


Predictors of Anemia Among Adult HIV Positive Patients on First-Line Antiretroviral Therapy in Northwest Ethiopia: A Retrospective Follow-Up Study

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Background: Globally, anemia is a common hematological disorder among HIV-infected patients. People with anemia often suffer from impaired physical functioning, psychological distress, and poor quality of life. Therefore, the aim of this study was to determine the incidence of anemia and its determinants among HIV positive individuals in northwest Ethiopia.

Methods: A total of 486 adult HIV positive patients on the first-line ART with complete information were enrolled in the adult care clinics of northwest Amhara referral hospitals from December 2015 to December 2018. EpiData version 4.2 was used for data entry and Stata version 14 for analysis. Variables having time to event nature were presented with the Kaplan–Meier function. The Cox regression model was used to identify predictors of anemia. Variables with P-values less than 0.2 in the bivariable analysis were considered in the multivariable regression. Adjusted hazard ratio with 95% CI was computed, and variables with less than 0.05 P-values in the multivariable Cox regression were taken as significant predictors of anemia.

Results: This study noted an overall 26.4 per 100 person-year observations (95% CI: 23.46, 30.74) incidence rate of anemia. According to the multivariable Cox regression, TB co-infection (AHR =1.99, 95% CI: 1.45, 2.74), zidovudine-based regimen (AHR=1.39, 95CI: 1.1, 1.85), CD4 level (AHR= 1.7, 95% CI: 1.23, 2.35), advanced WHO stage (AHR=1.32, 95% CI: 1.01, 1.74), and being underweight (AHR= 1.53, 95% CI: 1.14, 2.07) were predictors of anemia.

Conclusion: Anemia is a burden among HIV patients in the study setting. Baseline clinical variables, TB co-infection, and zidovudine-based were predictors of anemia. Therefore, early identification of anemia and addressing significant predictors are highly suggested to the study setting.

Keywords: anemia incidence, HIV, first-line HAART, Ethiopia

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Background

Anemia is the frequent hematological disorder among people living with HIV.^{1–3} It is a condition occurred when the number of red blood cells (RBCs) or the amount of hemoglobin decreases in the blood. Red blood cells and hemoglobin are responsible for carrying oxygen to vital organs throughout the body.⁴ Patients with anemia experience easy fatigability, increase heartbeat, shortness of breath, and dizziness.⁵

These symptoms occurred when the body attempts to deliver poorly oxygenated blood to all of the vital organs. The cause of anemia in people with HIV is multifactorial and results in poor treatment outcomes.⁶ The virus itself can infect and induce the myelosuppressive effect on the bone marrow, resulting in decreased RBC.⁷ Several pathogenetic mechanisms have been implicated for the myelosuppressive effect on the hematopoietic system occurring during the course of HIV infection. Some of which includes altered cytokine production by infected CD4⁺ marrow cells, production of inhibitory factors by infected marrow stromal cells, antibody-mediated suppression of hematopoietic progenitors, direct infection of hematopoietic progenitors and/or precursors, and HIV-1 mediated suppression of CD34⁺ cell growth in the absence of a complete viral replication cycle.

Besides, opportunistic infections, nutritional deficiencies, bleeding, and multiple drugs of antiretroviral therapy results in the development of anemia.⁸

The use of highly active antiretroviral therapy (HAART) has the capacity of reducing the incidence of severe anemia by suppressing viral replication and increase CD4 cell count. In spite of this, mild-to-moderate forms of anemia continue to be common problem. Although Antiretroviral Therapy (ART) increases hemoglobin concentrations and are effective in viral load reduction and restoration of the immune system, people with anemia often suffer from impaired physical functioning, psychological distress and poor quality of life.⁹ Anemia also facilitates the progression of HIV to acquired immune deficiency syndrome (AIDS) despite the initiation of HAART. This would happen because of anemic patients could face failure to make neutralising antibodies, develop persistent viremia, and chronic red cell aplasia all of which lead to immune-compromised state and thereby increased risk of progression of the disease.^{8,10} Besides, the adverse drug reaction, malabsorption, and nutritional abnormalities associated with anemia subsequently result in the occurrence of opportunistic infections, neoplasm, and death. It is suggested that if anemia is not treated, it will accelerate disease progression and decrease the chance of survival.¹¹

More than two billion people are estimated to have anemia worldwide where young children bear the world's highest prevalence rate of anemia.¹² The problem is more devastating among people living with HIV. About 30% of patients with an asymptomatic infection and as many as

75–80% of those with AIDS have anemia.¹³ Crudely, the magnitude of anemia among HIV patients varies significantly, ranging from 1.3% to 95%.^{8,14} In Africa, where HIV/AIDS is a high burden, severe anemia accounted for 3% to 8%.¹⁵ Cognizant of this, anemia is a public health problem that affects significantly resource limited settings including Ethiopia. Consequently, it causes significant adverse health consequences and detrimental effects on countries' social and economic development.

Despite the consensus on anemia as the global public health problem, its incidence has been diverse and affected by several predictors.⁶ A number of scholars indicated that the occurrence of anemia is mainly related to an advanced stage of HIV, lower CD4 level, co-infection,¹⁶ duration of infection,¹⁷ age, and sex.⁸ For instance, studies from Ethiopia at Menelik II¹⁸ and Zewditu Memorial II,⁸ hospitals indicated that initiation of HAART decreases the incidence of anemia. On the contrary, there is evidence that showed multiple drugs used for the treatment of HIV/AIDS results in side-effects including anemia. For instance, drugs such as AZT, cotrimoxazole, amphotericin, interferon, dapsone, and hydroxyurea-based drugs can cause anemia.¹⁹

Our country, Ethiopia is one of the Sub-Saharan Africa countries that are severely affected by HIV/AIDS. It is estimated that more than 610,335 people were living with HIV in 2018.²⁰ The prevalence of anemia among people living with HIV/AIDS in Ethiopia ranged from 21% to 70%. A study at Tikur Anbessa Specialized Hospital, Ethiopia indicated that more than one-third (34.6%) of people living with HIV developed anemia. A similar study at the University of Gondar, Ethiopia indicated that the prevalence of anemia was 1.7% among children who had ART follow-up.²¹

Hence, anemia becomes a critical challenge in patients with HIV/AIDS. However, there is a dearth of literature on the incidence of anemia and its predictors in Ethiopia. Hence, this study aimed to determine the incidence of anemia and its predictors among HIV-infected individuals at referral hospitals in the Amhara region, Ethiopia. Understanding the predictors of anemia in HIV will help practitioners and policymakers to develop cost-effective interventions that would improve survival and reduce morbidity and mortality due to anemia among HIV patients.

Methods

Study Design and Setting

An institutional-based retrospective follow-up study was conducted from September 2015 to December 2018 at three referral hospitals in Amhara regional state including; the University of Gondar Comprehensive Specialized Hospital, Bahir Dar Felege Hiwot Referral Hospital, and Debre Markos Referral Hospital. As part of the national AIDS control Program, in Amhara regional referral hospitals have been providing free ART services from 2005 to date. The hospitals provide clinical care, including laboratory and pharmacy services.

Population, Sample Size Determination, and Sampling Procedures

The source population includes all patients ≥ 15 years of age enrolled in ART clinic for first-line ART treatment in Amhara regional state referral hospitals. Whereas the patients enrolled in the selected referral hospitals of ART clinic from September 2015 to December 2018 were the study population.

For the first objective, the sample size was determined by using single population proportion formula with considerations of the following statistical assumption; confidence level 95%, incidence rate of anemia =35% (on a study conducted at a tertiary hospital in Addis Ababa among adult HIV positive patients on first-line ART) and 5% margin of error (W).

$$n = \frac{(Z_{\alpha/2})^2 \cdot p(1-p)}{(W)^2}$$

Where;

n= sample size

Z=1.96 the corresponding Z-score for the 95% CI

W= error of margin

α =confidence level (95%)

p = proportions of virological failure on ART

$n = \frac{(1.96)^2 \cdot (0.35)(0.65)}{(0.05)^2} = 350$ by considering the incomplete patient record, 10%³⁵ was added from the initial sample size and the final sample was 385.

To check the adequacy of the sample for the second objective: we used a survival sample size calculation power approach using Stata 14.1 software with Cox proportional hazard assumptions. The sample size was calculated for the three predictor variables including CD4 count (HR= 5.9), baseline ART (HR= 1.52), and chronic diarrhea (HR= 1.85)

from retrospective follow up study done in territory hospital Addis Ababa²² (Table 1) and by using Schoenfeld²³ formula.

$$E = \frac{(Z_{\frac{\alpha}{2}} + Z\beta)2}{p1p2(\ln HR)2}, \text{ } pev = 1 - (\pi 1S1(T)) + \pi 2S2(T)N$$

$$= \frac{E}{Pev}$$

where E= number of event

N= number of sample size

P1 = proportion of event among exposed. Prev. = probability of an event.

P2 = proportion of event among non-exposed.

By considering 10% incomplete data The minimum sample size was 498. A simple random sampling technique was used in each hospital based on their allocation.

Variables of the Study

The outcome variable, anemia was defined as a hemoglobin (Hgb) level of less than 12 g/dl in women and less than 13 g/dl in men.²⁴ It was collected by reviewing the patient card and medical registration in the ART care units. The independent variables include sociodemographic characteristics (age, sex, residency, marital status, belonging to support group and HIV disclosure status), antiretroviral medication-related and Clinical ART-related characteristics such as adherence, type of ART regimen, baseline BMI, baseline WHO clinical stage, baseline CD4 count, TB/HIV co-infection status, past opportunistic infection and baseline functional status. Survival time was defined as the time in year from the start of first-line ART treatment to the development of anemia. The event was defined as patients who developed anemia during the follow-up time.

Data Collection Procedures and Quality Control

Data were extracted by using the appropriate data extraction tool adapted from the national HIV intake and follow-up care form. Data were collected by six nurses working in the ART clinics and training was given about the objective of the study. Structured data extraction tools were used to extract data from patient's medical records, pre ART intake, follow up, and laboratory request forms. Medical charts of patients and the ART unit registration book were the sources of data extraction. To ensure the quality of data, a one-day training was given to six data collectors and three supervisors on the significance, variables of the research, and how to review the documents by using the extraction tool. Furthermore, after collecting the data from the registration

book its consistency was re-checked from the patients' chart by clinicians working in the ART treatment centres.

Data Analysis

Data was entered into EpiData version 4.2.0.0 and exported to Stata 14 software for analysis. Descriptive statistics were carried out and incidence rate (IR) was calculated for the events of anemia. The Kaplan–Meier (KM) failure curve and Log rank test were used to describe the survival experiences among groups of key categorical variables. The proportional hazard assumption was checked both graphically and using a Schoenfeld residual test. The goodness of model fitness was also checked using the Cox-Snell residual plot. Variables having P-values ≤ 0.2 in the bivariable analysis were entered into the multivariable analysis and variables with P-value ≤ 0.05 and an adjusted hazard ratio (AHR) with a 95% confidence interval (CI) were considered as statistically significant predictors of anemia.

Result

Description of Study Participants

A total of 2230 adult HIV/AIDS patients on the first-line ART were enrolled between December 2015 and December 2018 in northwest Amhara referral hospitals. Based on our sample size determination, 498 HIV/AIDS patients on the first-line ART would have been included for this study. But, we were unable to access medical follow-up charts of 5 patients. Another 7 charts were also excluded due to the development of the event (anemia) at baseline. Finally, 486 patients were included in the analysis.

Socio-Demographic Characteristics of the Patients

The median age of the patients was 32 with IQR^{26,40} years. Of all the patients, 437 (89.9%) were orthodox Christian. Regarding sex, 207 (42.6%) were male. More than half (55.5%) of the patients were self-employed and 348 (71.6%) were urban dwellers at the moment. Nearly half

(48.8%) of the patients were secondary and above by educational status. Among the total, 126 (40.1%) of the patients were married. More than half (60.5%) of patients disclosed their status with 80% of the patients had also support group/caregiver (Table 2).

Baseline Clinical and Antiretroviral Medication-Related Characteristics of Patients

Of the total 486 patients, 183 (37.5%) had taken Isoniazid Preventive Therapy (IPT). Nearly one-third 142 (29.2%) of the patients had TB/HIV co-infection. About 30.45% of the patients had a past opportunistic infection and more than 55.5% of the patients had taken Cotrimoxazole Preventive Therapy (CPT). Among the total, 164 (37.4%) of the patients were treated by a zidovudine-based ART regimen. More than two-thirds of 328 (67.5%) of the patients had good treatment adherence. More than half (53.3%) and (58.64%) of the patients were on stage I/II and had CD4 count less than 350 cells/mm³, respectively. Only 130 (27%) of their nutritional status were categorized as underweight (Table 3).

The Incidence Rate of Anemia

Four hundred eighty-six (486) adult HIV patients on first-line ART were followed for a total of 841.31 Person-Year (PY) of observations.

A total of 225 (46.29% (95% CI, 41.88, 50.76)) patients developed anemia during the follow-up period. The overall incidence rate of anemia among people living with HIV in the follow-up period was 26.4 (95% CI: 23.46, 30.74) per 100 PY of observations. The median time to develop anemia was 30.63 months (95% CI: 28.33, 32.53).

A graph of the Kaplan–Meier (KM) failure function was used to describe the cumulative probability of the occurrence of anemia over the follow-up period. The cumulative hazard of anemia at 10, 20, 30, and greater than 30 months after starting ART was 1.1, 2.3, 3.3, and 11.2 per 100 person-month observation, respectively (Figure 1).

Table 1 Sample Size Determination of Adult HIV/AIDS Patients on First-Line ART in Northwest Amhara Referral Hospitals, Ethiopia from December 2015 to December 2018

Assumptions	Probability of Event	Variables	Hazard Ratio	Probability of Withdrawal	Sample Size
Power =80	0.058	CD4 count	5.9	0.1	191
Significance level (α)=0.05	0.4	Base line ART	1.52	0.1	498
Allocation ratio 1:1	0.39	Chronic diarrhoea	2.0	0.1	237
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Table 2 Socio-Demographic Characteristics of Adult HIV Patients on First-Line ART in Amhara Regional Referral Hospitals, Ethiopia from December 2015 to December 2018 (N=486)

Variables	Frequency	Percent
Age in years		
15–24	76	15.6
25–34	194	40
35–44	142	29.2
≥45	74	15.2
Sex		
Male	207	42.6
Female	279	58.4
Religion		
Orthodox Christian	437	89.9
Muslim	36	7.4
Others*	13	2.7
Occupation		
Unemployed	103	21.2
Employed	89	18.3
Daily laborer	24	5
Self-employed	270	55.5
Residency		
Urban	348	71.6
Rural	138	28.4
Educational status		
No education	128	26.3
Primary	121	24.9
Secondary and above	237	48.8
Marital status		
Single	126	26
Married	195	40.1
Divorced	124	25.5
Widowed	36	7.4
Separated	5	1
Disclosure status		
Disclosed	294	60.5
Not disclosed	192	39.5
Support group/caregiver		
Yes	389	80
No	97	20

Note: *Others protestant, catholic.

Predictors of Time to Anemia

The Log rank test and Kaplan–Meier failure function were used to show differences in survival experiences among different groups of categorical variables at baseline.

Table 3 Baseline Clinical and Antiretroviral Medication-Related Information, Among Adult HIV Patients on First-Line ART in Amhara Regional Referral Hospitals, Ethiopia from December 2015 to December 2018 (N=486)

Variables	Frequency	Percent
Past opportunistic infection		
Yes	148	30.45
No	338	69.55
CPT		
Yes	267	55
No	219	45
IPT		
Yes	183	37.65
No	303	62.35
TB/HIV co-infection		
Yes	142	29.2
No	344	70.8
Baseline functional status		
Working	334	68.7
Ambulatory/Bedridden	152	31.3
Adherence on ART		
Good	328	67.5
Fair/poor	158	22.5
First-line drug regimen		
Zidovudine based	164	33.74
Non –zidovudine based	322	66.26
Baseline clinical WHO stage		
Stage I/II	259	53.3
Stage III/IV	227	46.7
Nutritional status		
Underweight	130	27
Normal	299	61
Overweight	57	12
Baseline CD4 count		
≤ 350 cells/mm ³	285	58.64
> 350 cells/mm ³	201	41.34

In case of survival experience without adjusting other covariate, patients who had CD4 count less than 350 cells/mm³ had a higher rate of anemia as compared to CD4 count greater than 350 cells/mm³ (P-value <0.001). Those patients who were treated in Non-zidovudine-based regimen had a lower rate of anemia than the zidovudine-based regimen (p-value <0.001) (Figure 2).

The survival curve plotted below indicated that the estimated hazard curves of the hospital and the Log rank

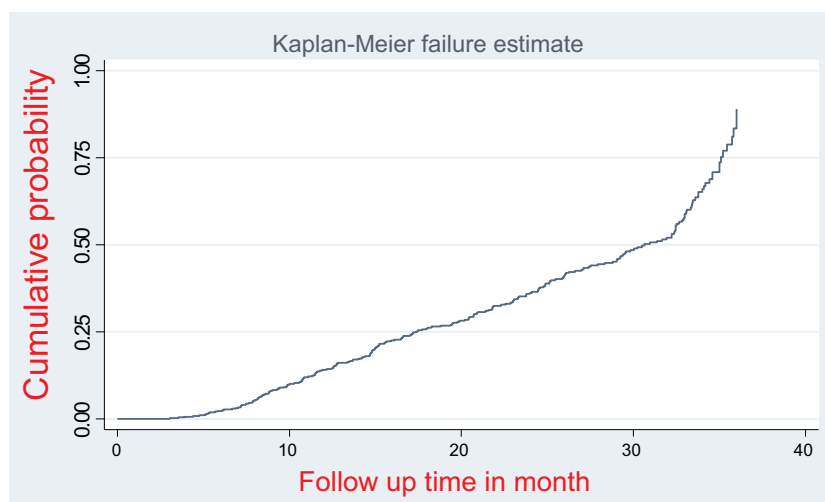


Figure 1 Kaplan–Meier failure hazard function of anemia among HIV/AIDS patients on the first-line ART in northwest Amhara referral hospitals, northwest Ethiopia, Ethiopia from December 2015 to December 2018.

test used for checking the differences in hazard curves displayed. There was no overall difference among the hazard curves of the hospitals and supported by the Log rank test (Log-rank Chi-square² = 0.86, $p = 0.16$) (Figure 3).

The Proportional Hazard Assumption

To fit the appropriate model, we have to describe the nature of the data. In this setting, the main aim of testing proportional hazard assumption and measuring the overall goodness of the fit model. The global test of proportional hazards assumption based on the Schoenfeld residuals was done and it was found that all of the covariates and full model satisfy the proportional hazard assumption (Chi-square=19, p -value=0.58) (Table 4).

Cox Regression Analysis

The bivariable cox-regression analysis revealed that age, sex, educational status, occupation, residency, marital status, TB/HIV co-infection, IPT prophylaxis, first-line drug regimen, baseline CD4 count, baseline WHO stage, CPT, and nutritional status were significantly associated with anemia (p -value <0.2).

However, TB/HIV co-infection, zidovudine-based first-line drug regimen, baseline CD4 count, WHO stage, and nutritional status were significantly associated with anemia after controlling for the confounders.

After adjusting all other variables constant, the hazards of developing anemia among TB/HIV co-infection patients were 1.99 times (AHR =1.99, 95% CI: 1.45, 2.74) more likely than their counterparts.

Keeping other variables constant, patients who were treated with a zidovudine-based first-line drug regimen had 1.39 times (AHR=1.39, 95CI: 1.1, 1.85) the hazard of developing anemia compared to patients who were treated in a non-zidovudine regimen.

The hazard of developing anemia among patients who had CD4 count ≤ 350 cells/mm³ was 1.7 times (AHR= 1.7, 95% CI: 1.23, 2.35) higher than patients having CD4 count >350 cells/mm³, with adjusting all other variables constant.

Holding other variables constant, patients with WHO stage III/IV had 1.32 times (AHR=1.32, 95% CI: 1.01, 1.74) higher hazard of developing anemia compared to WHO stage I/II.

The hazard of developing anemia among patients with underweight nutritional status was 1.53 times (AHR= 1.53, 95% CI: 1.14, 2.07) more likely than patients with normal nutritional status (Table 5).

Discussion

This study investigated the incidence and predictors of anemia among adult HIV/AIDS patients on the first-line ART in northwest Amhara referral hospitals.

Accordingly, the overall incidence rate of anemia among HIV patients in this study was 26.4 per 100 PY observations (95% CI: 23.46, 30.74). This finding was comparable with the figure generated from similar studies done in South India,²⁵ Uganda,²⁶ and at Bahir Dar, Ethiopia.²⁷ The agreement of our study finding with others such as the study in Bahir Dar might have been due to the similarity of population characteristics as the two studies were conducted in the same region, similar study setting

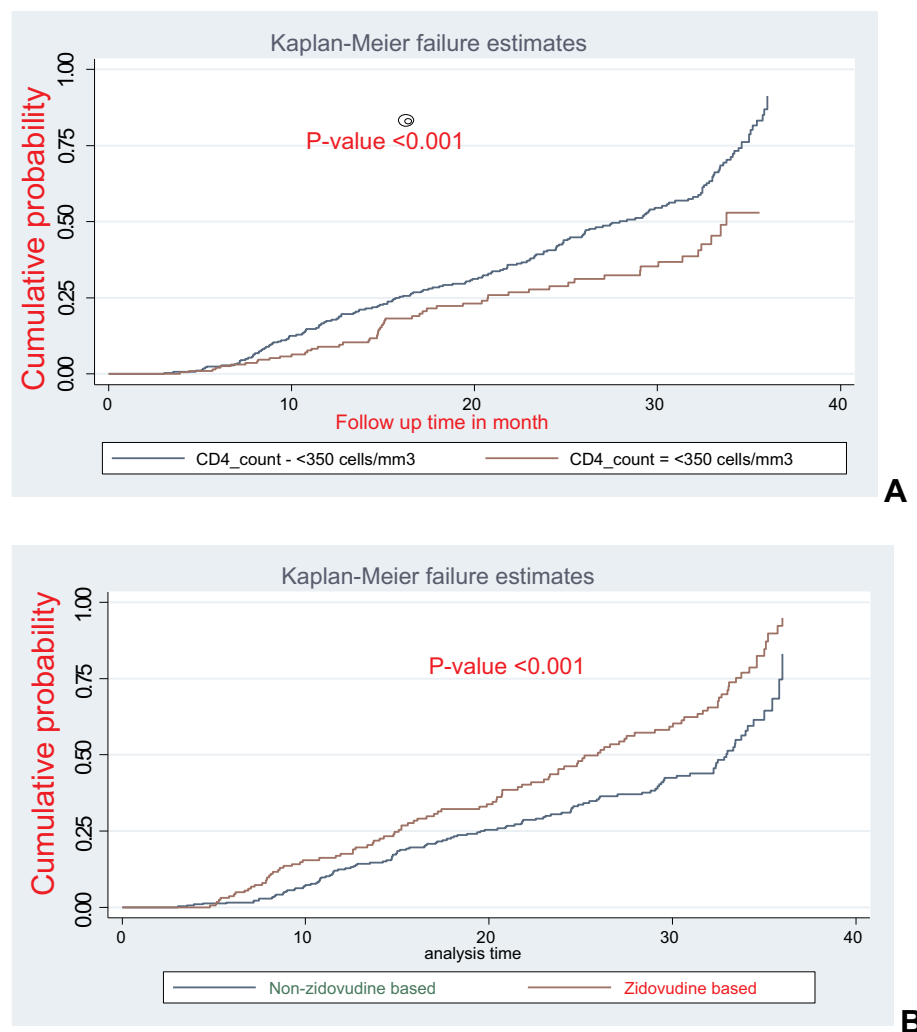


Figure 2 Kaplan–Meier hazard curve by (A) CD4 count (B) first-line drug regimen of anemia among adult HIV/AIDS patients on the first-line ART in northwest Amhara referral hospitals, northwest Ethiopia, Ethiopia from December 2015 to December 2018.

where both were conducted in tertiary hospitals, and relatively similar duration of the studies, and similar definition for anemia used in both studies.

However, the incidence of anemia in our study was lower compared to studies conducted in Nigeria²⁸ and Addis Ababa.²² The cut-off value used for the definition of anemia was one of the possible explanations for the observed difference in the incidence rate of anemia between our findings and the other studies. For instance, the higher incidence rate of anemia in Nigerian study can be explained in that a study in Nigeria defined anemia as patients having hemoglobin level of less than 10.5gm/dl irrespective of gender whereas a cut-off value less than 12 gm/dl hemoglobin level for women and less than 13 gm/dl for men was used to define anemia in our study. The type of ART regimen patients were taking could also be the

other justification for the variations in the incidence rate of anemia across studies. For example, the proportion of patients on the Zidovudine (AZT)-based regimen in our study was 33.74% but 50% in the study from Addis Ababa. Hence, the known myelosuppressive effect of AZT-based regimen might have been responsible for the higher incidence rate of anemia in the study from Addis Ababa compared to our finding.¹⁹

Different factors are found to affect the occurrence of anemia among people living with HIV. Accordingly, TB/HIV co-infection, zidovudine-based regimen, baseline CD4 count ($\leq 350 \text{ cells/mm}^3$, WHO stage III/IV, and underweight nutritional status were significantly associated with the occurrence of anemia.

This study presented that the hazards of developing anemia among patients with TB/HIV co-infection were

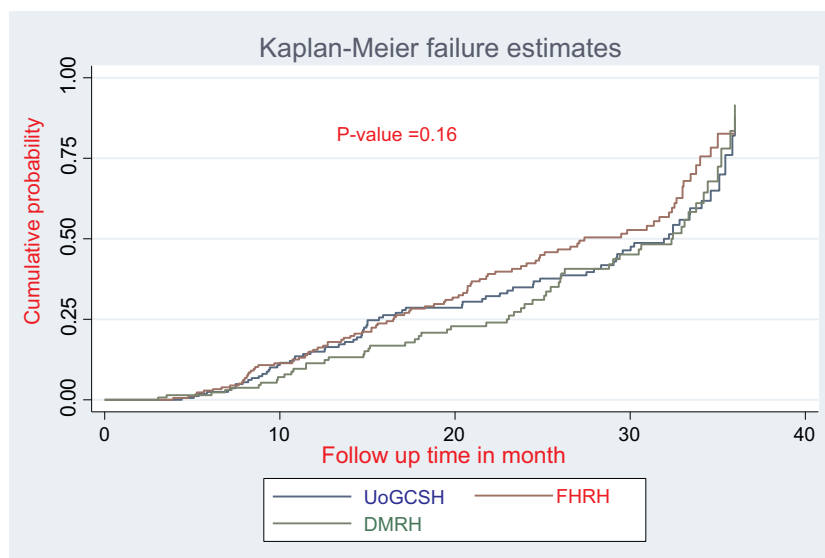


Figure 3 Kaplan–Meier failure curve of by hospitals anemia in adult HIV/AIDS patients on the first-line ART in northwest Amhara referral hospitals, northwest Ethiopia, Ethiopia from December 2015 to December 2018.

nearly two times higher than that of their counterparts. This finding was supported by studies done in Addis Ababa Zewditu Memorial Hospital,⁸ and North Wollo, Ethiopia.²⁹ Increased risk of anemia had been observed in patients with TB/HIV co-infection. These could be different explanations for the observed association of HIV/TB co-infection and anemia. For instance, tuberculosis by itself is a chronic infection which causes a moderate degree of anemia.³⁰ It is the fact that TB/HIV co-infection predispose patients for further infection by suppressing the

immune system, and also have a direct impact on decreasing and hemoglobin level.^{31,32} Zidovudine-based regimen was found to be the other important predictor of anemia. The risk of developing anemia among patients who were treated with zidovudine based first-line drug regimen was nearly one and a half times higher than that of patients who were treated with non-zidovudine-based regimen. This finding was in agreement with studies done in South Africa,³³ Addis Ababa,²² Nigeria,²⁸ and Debre Tabor, Ethiopia.^{34,35} Zidovudine containing regimen is associated with suppression of bone marrow and will be risk factor for developing anemia. It causes low production of the red blood cells and platelets in the bone marrow.^{15,36}

The hazard of developing anemia among patients who had CD4 count ≤ 350 cells/mm³ was 1.7 times higher than patients having CD4 count >350 cells/mm³. This result was in agreement with studies done in South Africa,³³ Addis Ababa,²² Wolaita Sodo, Ethiopia,³⁷ Debre Tabor, Ethiopia,^{34,35} and Gondar.³⁸ There might be several explanations for this relationship. For instance, it is well known that HIV patients with low CD4 count are known to be at risk of various opportunistic infections which are known to be the cause of anemia. Besides, immune-compromised patients are also likely to have a high viral load which could lead to viral infiltration of the bone marrow and causes anemia.

This result presented that patients with WHO stage III/IV were at 1.32 times higher hazard of developing anemia compared to WHO stage I/II. This result is supported by

Table 4 Results of Proportional Hazard Assumptions on Key Categorical Variables of Anemia in HIV/AIDS Patients on the First-Line ART in Northwest Amhara Referral Hospitals, Ethiopia from December 2015 to December 2018

Covariate	Chi-Square	Df	P-value
Sex	0.17	1	0.68
Residency	0.94	1	0.33
CPT	0.14	1	0.70
TB/HIV co-infection	1.25	1	0.26
Age in year	0.12	1	0.72
Occupational status	0.06	1	0.80
Marital status	0.2	1	0.65
First line drug regimen	0.33	1	0.56
IPT	0.12	1	0.73
Educational status	0.18	1	0.67
Baseline CD4 count	0.11	1	0.75
Baseline clinical WHO stage	3.28	1	0.07
Nutritional status	0.24	1	0.62
Global test	19	13	0.58

Table 5 Bivariable and Multivariable Cox-Regression Analysis for Predictors of Anemia Among Adult HIV Patients on First-Line ART in Amhara Regional Referral Hospitals, Ethiopia from December 2015 to December 2018 (N=486)

Variables Categories		Status		CHR (95% CI)	AHR (95% CI)
		Event	Censored		
Age in year	15–24	39	37	1.49 (0.92,2.41)	1.54 (0.88,2.68)
	25–34	83	111	1.20 (0.79,1.83)	1.11 (0.72,1.72)
	35–44	73	69	1.50 (0.98, 2.33)	1.29 (0.83,2.01)
	≥45	30	44		
Sex	Male	100	107		
	Female	125	154	0.79 (0.60,1.04)	0.80 (0.60,1.05)
Educational status	No education	71	57		
	Primary	56	65	0.86 (0.60,1.22)	0.94 (0.65,1.38)
	Secondary above	98	139	0.76 (0.56,1.04)	0.80 (0.57,1.14)
Occupation	Un employed	52	51	1.09 (0.72,1.65)	0.94 (0.57,1.57)
	Employed	38	51		
	Daily laborer	15	9	1.96 (1.08, 3.58)	1.43 (0.76, 2.70)
	Self-employed	120	150	1.04 (0.72,1.50)	0.93 (0.61,1.41)
Residency	Urban	159	189		
	Rural	66	72	1.46 (1.1, 1.95)	1.29 (0.95, 1.74)
Marital status	Single	63	63	1.12 (0.80,1.56)	1.00 (0.68,1.48)
	Married	81	114		
	Divorced	67	56	1.33 (0.96,1.84)	1.23 (0.86,1.76)
	Widowed	14	128	0.97 (0.55,1.72)	1.17 (0.65, 2.07)
TB/HIV-co-infection	Yes	69	73	2.01 (1.50,2.68)	1.99 (1.45, 2.74)**
	No	156	188		
IPT prophylaxis	Yes	73	110	1.26 (0.95,1.66)	1.27 (0.95, 1.70)
	No	152	151		
First-line drug regimen	Zidovudine based	102	62	1.69 (1.30, 2.20)	1.39 (1.1,1.85)**
	Non-zidovudine based	125	129		
Baseline CD4 count	≤350 cells/mm ³	172	113	1.70 (1.25, 2.32)	1.7 (1.23,2.35)**
	>350 cells/mm ³	53	148		
Baseline WHO stage	Stage I/II	108	151		
	Stage III/IV	117	110	1.35 (1.05,1.76)	1.32 (1.01,1.74)**
CPT	Yes	125	142	1.19 (0.91,1.55)	1.32 (0.99,1.74)
	No	100	119		

(Continued)

Table 5 (Continued).

Variables Categories		Status		CHR (95% CI)	AHR (95% CI)
		Event	Censored		
Nutritional status	Underweight	77	53	1.69 (1.27,2.25)	1.53 (1.14, 2.07)**
	Normal	129	170	1	1
	Overweight	19	38	0.76 (0.47,1.23)	0.92 (0.55, 1.53)

Note: **p-value <0.05 statistically significant.

studies done in South Africa,³³ Ethiopia,³⁹ Debre Birhan, Ethiopia.⁴⁰ The possible explanation could be that advanced clinical stage is characterized by marked weight loss, consistent diarrhea, systemic bacterial infection, oral candidiasis, cytomegalovirus, and other complications.⁴¹ Therefore, all these complications in stage III/IV of HIV patients might lead to anemia because of excessive fluid loss due to continued diarrhea as a result of different opportunistic infections of bacterial and viral origins that cause immune suppression.

The hazard of developing anemia among underweight nutritional status patients was nearly one and a half times more likely than patients with normal nutritional status. This result is supported by studies done in Rwanda,⁴² and Debre Birhan.⁴⁰ This can be justified in that HIV/AIDS causes malnutrition in many individuals due to loss of appetite, opportunistic infection, and treatment side effects. This, in turn, might lead to diarrhea, which might limit the uptake of nutrients including iron malabsorption that results in the development of anemia.

The strength of this study is its multicenter nature which gives replicable results. However, our study was not without its limits. As the study was based on secondary data, some follow-up data such as CD4 count, T-staging, and viral load does not test as predictors. Besides, it was not possible to address the behavioral characteristics of the patients like smoking, and alcohol.

Conclusion

The incidence rate of anemia was lower among HIV patients on the first line ART at the Northwest Amhara regional referral hospitals, Northwest, Ethiopia. TB/HIV co-infection, first-line drug regimen, baseline CD4 count, WHO stage, and nutritional status were significantly associated with anemia. The problem of anemia remains a public health challenge in

the study setting, with serious consequences for the most vulnerable populations such as HIV patients. Therefore, to reduce the burden of anemia among ART patients, policies, strategies, and programs should consider the identified predictors of anemia and emphasize after two years of treatment to reduce the complication of HIV patients.

Abbreviations

AHR, adjusted hazard ratio; AIDS, acquired immune deficiency syndrome; AZT, azidothymidine; CHR, crude hazard ratio; HARRT, highly active antiretroviral therapy; HIV, human immune virus; TB/HIV, tuberculosis/human immune virus; WHO, World Health Organization; IPT, isoniazid preventive therapy; CPT, cotrimoxazole preventive therapy.

Data Sharing Statement

All relevant data supporting the current study are available upon reasonable request from the lead author.

Ethics Approval and Consent to Participate

Ethical clearance was obtained from the Ethical Review Committee of the Institute of Public Health, University of Gondar. A permission letter was obtained from the University of Gondar Comprehensive Specialized Hospital, Debre Markos Referral Hospital, and Bahir Dar Felege Hiwot Referral Hospital management and the HIV care clinic's focal person. To ensure the confidentiality, personal identifiers were not included in the data. Our study was based on a retrospective review of secondary data from medical records of patients. Hence, the Ethical Review Committee of the University of Gondar waived the requirement for consent. This study was conducted in accordance with the Declaration of Helsinki.

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Author Contributions

All the listed authors made a substantial contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, studying or critically revising the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the and any significant changes introduced at the proofing stage, agree to take responsibility and be accountable for the contents of the article. Finally approved the content of the manuscript.

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Disclosure

The authors reported no conflicts of interest for this work.

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