Anemia and thrombocytopenia in the cohort of HIV-infected adults in northwest Ethiopia: a facility-based cross-sectional study

Tekalign Deressa[1,2], Debasu Damtie[2], Meseret Workineh[2], Meaza Genetu[2], Mulugeta Melku[3]

[1] Ethiopian Public Health Institute, Addis Ababa, Ethiopia

[2] Department of Immunology and Molecular Biology, School of Biomedical and Laboratory Sciences, College of Medicine and Health Sciences, University of Gondar, Ethiopia

[3] Department of Hematology and Immunohematology, School of Biomedical and Laboratory Sciences, College of Medicine and Health Sciences, University of Gondar, Ethiopia

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Corresponding author:
Mulugeta Melku
Department of Hematology
and Immunohematology
School of Biomedical and Laboratory Sciences
College of Medicine and Health Sciences
University of Gondar
P.O. Box.196, Gondar
Ethiopia
E-mail: mulugeta.melku@gmail.com

ABSTRACT

Background

Anemia and thrombocytopenia are frequent hematological abnormalities in patients with human immunodeficiency virus (HIV) infection and have been associated with increased morbidity and mortality. However, there is a paucity of data on the prevalence and correlates of these hematological abnormalities among HIV infected adults in Ethiopia. The aim of this study was to determine the prevalence and correlates of anemia and thrombocytopenia in a cohort of HIV-1 infected adults in northwest Ethiopia.

Methods

A total of 320 HIV-infected adults were enrolled into the study, from March 2016 to July 2016. Sociodemographic and clinical characteristics of the study participants were recorded. Blood samples were collected from each patient to determine hematological and immunological parameters. A binary logistic regression model was fitted to identify factors associated with each hematological abnormality. The odds ratio with a 95% confidence interval was

calculated. A p-value <0.05 was considered statistically significant.

Results

Out of 320 HIV-1 positive participants, 203 (63.4%) were female. Overall, anemia was found in 25% (95% CI: 20.23 - 29.8%) of the study participants, of whom 2.5% (n=2) had severe and 21.2% (n=17) had moderate anemia. About 83.8% (67/80) anemic patients were on highly active antiretroviral therapy (HAART) for a minimum of six months, and 31 of them were receiving Zidovudine (AZT)-based HAART regimen. Multivariable logistic regression analysis showed that being HAART-naïve (AOR= 5.5, 95% CI: 1.5-19.9) and having CD4 count below 200 cells/µl (AOR= 2.4, 95% CI: 1.3-4.9) were independent and significant predictors of anemia. Thrombocytopenia was noted in 6.3% (95% CI: 3.58-8.9%) of the study participants. Sixty percent of thrombocytopenic (n=12) subjects were over the age of 40 years.

Conclusion

We found an overall high prevalence of anemia in the cohort of HIV-infected adults in northwest Ethiopia. HAART naïve subjects and those with CD4 count less than 200 cells/µl were found to be at higher risk for developing anemia. This data has an important implication for management of hematological abnormalities in HIV patients and highlights the need for early initiation of HAART to reduce the burden of anemia.

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BACKGROUND

Human immunodeficiency virus (HIV) is a retrovirus which can be transmitted via sexual intercourse, shared intravenous drug paraphernalia, and mother-to-child transmission (1). As to UNAIDS estimation, in 2013 an estimated 35 million people were living with HIV worldwide.

Sub-Saharan Africa accounted for 71% of the global burden of HIV infection. According to this estimate, ten countries that include South Africa (25%), Nigeria (13%), Mozambique (6%), Uganda (6%), Tanzania (6%), Zambia (4%), Zimbabwe (6%), Kenya (6%), Malawi (4%) and Ethiopia (3%) accounted for almost 80% of all people living with HIV in Sub-Saharan Africa (2, 3).

Human immunodeficiency virus (HIV) infection is associated with profound hematological abnormalities. Anemia is one of the major hematological problems, frequently observed in patients with HIV infection. It has been estimated to vary from 30% to 95%, with the greatest burden in patients with advanced disease (4-6). The etiology of anemia in HIV patients may be related to factors such as opportunistic infections, HIV-associated neoplastic diseases, HIV medications, and the virus itself (7-10). HIV has shown to induce anemia either by direct infection of hematopoietic progenitor cells or by inducing autoantibody against erythropoietin, thus, blunting the physiological response to this cytokine (11).

Anemia has been associated with diverse consequences that compromise the quality of life and survival of HIV patients that leads to fatigue, congestive cardiac failure, and an increased risk of HIV-associated dementia (12, 13). Furthermore, anemia has been correlated with accelerated disease progression, deteriorated clinical outcomes, and increased mortality (14). Studies in large cohorts of HIV patients showed that anemia associated with a high risk of mortality irrespective of the first CD4 count and opportunistic infections. On the other hand, recovery from anemia has been demonstrated to correlate with improved survival (15-16). Therefore, it is vital to monitor the magnitude and associated factors of anemia in this vulnerable group, particularly in poor settings to improve therapeutic options and disease management.

Thrombocytopenia is another hematological complication that occurs in HIV patients. The prevalence of thrombocytopenia ranges from 4-40% in different study settings, and it was found to associate with all stages of the disease (17-19). It has also been linked to an increased morbidity and mortality of HIV patients, due to its association with risks of bleeding in different tissues. Mechanisms of thrombocytopenia development in the context of HIV-infection include immune-mediated destructions of platelets, toxic effects of HIV medications, and impaired hematopoiesis (20, 21). A decline in platelet count has been associated with increased viral load and predicted a rapid decline of CD4 cells count (22). Several studies have reported that highly active antiretroviral therapy (HAART) has reduced the prevalence of thrombocytopenia (23, 24). However, there are also considerable numbers of reports that showed an ongoing occurrence of this hematological abnormality even in patients receiving HAART (25).

Although hematological abnormalities of different blood cell lineages in HIV-infected adults have been widely reported, there is a paucity of data on the prevalence and correlates of anemia and thrombocytopenia from Ethiopia. We hypothesize that the risk factors for anemia and thrombocytopenia in our setting could be different from those in developed countries due to the prevailing high rates of parasitic infections and nutritional factors. Therefore, this study sought to investigate the prevalence and correlates of anemia and thrombocytopenia in a cohort of HIV-1 infected adults in northwest Ethiopia.

MATERIALS AND METHODS

Study design and settings

This cross-sectional study was conducted from March 2016 to July 2016 in an out-patient setting, in the antiretroviral treatment (ART) clinic of the University of Gondar Hospital. The hospital provides medical services, including HIV care and treatment, for about five million people in northwest Ethiopia. The ART for HIV has been available in the hospital since 2005 and the regimen consisted of a combination of nucleoside and non-nucleoside reverse transcriptase inhibitors (NRTI and NNRTI). As of 2014, there were about 10,000 HIV-positive patients with ongoing follow-up at the University of Gondar hospital ART clinic, of which 6000 were on combination ART. Gondar is located in North of Lake Tana and Southwest of the Siemen Mountains. It has a latitude and longitude of 12°36'N 37°28'E with an elevation of 2133 meters above sea level.

Study population and sampling

The sample size was determined based on a single population formula, considering the previously reported 20.7% prevalence of anemia (19), with 95% confidence interval (CI) and 5% margin of error. A total of 320 HIV-infected adults were selected by a systematic random sampling technique in an outpatient setting and provided the necessary information and samples. On a daily basis, an average of 15 adult HIV-children patients were getting service at ART Clinic of University of Gondar Referral Hospital.

A total of 1200 study participants were estimated to visit the ART clinic during the study period. The study participants were chosen at regular intervals from their sequence of ART clinic visit at approximate sampling interval of four (1,200/320). The first sample order to be included in the study was selected by lottery from the first four order of adult HIV-infected who were visiting ART clinic. Thereafter, at every 4th interval study participants were included in the study until the total sample was achieved.

The study populations were all HIV-infected adults who were on follow-up at the ART clinic of the University of Gondar Hospital during the study period. HIV-infected adults with chronic renal failure, pregnancy, cancer, and a history of blood transfusion (within three months) and radiotherapy/cytotoxic chemotherapy (within two months) prior to data collection were excluded.

Information regarding socio-demographics of the study participants was collected using pre-tested questionnaires as pretesting is the means to test the consistency, validity and reliability of the survey questions before the commencement of data collection. Variables were chosen for inclusion based on their clinical relevance, and included age, sex, marital status, residence, occupation, and education levels. Clinical data were extracted from patients' charts.

Laboratory procedures

About 4 mL of venous blood was collected in EDTA vacutainer tubes from each participant in the morning, from 8:00 am to 11:00 am, and processed within three hours of collection. Hematological parameters were determined by a Cell-Dyn® 1800 (Abbott Laboratories, USA) which was standardized against a 4C® Plus blood control. Immunological parameters were analyzed using the BD FACSCount™ system (Becton Dickinson, San Jose, CA, USA). Performances of the instruments were controlled by running control samples prior to the test samples.

Definitions of study outcomes

The laboratory limits for hematological abnormalities were defined based on WHO criteria as follows (26): anemia in men was defined as an adjusted hemoglobin (Hb) concentration <13 g/dL (11.0–12.9 g/dL=mild; 8.0– 10.9 g/ dL= moderate, and <8.0 g/dL=severe), whereas anemia in non-pregnant women was defined as an

adjusted Hb <12.0 g/dL (11.0–11.9 g/ dL=mild, 8.0–10.9 g/dL=moderate, and <8.0 g/dL=severe). Anemia was further defined based on mean corpuscular volume (MCV); as microcytic for MCV value <80 fL, normocytic if it was between 80-100 fL and macrocytic if MCV was >100 fL. Furthermore, it was defined as hypochromic if mean corpuscular hemoglobin (MCH) was <27 pg. Thrombocytopenia was defined as platelets count (PLT) < 150,000 cells/μL (19).

Data analysis

Data analysis was performed using SPSS version 20 statistical package software (SPSS Inc., Chicago, IL). Descriptive statistics as percentages, mean, median, IQR and standard deviation were applied as appropriate. Bivariate and multivariable logistic regression analyses were performed to determine the association between variables. Odds ratio and its 95% confidence intervals were calculated to determine the strength of association between hematological abnormalities and relevant socio-demographic and clinical factors.

Variables having p-value less than or equals to 0.2 in univariable binary logistic regression analysis were fitted to the final multivariable logistic regression model. P-values less than 0.05 in multivariable logistic regression analysis were considered statistically significant.

Ethical approval

The study was ethically approved by the Institutional Review Board of the University of Gondar. All subjects provided written informed consent for their participation. To ensure the confidentiality of participants and their information, no patient identifiers were included in the dataset. Laboratory findings of study participants were communicated with the responsible clinicians at the ART Clinic. This study was performed according to the declaration of Helsinki.

RESULTS

Socio-demographic and clinical characteristics of study participants

A total of 320 HIV positive adults were recruited into this study, of which 203 (63.4%) were female with a female-to-male ratio of 1.7. The Demographic and clinical characteristics of the study participants are shown in Table 1.

The median age was 38 years (IQR: 27-49 years), and the median CD4+ T lymphocytes count was 412 cells/mm3 (IQR: 91-733). Most of the participants (94.4%) included in this study were on HAART containing combinations of three drugs; two NRTIs and one NNRTIs.

Zidovudine (AZT) containing drugs were found to be the most frequently used ART regimen in

Table 1	Sociodemographic and clinical characteristics of study subjects at ART clinic of the University of Gondar Hospital, northwest Ethiopia	
Characteristics		**Number (%)**
Sex	Male	117 (36.6)
	Female	203 (63.4)
Age, years	18- 30	50 (15.6)
	31-40	157 (49.1)
	>40	113 (35.3)
	Median (IQR)	38.0 (27-49)
Marital status	Married	194 (60.6)
	Single/divorced	126 (39.4)
Residence	Urban	280 (87.5)
	Rural	40 (12.5)
Educational status	Unable to read and write	134 (41.9)
	Primary education	65 (20.3)
	Secondary education	82 (25.6)
	Tertiary education	39 (12.2)
HAART status	On HAART	302 (94.4)
	HAART-Naïve	18 (5.6)

HAART duration, years (n=302)	Median (IQR)	6.0 (4.0)
HAART regimen (n=302)	Stavudine (d4T) based	49 (16.2)
	Zidovudine (AZT) based	157 (52.0)
	Tenofovir (TDF) based	96 (31.8)
CD4 count (cell/µl)	Mean (SD)	431.1 (243.9)
	Median (IQR)	410 (91-733)
WHO clinical stage	I	296 (92.5)
	II-IV	24 (7.5)

CD4: Cluster of differentiation 4; HAART: highly active antiretroviral therapy; IQR: Interquartile Range; SD: standard Deviation; WHO: World Health Organization

our setting (52%), followed by a Tenofovir (TDF) based regimen (31.8%).

Prevalence and correlates of anemia

Overall, anemia was found in 25% (95% CI: 20.23 - 29.8%) of the study participants, of which 2.5% (n=2) had severe and 21.3% (n=17) moderate anemia. In terms of RBCs morphologic classification of anemia, 7.5% (n=6) were microcytic-normochromic, 47.5% (n=38) normocytic-normochromic and 45% macrocytic-normochromic (Table 2).

Out of the 80 anemic patients, 67 were on HAART for a minimum of six months (Table 3), and 31 of them were receiving AZT-based HAART regimen.

Bivariate and multivariable binary logistic regression analyses were performed to identify risk factors for anemia in HIV-infected adults. Variables like age, sex, residence, occupation, current CD4+ T lymphocytes count, co-morbidities with other infections, alcohol abuse, history of surgery, WHO stage, HAART status, HAART regimen, and HAART duration were included in the analysis. After controlling confounders, we found that being HAART-naïve (AOR= 5.5, 95% CI: 1.5-19.9)

and having CD4 count less than 200 cells/µl (AOR= 2.4, 95% CI: 1.3-4.9) were independent and significant predictors of anemia (Table 3).

Prevalence and correlates of thrombocytopenia

Thrombocytopenia was detected in 6.3% (95% CI: 3.58-8.9%) of the study participants (Table 2). All of the thrombocytopenic subjects were on HAART, and 60% (n=12) were in the age group of above 40 years (Table 4).

We analyzed factors associated with the thrombocytopenia among HIV-infected patients in a logistic regression model. As depicted in table 4, none of the variables were significantly associated with thrombocytopenia.

DISCUSSION

Anemia and thrombocytopenia are frequent hematological abnormalities in patients with HIV, and have been associated with increased morbidity and mortality.

These abnormalities can be reversed by proper care and treatment. Results from the present study revealed that having low CD4+ T cells

Table 2	Prevalence of anemia and thrombocytopenia in cohort of HIV-infected adults in Gondar, northwest Ethiopia	
Characteristics		**Number (%)**
Overall Anemia, N=320		80 (25)
Severity of Anemia, n=80	Mild	61 (76.2)
	Moderate	17 (21.3)
	Severe	2 (2.5)
MCV-MCH, n=80	Microcytic-normochromic	6 (7.5)
	Normocytic-normochromic	38 (47.5)
	Macrocytic-normochromic	36 (45.0)
Thrombocytopenia, N=320		20 (6.3)

MCV: mean cell volume; MCH: mean cell hemoglobin.

count (<200cells/mm3) and being HAART-naïve were significantly associated with an increased risk of developing anemia. Although it was not statistically significant, thrombocytopenia was more frequent in subjects over the age of 40 years.

The overall prevalence of anemia in this study was 25%, with the majority of subjects having mild to moderate anemia. This prevalence rate was within similar range with those in previously published reports from Jimma (23.1%), Debre Tabor (23%), and Gondar (20.7%), Ethiopia (19, 27, 28).

However, it was considerably lower when compared to the 37% prevalence rates in West Africa cohort, 65.5% in India, and 60.6% in Nigeria (29-31). The difference between our finding and others may be explained by the fact that in our study, the proportion of subjects with an advanced stage of HIV was very small.

Therefore, the observed dissimilarities in the prevalence of anemia could be ascribed to variations in the study population with respect to their HIV clinical stages, and other sociodemographic factors.

Furthermore, majorities of the subjects in our study had received HAART (94%) for a minimum of six months. Thus, the relatively lower prevalence rate of anemia in this study could be attributed to the effect of HAART suppression of viral load, which might have improved erythropoiesis and/or reduced destruction of hematopoietic cells (24).

In addition, immune restoration by HAART could also play a role by decreasing the incidence of opportunistic infections. Taken together, in spite of the relatively low prevalence rate, the result of this study showed that anemia is still a public health concern in the cohort of HIV-infected adults in the study area.

| Table 3 | Bivariate and multivariable binary logistic regression analysis of associated factors for anemia in cohort of HIV-infected adults in Gondar, northwest Ethiopia |

Variables	Anemia		COR (95% CI)	P-value	AOR (95% CI)	P-value
	Yes (%)	No (%)				
HAART						
Yes	67 (22.2)	235 (77.8)	1.0	-	1.0	-
No	13 (72.2)	5 (27.8)	9.1 (3.1-26.5)	<0.001	5.5 (1.5-19.9)	0.01
WHO clinical stage						
I	68 (23.0)	228 (77.0)	1.0	-	1.0	-
II-IV	12 (50.0)	12 (50.0)	3.4 (1.4-7.8)	0.005	1.3 (0.4-4.1)	0.68
CD4 count						
<200	24 (47.1)	27 (52.9)	3.4 (1.8-6.3)	<0.001	2.4 (1.3-4.9)	0.008
>200	56 (20.9)	212 (79.1)	1.0	-	1.0	-

CI: confidence interval; COR: crude odds ratio; AOR: adjusted odds ratio; HAART: highly active antiretroviral therapy; WHO: World Health Organization.

In this study, normocytic-normochromic anemia was predominant. This was comparable with previous studies (19, 32). Furthermore, our result showed that macrocytic-normocytic anemia was found to be the second common type of anemia, 45 % (n=36). This could be due to the well-established effect of AZT on the MCV, as the majority of anemic cases in this study were receiving AZT based regimens (35/67) (33).

This study revealed that HIV-infected adults with CD4 count less than 200 cells/μl were at higher risk of developing anemia (AOR= 2.4, 95% CI: 1.3-4.9). This could be due to erythropoietic dysfunction resulting from the increased viral load as immunity deteriorates. However, we could not verify the effect of viral load on the risk of developing anemia as data on this parameter is lacking.

Similarly, being HAART-naïve was significantly associated with a risk of developing anemia as previously described (14, 15, 24). It is of note that all but 5 non-anemic study participants were on HAART. This may substantiate the role of HAART in reducing the risk of developing anemia. Collectively, our data suggesting that there is a need for routine monitoring of HIV patients for anemia, particularly HAART-naïve subjects and those with CD4 count <200 cells/μl.

The overall prevalence of thrombocytopenia in this study was 6.3%, which was similar to the previous report from Ethiopia (19).

| Table 4 | Bivariate and multivariable binary logistic regression analysis of sociodemographic and clinical risk factors for thrombocytopenia in cohort of HIV-infected adults in Gondar, northwest Ethiopia | | | | | | |

Variables	Thrombocytopenia		COR(95%CI)	P value	AOR (95%CI)	P-Value
	Yes (%)	No (%)				
Sex						
Male	11(9.4)	106(90.6)	2.2(0.9-5.6)	0.08	1.7(0.7-4.5)	0.27
Female	9(4.4)	194(95.6)	1.00	-	1.00	-
Age category						
<30 years	2(4.0)	48(96.0)	1.00	-	1.00	-
30-40 years	6(3.8)	151(96.2)	1.0(0.2-4.9)	0.90	0.8(0.2-4.3)	0.81
>40 years	12(10.6)	101(89.4)	2.9(0.6-13.2)	0.1	2.6(0.5-13.1)	0.25
CD4 count						
<200	5(9.8)	46(90.2)	1.8(0.6-5.3)	0.2	0.4(0.2-1.4)	0.16
>200	15(5.6)	253(94.4)	1.00	-	1.00	-

CI: confidence interval; CD4: cluster of differentiation 4; COR: crude odds ratio; AOR: adjusted odds ratio.

However, it is lower when compared with 26% rate in Australia (22), 17.4% in Uganda (34), and 20% in Iran (35). This is probably due to higher proportions of subjects with previously established risk factors for thrombocytopenia such as advanced HIV disease, injection drug users or low compliance to HAART regimen in the aforementioned studies. Furthermore, most of our study subjects were on HAART with over half of the participants receiving AZT containing combination antiretroviral drug.

Therefore, the low prevalence of thrombocytopenia in this study could also be partially attributed to the role of HAART in restoring platelets count (36). Similar to other reports, we found a high prevalence of thrombocytopenia in subjects over the age of 40 years (19, 37). This could be related to increased cases of myelodysplasia in older patients (22, 37).

This study has some limitations in that we lack data on the prevalence of helminth infections like hookworm, one of the risk factors for anemia in sub-Sahara Africa.

Besides, inconsistencies of cut-of value to define anemia and thrombocytopenia between different studies have imposed some limitation in comparing our estimate with other studies. However, given that very few anemic patients

(12/80) were from a rural area (i.e., high-risk area for helminths infection), the contribution of this parameter to anemia could be minimal. In addition, our study lacks data on economic status and lifestyle of the study participants which might affect their hematologic profiles.

CONCLUSION

In conclusion, we found an overall high burden of anemia in the cohort of HIV-infected adults in northwest Ethiopia. HAART naïve subjects and those with CD4 counts less than 200 cells/μl were found to be at higher risk for developing anemia. Therefore, routine monitoring of at risk groups for anemia and early initiation of HAART could be beneficial to reduce the burden of these hematological abnormalities.

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Abbreviations

AOR: *Adjusted odds ratio*
CD4: *Cluster of differentiation 4*
CI: *Confidence interval*
COR: *Crude odds ratio*
HAART: *Highly active antiretroviral therapy*
HIV: *Human Immunodeficiency Virus*
MCH: *mean cell hemoglobin*
MCV: *mean cell volume*
WHO: *World Health Organization*

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Authors' Contributions

Conceived and designed the experiments: TD, DD; performed the experiments: TD, DD, MW, MG, MM; Analyzed the data: TD, DD, MM; interpreted results: TD, DD, MW, MG, MM. All authors contributed to the writing and editing of the manuscript and approved the final version.

Availability of data and materials

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

Competing interests

The authors have declared that no competing interests exist.

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