | 28 | 5.52 |
| Adherence | Poor | 399 | 78.57 |
| | Good | 110 | 21.43 |

OI=Opportunistic infection, TB=Tuberculosis, RX=Treatment

### Treatment failure on first-line ART

Among a total of 509 adult HIV-infected patients on first-line ART treatment, 95 (18.5%) had reported treatment failure; of which, close to three-fourth or 69 (72.63%) had immunological while the rest 12 (12.63%), 7 (7.31%) had virological, and clinical treatment failures, respectively. Nearly one in every 13 or 7 (7.35%) had all three types (immunological, virological, and clinical) of treatment failure. The mean follow-up time of the patients on first-line ART was 49.51 months (sd=28.18) while the study cohort had contributed to a total of 3157 person-years of follow-up. Over the study period, the total treatment failure rate was three per 100 person-years.

### Predictors of treatment failure on first-line ART

In the bi-variable cox proportional hazard analysis,educational status, INH, CPT, nutritional status, and adherence were statistically significant factors of treatment failure in adult HIV-infected patients on first-line ART. In the advanced multivariate Cox regression analysis; however, CPT (AHR 2.96; 95% CI 1.35 -6.47), poor adherence (AHR 1.31; 95% CI 1.12 -1.72), being malnourished (AHR 1.78; 95% CI 1.03 -3.12), and lack of formal education (AHR 2.25; 95% CI 1.24 -4.08) remained to be independent significant predictors of treatment failure.

The rate of treatment failure was 2.25 times higher among those who had no formal education as compared with those who had secondary educational status. Good adherence and taking CPT had a protective effect on treatment failure. The risk of treatment failure was 1.31 times more likely among patients who had poor adherence as compared tothose who had good adherence. Patients who did not take CPT were 2.96 times more likely to have treatment failure as compared to those who were taking CPT. The risk of treatment failure was 1.78 times more likely among malnourished patients as compared to those who were not malnourished (Table3).

**Table 3** Bi-variable and multivariable Cox regression analysis of treatment failure and predictors of first-line antiretroviral therapy among adults living with HIV in the Gedeo zone, SNNPR, Ethiopia, 2018

| Variable | Failure status | | Crude HR (95% CI) | Adjusted HR (95% CI) |
|---|---|---|---|---|
| | Event | Censored | | |
| **Educational status** | | | | |
| No formal education | 21 | 98 | 1.6 (.950-2.83) | 2.25 (1.240-4.082) * |
| Primary | 28 | 133 | 1.6 (.939- 2.759) | 1.5 (0.865-2.793) |
| Secondary | 19 | 75 | 1 | 1 |
| Tertiary | 14 | 30 | 0 .64 (0.268- 1.539) | 0.73 (0 .27-1.92) |
| **CPT** | | | | |
| No | 11 | 52 | 1.64 (0.87-3.11) | 2.96 (1.35-6.47) * |
| Yes | 81 | 352 | 1 | 1 |
| **Nutritional status** | | | | |
| Not malnourished | 64 | 259 | 1 | 1 |
| Malnourished | 20 | 71 | 1.41 (0.89-2.27) | 1.78 (1.03-3.12) * |
| **Adherence** | | | | |
| ≥85% (good) | 56 | 288 | 1 | 1 |
| <85% (poor) | 31 | 80 | 1.38(1.102-1.74) | 1.31 (1.12-1.72) * |
| **Functional status** | | | | |
| Working | 63 | 277 | 1 | 1 |
| Ambulatory | 27 | 117 | 0.97 (0.662-1.438) | 0.87 (0.562 - 1.37) |
| Bedridden | 4 | 19 | 2.6 (1.467-4.640) | 1.4(.671-2.91) |
| **WHO stage** | | | | |
| Stage 1 & 2 | 39 | 174 | 1.48 (0 .856-2.569) | 1.1 (0.606 - 2.33) |
| Stage 3 | 48 | 216 | 1 | |
| Stage 4 | 6 | 22 | 0.75 (0.433- 1.299) | 0.56( 0.234 - 1.37) |

Event=treatment failure; Censored=transfer out + lost to follow up+death+alive(on treatment at the end of the study); CPT= cotrimoxazole preventive therapy,HR=Hazard ratio; CI=Confidence interval; * is to indicate significant factors; 1=reference

## Discussion

This study aimed to measure the treatment failure rate and predictors of first-line antiretroviral therapy among adults. The incidence of treatment failure in this study was three per 100 person-years which is lower as compared with an incidence rate of 8 per 100 person-years in a study done in DebreMarkos, Ethiopia [9]. In this 7- year's retrospective follow-up study, 18.5% of the adult HIV-infected patients on first-line ART had treatment failure which is in agreement with a study done in southern Ethiopia 17.6% patients were found to have treatment failure [11]. However, the prevalence of treatment failure in this study is lower than in a study done in Debremarkos (21%) [9] and it is higher in contrast to a study done in India (12.4%) [7] and the University of Gondar (4.1%) [10]. The reason for this might be due to the differences in the study settings, follow-up time, sample size, and the diagnostic criteria of treatment failure.

In this study, different factors have been identified as predictors of treatment failure on first-line ART. In the multivariate analysis; nutritional status, educational status, adherence, and cotrimoxazole preventive therapy were found as significant determinants of treatment failure. In our study nutritional status was the determinant factor of ART treatment failure. The rate of treatment failure was higher among malnourished patients as compared with those none malnourished patients. This finding is consistent with the study done in India [7]. The reason for this might be that malnutrition reduces the capacity of the body to fight infection by compromising various immune parameters. Malnutrition in HIV patients contributes to the rapid progression of HIV infection to AIDS [16]. So these patients should take medications to treat these infections. During taking these medications there might be drug interaction that could lead to treatment failure.

Educational status was also a determinant factor of treatment failure. This finding is consistent with a study done at the University of Gondar [12]. The reason might be having no formal educational status might be associated with ART non-adherence and this might lead to treatment failure.

Poor adherence was also a determinant of treatment failure in this study. Poorly adhered patients had a higher risk of ART treatment failure. This finding is consistent with the study done among HIV-infected African patients [13]. This might be because adherence to ART plays a vital role in the success or failure of therapy for HIV infection. Low levels of adherence are a great problem among these patients due to that Poor adherence leads to virologic failure and a high risk of drug resistance, progression to AIDS, and death [17-19].

In this study, those patients who took cotrimoxazole preventive therapy were at a lower risk of developing ART treatment failure as compared to those who did not take this preventive therapy. This finding is consistent with the study done university of Gondar [15]. This might be because cotrimoxazole preventive therapy reduces severe bacterial infections, malaria, and also hematological adverse events [20].

The main strength of this study is the large sample size, and the follow-up time was long enough to estimate ART treatment failure and its determinants. Among the major limitations, attributable to the use of retrospective documented data, there were incomplete follow-up records (due to patients' missed clinical visits, under-reporting of clinical conditions, and laboratory results like CD4 count). The other limitation is the viral load was not done continuously, because of the cost burden to the client, which made the study difficult to estimate correct viral load characteristics. In this study, treatment failure is a composite variable of clinical, immunological, and virological failure. So under-reporting of these three variables might under-estimate the outcome variable.

## Conclusion

The rate of treatment failure was higher and higher treatment failure among adult HIV-infected patients was associated with poor adherence, no formal educational status, not taking CPT, and being malnourished. Cotrimoxazole prophylaxis should be given to the recommended patients. The ART centers need to establish and rapidly expand awareness and counseling programs to facilitate and motivate HIV-infected patients to improve adherence and nutritional intake. ART centers and those who treat patients should record the treatment failure appropriately.

## Assertions

### Abbreviations and Acronyms

| | |
|---|---|
| AIDS | Aquired Immune-Deficiency Syndrom |
| AHR | Adjusted Hazard Ratio |
| ART | Anti Retroviral Therapy |
| CI | Confidence Interval |
| CPT | Cotrimoxazole Preventive Therapy |
| EDHS | Ethiopian Demographic and Health Survey |
| HAART | Highly Active Antiretroviral Treatment |
| HIV | Human Immunodeficiency Virus |
| HR | Hazard Ratio |
| INH | Isonizid Proplaxis |
| NGO | Non-Governmental Organization |
| NNRTI | Non-Nucleoside Reverse Transcriptase Inhibitors |
| NRTI | Nucleoside/Nucleotide Reverse Transcriptase Inhibitors |
| OI | Opportunistic Infection |
| SD | Standard Deviation |
| SNNPR | Southern Nations, Nationalities and Peoples Regional State |
| TB | Tuberculosis |
| WHO | World Health Organization |

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**Consent for Publication**: Not applicable

### Competing Interests

The authors declare that they have no competing interests.

### Availability of Data and Materials

All the data included in the manuscript can be accessed from the corresponding author Wagaye Alemu upon request through the email address "wagaye6alemu@gmail.com".

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### Author's Contributions

WA designed the study, coordinated the data collection, analyzed the data, interpreted study findings, wrote up the primary draft of the manuscript,and also revised the manuscript. ZB involved in the interpretation of the study findings, reviewed, and assisted with the critical revision of the manuscript. TS was significantly involved in the selection of articles, and manuscript preparation and revision. All authors contributed to the writing of the paper. All authors read and approved the final manuscript to be published and agreed to be accountable for all aspects of the work.

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