

Late ART Initiation among adult HIV patients at university of Gondar Hospital, NorthWest Ethiopia

Degefaye Zelalem Anlay¹, Bewket Tadesse Tiruneh², Berihun Assefa Dachew³

1. University of Gondar, College of Medicine and Health Science, school of Nursing, Gondar, Ethiopia.

Email- degefaye@gmail.com

Mobile: +251945283077

2. University of Gondar, College of Medicine and Health Science, school of Nursing, Gondar, Ethiopia.

Email: bewkettadesse21@gmail.com

Mobile-+251913201985

3. University of Gondar, College of Medicine and Health Science, Institute of Public Health, Department of Epidemiology and Biostatistics, Gondar, Ethiopia.

Email- berihunassefa21@gmail.com

Mobile: +251911-54-23-48

Abstract

Introduction: Late initiation of anti-retroviral therapy (ART) is associated with low immunologic response, increase morbidity, mortality and hospitalization. Therefore, this study aimed to assess the prevalence and factors associated with late ART initiation among adult HIV patients in NorthWest Ethiopia.

Methods: Retrospective cross-sectional study was conducted among 412 HIV patients who started ART between January/2009 and December/2014. Simple random sampling technique was used to select patient records. Data were collected by using pre-tested and structured extraction tool. Binary logistic regression model was fitted to identify factors associated with late ART initiation.

Result: A total of 410 participants were included for analysis after excluding 2 participants with incomplete data. The prevalence of late ART initiation was 67.3%. Age between 35-44 years(AOR=3.85; 95%CI:1.68-8.82), duration between testing and enrollment to care<1year (AOR=2.19;95%CI:1.30-3.69), secondary education (AOR=2.59; 95%CI 1.36-4.94), tertiary education(AOR=3.28; 95%CI 1.25-8.64), being unmarried(AOR=1.88; 95%CI 1.13-3.03), bedridden and ambulatory patients (AOR=4.68 95%CI:1.49-14.68), other medication use before ART initiation(AOR=2.18; 95%CI 1.07-4.44), starting ART between 2009-2010 (AOR=5.94; 95%CI 2.74-12.87) and 2011-2012(AOR=2.80; 95%CI 1.31-5.96) were significantly associated with late ART initiation at p-value <0.05.

Conclusion: The prevalence of late ART initiation was high. Strengthening the mechanisms of early HIV testing and linkage to care are recommended to initiate treatment earlier.

Keywords: Associated factors, Late ART initiation, Ethiopia.

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Introduction

Antiretroviral therapy (ART) has significantly improve the quality of life of the patient by reducing morbidity and mortality^{1,2}. Early diagnosis of HIV and initiation

of ART in low resource and high HIV prevalent countries minimize the cost of hospitalization and maximize the benefit of ART^{3,4}. However, the high magnitude of late ART initiation causes low immunologic response, increased HIV related morbidity, mortality and hospitalization of the patient^{1,5,6}.

There were frequent changes in ART guideline to expand ART eligible patients in resource limited settings, including Sub Saharan Africa. Despite this change most HIV patients still starting treatment at a very low CD4 cell count and advanced disease^{5,7,8}. The median CD4 cell count at initiation of ART was 150 cell/ μ l in Asia⁹,

Corresponding author:

Degefaye Zelalem Anlay,
University of Gondar,
College of Medicine and Health Science,
school of Nursing, Gondar, Ethiopia.
Email: degefaye@gmail.com

122 cells/ μl in sub-Saharan region^{5,9}, and 132 cell/ μl in Uganda¹⁰. It is still a major challenge for the success of treatment. The prevalence of late ART initiation in Latin America and Caribbean was found to be 76 %¹¹, Canada 48%², Australia 20 %⁶, Nigeria 63 %¹², Lesotho 45.7 %¹, Mozambique 38 %¹³, Uganda 37.7%¹⁰, Cameroon 35.5 %¹⁴, and Ethiopia 31.2%¹⁵.

In Ethiopia, the median CD4 count at enrollment to care is increased from 158 cell/ μl to 208 cell/ μl but the median CD4 cell count at ART initiation remained stable and pre-ART attrition contributed a lot¹⁶. In response to this, since 2010, the Ethiopian government updated ART initiation criteria three times. In 2010 the initiation criteria were CD4<350 cell/ μl and/WHO Stage III/IV, whereas in 2014 the initiation criteria was CD4 count<500 cell/ μl ¹⁷. Since 2015, to scale up the ART program, Ethiopia has implemented the HIV/AIDS prevention care and treatment strategic plan in an investment case approach with United Nations Programme on HIV/AIDS (UNAIDS) 90-90-90 strategies. One of the regional as well as national strategies for achievement is the test and treat initiatives¹⁸.

Late initiation causes a serious public health problems which results inadequate immune response, premature mortality of patients and increased HIV transmission¹⁹. Additionally, high levels of virological failure are common among those individual who start ART at low CD4 count²⁰. To prevent the problem it is important to identify factors contributing for late initiation. Studies in sub-Saharan Africa reported many contributing factors for late ART initiation⁸, which includes; late HIV diagnosis^{7,21}, late enrollment to care, years of ART initiation^{9,12,13}, low CD4 count at enrollment to care, female sex, younger and older age^{2,14}, unmarried and low level of education^{10,14}. Therefore, the aim of this study was to determine the prevalence and associated factors of late ART initiation among adult HIV infected patients who started highly active Anti retro viral therapy (HAART) at University of Gondar Hospital from January 2009 to December 2014. The result of this study will help to evaluate the HIV treatment program over time and provide evidence for future intervention in prevention of late ART initiation.

Methods

Study design and period

An institution based retrospective cross-sectional study was conducted at the university of Gondar hospital ART clinic from January 2009 to December 2014. Gondar is about 750 km far from the NorthWest of Addis Ababa, which is the capital city of Ethiopia. Gondar hospital is a teaching Hospital, which serves more than five million people. The hospital started ART service in 2005. More than 7500 adults and 700 pediatric patients were enrolled in the HIV care from the time in which the hospital started HIV care. Currently more than 4900 adults are actively receiving care in this hospital. For this particular study participants were adult HIV patients who were started HAART at University of Gondar Hospital from January 2009 to December 2014.

Inclusion criteria

All patients aged 15 and above who were started HAART at university of Gondar Hospital, from January 2009 to December 2014. Within this period, a total of 2,520 patients started ART and fulfilled the inclusion criteria. Records with no CD4 measurement and/WHO staging one months before or after ART initiation were excluded.

Sample size and sampling technique

The sample size was determined by using single population proportion formula through EPI INFO StatCalc program with the assumption of 95% level of confidence, 5% of marginal error, and by taking 50% prevalence for late ART initiation. With these assumptions, the calculated sample size was 384. Considering 10% expected incomplete record the final sample size was 412. The patients' chart number was taken from the electronic data base of the Hospital and 412(out of 2520) charts were selected through a computer generated random number.

Operational definition

Late ART initiation was defined as having a CD4 count of below or through 200 cell/ μl and/AIDS defining illness¹⁷. CD4 count or WHO stage at ART initiation included those measurement taken with in one months before and after initiation of ART. Those participants who were taking any of the three commonly used psychoactive substances: alcohol, cigarette and/or Khat in the past 30 days/span> were considered as substance user²².

Data collection tools and procedures

Data were collected by using data extraction tool. The tool was developed from different literature^{2,13}, patient's national standard follow up chart which was adapted from WHO guidelines²³ and patients medical records. The data were collected by four nurses who took an ART training. A data clerk supported data collectors in identifying the charts. Charts were retrieved using the patient's registration number which was found in the electronic database established by I-TECH Ethiopia.

Data quality control

To maintain quality of data the recruited data collectors were trained for ART training. Prior to data collection, One day training was given to data collectors about the aim of the study and how to retrieve data. Pretest was done on 20 patients' records to check the consistency and completeness of the data item. The data collection process was monitored by the investigator throughout the data collection period. Completed extraction tool were checked regularly for completeness of information.

Data processing and analysis

Before the analysis, the collected data was checked for its completeness before and after entry. For those having incomplete or missing data, the collected data from the extraction tool and the original patient records were reviewed again by using the assigned code. Data were checked, coded and entered to EPI INFO version 7 then it was exported to SPSS version 20 for analysis. Both descriptive and analytical statistical procedures were utilized. Descriptive statistics like percentage, mean, median standard deviation and Interquartile range (IQR) were used for the presentation of socio-demographic data and prevalence of late ART initiation. Tables were also used for data presentation. Binary logistic regression was used to identify factors associated with late ART initiation

among adult HIV patients. Multivariable logistic regression model was fitted to control the possible effect of confounders and finally the variables which had independent association with late ART initiation were identified on the basis of OR (95% CI) and p-value (less than 0.05). The variables were entered in the multivariable model using the Backward Stepwise regression method. Model fitness was checked using Hosmer and Lemeshow goodness of fit test (P= 0.51).

Ethical considerations

The study was approved by College of Medicine and Health Sciences Research and Ethical committee and Institutional Review Board of University of Gondar. A permission and supportive letter was obtained from clinical directors of the hospital. To retrieve the data from the patients' record permission was obtained from ART clinic head. To ensure confidentiality, personal identifiers like name were not registered in the extraction tool.

Results

Baseline socio-demographic, clinical and immunological status of the respondents

A total of 412 records were reviewed, of which two were excluded because of data incompleteness. Finally, 410 participants were included in the analysis (Table 1). More than half 265 (64.6%) of respondent were females. The mean (SD) age of the patients at ART initiation was 33.3 + 8.7 years. The majority of respondents, 337 (82.2%) were urban residents. Regarding the level of education; 123 (30.00%) of the respondents had completed their secondary education. One hundred seventy two (42.0%) and 150 (36.60%) of the respondent starts HAART at WHO stage III and between CD4 count of 100 and 199 cell/ μ l respectively. A total of 372 (90.7%) patients had disclosed their HIV status to either their family or other relatives. Three hundred fifty nine (87.6%) of the respondents did not use any type substance.

Table 1: Socio demographic and clinical characteristics of the respondents, University of Gondar hospital, Northwest Ethiopia, January 2009-December 2014 (n=410)

Characteristics		Frequency	Percentage (%)
Age in year	15-24	51	12.4
	25-34	181	44.1
	35-44	126	30.7
	> 45	52	12.7
Sex	Male	145	35.4
	female	265	64.6
Marital Status	single	73	17.8
	married	186	45.5
	divorce	96	23.44
	Widowed	31	7.6
Religion	Separated	24	5.9
	Orthodox	363	88.5
	Muslim	39	9.5
	Protestant	6	1.5
	Jewish and Catholic	2	0.4
Level of Educational	Not educated	127	31
	Primary	102	24.9
	Secondary	123	30
	Tertiary	58	14.1
Occupation	Unemployed	326	79.52
	Employed	84	20.48
Residence	Urban	337	82.2
	Rural	73	17.8
Disclosure status	Disclosed	372	90.7
	Not Disclosed	38	9.3
Substance use	No	359	87.6
	Yes	51	12.4
Functional status	Working	361	88
	Ambulatory	29	7.1
	Bedridden	20	4.9
CD4 count	<100 cell/mm ³	110	26.8
	100-199 cell/mm ³	150	36.6
	200-349 cell/mm ³	133	32.4
	>=350 cell/mm ³	17	4.1
WHO stage	I	105	25.6
	II	73	17.8
	III	172	42
	IV	60	14.6
Baseline weight	<70 kg	387	94.1
	>=70 kg	23	5.9
CPT	Yes	401	97.8
	No	9	2.2

Prevalence and trends of late ART initiation

The median (IQR) CD4 count at initiation of ART was 162.5 cell/ μ l (90.5-235.5). A total of 276 (67.3%, 95% CI

62.70 %-71.7%) patients were categorized as having late ART initiation (Figure 1). Between the year 2009-2014, the proportion of late ART initiation is decreased from 77.78% to 52.94%.

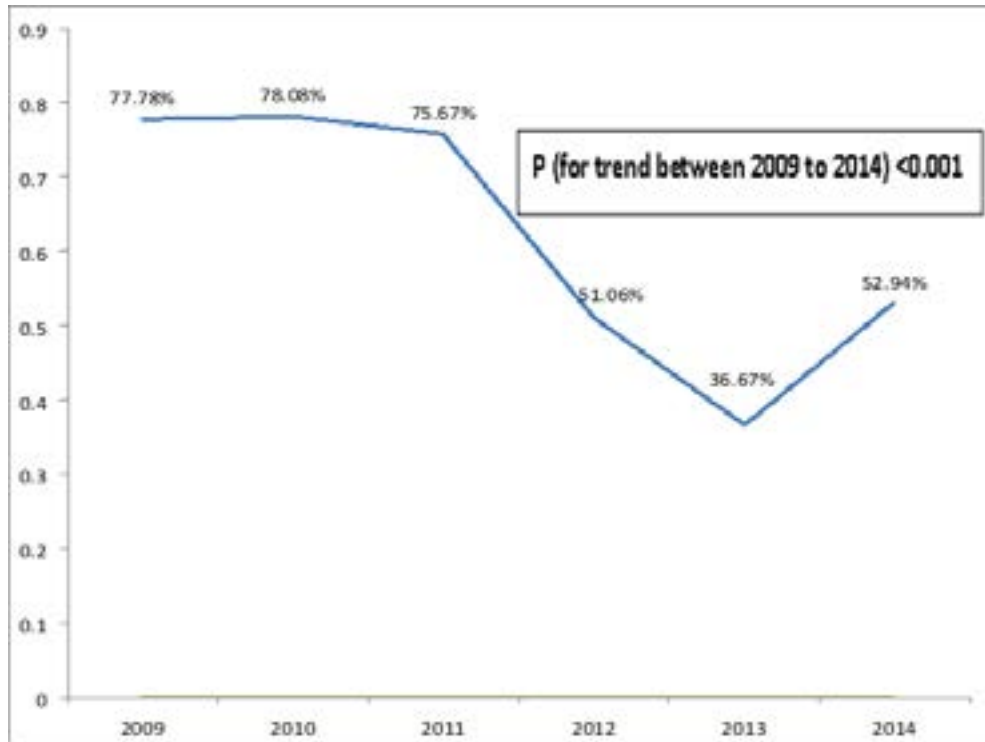


Figure 1: Proportion of patients with late ART therapy by calendar year

The overall median CD4 count over time increased from 138 (72-196) cell/mm³ in 2009-2010, to 285 (163-323) cell/mm³ in 2013-2014 (figure 2). Among patients with late ART initiation, the median (IQR) CD4 count at initiation of ART was 117.5 (66-164.5) cell/mm³.

Factors associated with late ART initiation

In multivariable logistic regression analysis, age, marital status, level of education, duration between HIV testing and enrollment to care, medication before ART initiation, years of ART initiation, and baseline functional status were significantly associated with late ART initiation (Table 2).

Table2: Bivariable and multivariable logistic regression analysis of factors associated with late ART initiation among adult HIV patients, University of Gondar Hospital, Northwest Ethiopia, January 2009-December 2014 (n=410).

Variable	Patients with		Crude odds ratio (COR)	Adjusted odds ratio (AOR)
	Late ART initiation(276)	Non-late ART initiation (134)		
Age in year	15-24	25	1	1
	25-34	119	1.99(1.06-3.74)	1.67(0.80-3.47)
	35-44	100	4.0(1.99-8.04)	3.85(1.68-
	>=45	32	1.66(0.76-3.64)	8.82)* 1.65(0.66-4.15)
Sex	Male	106	1	1
	female	170	0.65(0.44-1.027)	1.10(0.62-1.94)
Residence	Urban	222	1	1
	rural	54	1.47(0.83-2.60)	1.47(0.75-2.87)
Marital status	Unmarried	164	1.81(1.19-2.63)	1.88(1.13-
	Married	112	1	3.03)* 1
Educational status	Not educated	77	1	1
	Primary	60	0.92(0.54-1.57)	1.30(0.69-2.43)
	Secondary	91	1.84(1.07-3.16)	2.59(1.36-
	Tertiary	48	3.11(1.44-6.72)	4.94)* 3.28(1.25- 8.64)*
Religion	Christian	244	1	1
	Muslim	32	0.96(0.51-1.88)	1.20(0.55-2.60)
Occupation	Unemployed	211	1	1
	Employed	65	1.86(1.06-3.26)	1.60(0.75-3.38)
Years of ART initiation	2009-2010	152	4.77(2.44-9.32)	5.94(2.74-
	2011-2012	104	2.19(1.13-4.23)	12.87)*
	2013-2014	20	1	2.80(1.31- 5.96)* 1

Table2 (continued): Bivariable and multivariable logistic regression analysis of factors associated with late ART initiation among adult HIV patients, University of Gondar Hospital, Northwest Ethiopia, January 2009-December 2014 (n=410).

Variables	Patients with		COR	AOR
	Late ART initiation(276)	Non-late ART initiation (134)		
Duration in month Between HIV testing and enrollment to care	<12 month	201	1.64(1.06-2.55)	2.19(1.30-3.69)*
	>=12 month	75	1	1
Weight	<70 KG	262	1	1
	>=70kg	14	1.34(0.56-3.19)	0.57(0.20-1.61)
Medication before ART	Yes	71	3.22(1.71-6.06)	2.18(1.07-4.44)*
	No	205	1	1
Disclosure	Yes	247	1	1
	No	29	1.63(0.74-3.55)	2.11(0.85-5.21)
Substance use	Yes	38	1	1
	No	238	0.67(0.34-1.31)	0.82(0.37-1.85)
Baseline Functional status	Working	231	1	1
	ambulatory/bedridden	45	6.33(2.22-18.00)	4.68(1.49-14.68)*

*significant at p-value<0.05

Accordingly, the odds of late ART initiation among adult HIV infected patients who were in the age group between 35-44 years were 3.85 times higher as compared with age categories between 15-24 year at (AOR=3.85; 95% CI 1.68-8.82). Those adult HIV patients who were not married were 1.88 times more likely to initiate ART late (AOR=1.88; 95% CI 1.13-3.03) as compared to marrieds. This study also revealed that those adult HIV patients who had completed secondary and tertiary school were 2.59 (AOR=2.59; 95% CI 1.36-4.94) and 3.28(AOR=3.28; 95% CI 1.25-8.64) times more likely to initiate ART late as compared with the non-educated. Those patients who

had <1 year duration between HIV testing and enrollment to care were 2.19 times more likely to initiate ART lately as compared with those who had ≥ 1 year in duration (AOR=2.19; 95% CI 1.30-3.69). Those adult HIV patients who took other medication before ART were 2.18 times more likely to initiate ART late (AOR=2.18; 95% CI 1.07-4.44) compared with those who were not taking other medication. Moreover, the odds of late ART initiation among adult HIV patients who were ambulatory and bedridden were 4.68 times more likely to initiate ART late (AOR=4.68; 95% CI 1.49-14.68) compared to those who were working functional status at baseline.

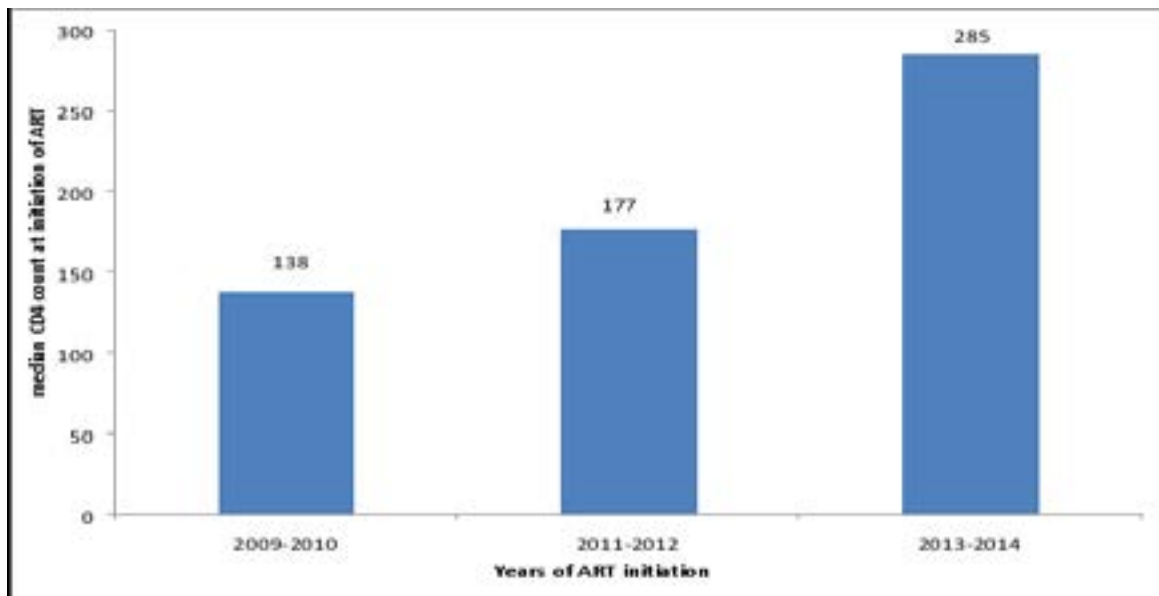


Figure 2: Median CD4 cell count at initiation of antiretroviral therapy by calendar year (n=410)

Discussion

In this study, the prevalence of late ART initiation among adult HIV patients was found to be 67.3% (62.70%-71.70%). The current prevalence is higher as compared to a previous study in Ethiopia which reported a prevalence of 31.2%¹⁵. Late ART initiation in the previous study was defined as (CD4 count <150 cells/mL or WHO Stage IV which might have contributed for the lower magnitude. Additionally, the earlier data collection period in the current study (from 2009 to 2014) might also contributed for the higher proportion of late ART initiation when compared with 2012-2013 data collection time for the previous study. This finding is in line with

study in Nigeria 63.0%¹², but higher than the findings in Lesotho 45.70%¹, Uganda 37.70%¹⁰, Cameroon 35.5%¹⁴, Mozambique 38.00%¹³, Canada 48.0%², and Australia 20.0%⁶. The higher magnitude of lost to follow up or pre-ART attrition after enrollment to HIV care and before initiation of ART, late HIV diagnosis and presentation to care in Ethiopia may attributed for this difference^{3,16}. In the contrary, the prevalence of late ART initiation in this study is lower as compared to a study done in Latin America and Caribbean 76.0%¹¹. This difference could be attributed to the difference in the time of CD4 count measurement between these two studies. The Caribbean study defined late ART initiation as CD4 counts less than

200 cell/ μ l at any time prior to initiation of ART, but in this study, we defined it as CD4 count less than 200 cell/ μ l within one month before and after initiation of ART. The time variation in the data collection period could also have contributed for this difference (from 1999-2010 for Caribbean study). Since, early in the era of HIV only limited number of patients were eligible for ART.

In this study, median CD4 count at initiation of ART over time (from 2009 to 2014) was 162.5 (90.5-235.5) Cell/ μ l. The median CD4 count over time increases from 138(72-196) cell/ mm^3 in 2009-2010 to 285 (163-323) cell/ mm^3 in 2013-2014. At the same time, the proportion of patients who started ART late decreased over time from 77.78% to 52.94% within the study period. This finding is consistent with other similar studies^{8,9,13}. This indicates the great improvement on HIV prevention and treatment that has been made in Ethiopia for the last few years. Since 2003, in which the first treatment guidelines developed, the guidelines were revised 4 times. Those patients' eligible for initiation can obtain ART for free. Routine CD4 cell count measure and regular clinical follow up support the HIV scale-up program and further contributed for the earlier initiation of ART. Despite this intervention, in 2014 more than half (52.94%) of patients initiate ART late and thus much more effort is still needed for future prevention and treatment strategy in accordance with UNAIDS 90-90-90 strategy by the year 2020²⁴

In this particular study, adult HIV patients who were in the age group between 35-44 years were 3.85 times higher to initiate treatment late as compared with those whose age was between 15-24 years (AOR=3.85; 95% CI 1.68-8.82). A study among adult HIV patients in Cameroon also revealed that age younger than 45 years was associated with late ART initiation^{10,14}. This age groups has more chance to present to HIV care late²⁵.

This study also found that late ART initiation was significantly associated with marital status. Unmarried adult HIV patients were 1.88 times more likely to initiate ART late (AOR=1.88; 95% CI 1.13-3.03) as compared to married once. This finding is in line with Mozambique and Ugandan studies^{10,13}. HIV care partner notification or disclosure could play a positive influence to initiate HIV early. Surprisingly, this study revealed that those adult HIV patients who have completed secondary and tertiary school were 2.59 and 3.28 times more likely to initiate ART late

as compared with the un-educated, (AOR=2.59; 95% CI 1.36-4.94) and (AOR=3.28; 95% CI 1.25-8.64) respectively. This finding is the contrary to the finding from a Mozambique study¹³. This could be explained by the educational status difference which might have an impact on HIV testing and earlier presentation to care among un-educated patients in our hospital. The expectation of health professional among educated patients' might create psychological and emotional stress to attend health institution before developing advanced disease. Duration between HIV testing and enrollment to care is also the other factor. The odds of late ART initiation among adult HIV patients who had less than one year's duration between HIV testing and enrollment to care were 2.19 times higher as compared with those who had greater or equal to one year in duration (AOR=2.19; 95% CI 1.30-3.69). This finding is contrary to the one from a study done in Nigeria and other four sub-Saharan African countries^{8,12}. Patients presented to care having advanced stages of disease need admission, and this enforces better health seeking behavior of the patient⁷. Additionally, poor socio-economical status might affect patients' strict follow up based on the recommendation, which in turn leads to late ART initiation.

Moreover, this study revealed that those adult HIV patients who took other medication before ART were 2.18 times more likely to initiate ART late (AOR=2.18; 95% CI 1.07-4.44) as compared with those who were not taking other medication. This could be due to the fact that many medications are given to the patient for management of opportunistic infection which might indicate the presence of advanced disease and/or severe immunosuppression before initiation of ART, which directly describe late initiation.

Finally, those adult HIV patients who were ambulatory and bedridden were 4.68 times more likely to initiate ART late (AOR=4.68; 95%CI 1.49-14.68) as compared with those who had a working functional status at baseline. Another study from South West Ethiopia also came up with a similar finding²⁶. This is due to the fact that ambulatory and bedridden functional status is an indicator of low immune status and the presence associated opportunistic infection²⁷.

Our study also had some limitations. First, many patients initiating ART with late stage of HIV already had advanced infection at enrollment in HIV care, and likely of-

ten at diagnosis making it challenging to directly identify correlates of late ART initiation from factors related to late enrollment or diagnosis. Second, because of the retrospective nature of the study some important variables like psychosocial and income related factors were missing in the patient's record which could affect the results.

Conclusion

The prevalence of late ART initiation was found to be high. The median CD4 count is increased over time. Accordingly, the proportion of late ART initiation decreased over time inconsistently. However, significant proportion of HIV patients started ART late. Patients who had finished secondary education and above, were aged between 35-44, were unmarried, were taking medication before ART initiation, years of ART initiation between 2009-2012, duration between HIV testing and enrollment to care less than one year, ambulatory and bedridden functional status were more likely to initiate ART late. This study highlights the need to strengthen the mechanisms of early HIV testing as well as early enrolment/linkage to care and early ART initiation among adults in the community by intensively involving the health professionals and other stakeholders by advocating the current novel strategies (90-90 strategy). It is also better to enhance an intensive counseling and education for unmarried, ambulatory/bedridden patient and patients on other medications. Further research to explore the socio-economical, institutional and contextual factors with appropriate study design is recommended.

List of abbreviation

AIDS	Acquired Immunodeficiency Syndrome
AOR	Adjusted Odds Ratio
ART	Anti-Retroviral Therapy
CI	Confidence Interval
COR	Crude Odds Ratio
CPT	Co-trimoxazole Preventive Therapy
HAART	Highly Active Anti-retroviral Therapy
HIV	Human Immune Deficiency Virus
IQR	Interquartile Range
I-TECH	International Training and Education Center for Health
UNAIDS	United Nations Programme on HIV/AIDS
WHO	World Health Organization

Declaration

Authors' contributions

DZ conceived the idea and wrote the proposal, participated in the data collection process, data analysis and drafted the paper. BA and BT approved the proposal with some revisions, participated in data analysis and reviewed the manuscript. All authors approved the final draft of the manuscript.

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Competing interests

The authors declare that they have no competing interests.

Availability of data and materials

All relevant data are available within the manuscript

Authors' information

1. DZ is a lecturer, Department of Nursing, College of Medicine and Health Sciences at University of Gondar, Ethiopia. DZ has Bachelor of Science Degree in Nursing and Masters Degree in clinical tropical infectious disease and HIV medicine.
2. BT is a lecturer, Department of nursing, College of Medicine and Health Sciences at University of Gondar. BT has Bachelor of Science Degree in Nursing, and Masters Degree in emergency and critical care nursing.
3. BA is an assistant Professor, Department of Biostatistics and Epidemiology, Institute of Public Health, College of Medicine and Health Sciences at University of Gondar, Ethiopia and community service coordinator of college of medicine and health science. BA has Bachelor of Science Degree in Nursing, MSc in Adult Health Nursing, Masters of Public Health in Biostatistics and Epidemiology Specialization.

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