ORIGINAL RESEARCH

Prevalence and Predictors of Cytopenias in HIV-Infected Adults at Initiation of Antiretroviral Therapy in Mehal Meda Hospital, Central Ethiopia

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Background: Hematologic abnormalities are common complications of patients infected with HIV associated with accelerated deterioration in CD4+ cell counts, disease progression, poor quality of life and death. Few studies have evaluated the magnitude of cytopenias at the initiation of antiretroviral therapy (ART) in sub-Saharan Africa. The aim of this study was to determine the prevalence and predictors of cytopenias among HIV-infected adults at initiation of ART in a resource-limited setting in Ethiopia.

Methods: A cross-sectional study was conducted among HIV-infected adults initiating ART at the HIV care and treatment clinic of Mehal Meda Hospital between September 2008 and June 2019. Demographic, clinical and laboratory data of patients were collected from medical records. Anemia was defined according to WHO guidelines as hemoglobin concentration <12 g/dl for non-pregnant females and <13 g/dl for males. Leucopenia was defined as total white blood cell count $<4.0 \times 10^3$ cells/μL and thrombocytopenia as platelet count $<150 \times 10^3$ cells/μL. Logistic regression analysis was used to determine factors associated with the presence of cytopenias.

Results: Out of the total 566 patients included, 36.6% (95% CI 32.7–40.6%) had anemia, 17.1% (95% CI 14.2–20.4%) had leucopenia and 14.5% (95% CI 11.8–17.6%) had thrombocytopenia. A total of 53.2% (95% CI 49.1–57.3%) of patients had at least one form of cytopenia, 14.1% (95% CI 11.4–17.2%) had bicytopenia, and only 0.5% had pancytopenia. Factors associated with the presence of any cytopenia in multivariable analysis were male sex, advanced clinical disease stage, low CD4+ cell count, low BMI, and decreased renal function.

Conclusion: A substantial burden of cytopenias was detected among HIV-infected adults enrolled for care and treatment services in our setting. Patients with HIV infection should be screened for hematological abnormalities at initiation of ART because of its potential for morbidity and mortality during ART.

Keywords: hematological abnormalities, cytopenia, HIV, Ethiopia

Introduction

Hematologic abnormalities especially cytopenias (anemia, leucopenia and thrombocytopenia) are common complications of patients infected with Human Immunodeficiency Virus (HIV). These abnormalities occur mainly due to direct effects of the virus on the bone marrow, suppression of bone marrow by secondary infections or neoplasms, nutritional deficiencies or side effects of the drugs used.[1–3] Hematologic abnormalities can occur at all stages of HIV infection, but are more prevalent in patients with advanced disease and in ART naive patients than treated patients.[4–7] In patients with HIV, cytopenias have been associated with accelerated deterioration in CD4+ cell counts, disease progression, poor quality of life and subsequent death.[8–11] Hematologic abnormalities have also been demonstrated to predict poor responses to ART, Acquired Immunodeficiency Syndrome (AIDS)-related morbidity and mortality, and have been suggested as important parameters for predicting the clinical course of patients living with HIV infection.[12,13]

Anemia is the most common hematologic abnormality seen in HIV infection, occurring in 1.3% to 95% of patients and has been associated with impaired quality of life, poor immune recovery, progression of disease and a high risk of

hospitalization or mortality.[14–16] It is also an independent predictor of morbidity and mortality even upon initiation of therapy.[12,13,17] The pathogenesis of anemia in HIV patients is complex and may result from opportunistic infections, nutritional deficiencies, AIDS-associated malignancies, medications, and alteration in hematopoiesis induced by HIV itself or the drugs included in ART.[3,8,18] Factors that are associated with anemia among HIV-infected antiretroviral-naive patients include older age, gender, presence of opportunistic infection, advanced clinical HIV disease stages, low CD4+ cell counts, low body mass index and decreasing renal function.[19–21]

Leucopenia is the common hematologic abnormality that occurs in patients with HIV-infection and results from a direct effect of HIV virus, autoimmune disease, neoplasm and ART drugs and opportunistic infection.[3] It can occur in as many as 26.8% of patients and is associated with adverse HIV-related outcomes including both death and AIDS-related morbidity.[6,13] Studies indicated that worsening HIV disease parameters, ie, advanced clinical stages and low CD4+ cell counts, are associated with an increased risk of leucopenia among antiretroviral-naive patients.[20,21] Thrombocytopenia is a frequent hematologic abnormality in HIV patients and can occur at all stages of HIV infection. It can be found in about 4–40% of HIV-infected patients and results from decreased production or accelerated destruction of platelets, with immune thrombocytopenic purpura the most common cause.[2,10,22] Thrombocytopenia is associated with a substantial decline in CD4+ cell count, poor quality of life and increased morbidity and mortality.[9–12,22] Advanced clinical stages and immunosuppression were the factors significantly related to thrombocytopenia among antiretroviral-naive HIV patients.

Although previous studies have demonstrated the importance of hematological alterations at baseline as influences of treatment failure and mortality during ART among patients treated in sub-Saharan African countries,[9,12,23] few studies have evaluated the magnitude of cytopenias at the initiation of ART among HIV patients in sub-Saharan Africa. The aim of this study was to determine the prevalence and predictors of cytopenias among adult HIV-infected patients at initiation of ART in a resource-limited setting in Ethiopia.

Methods

Study Design and Population

We performed a cross-sectional study of HIV-infected adult patients initiating ART at the HIV care and treatment clinic of Mehal Meda Hospital, Central Ethiopia between September 2008 and June 2019. Mehal Meda Hospital is found in Mehal Meda town in Menz Gera Midir Woreda NorthShewa Zone of the Amhara Region, Ethiopia. Mehal Meda town is about 280 km away from the capital city Addis Ababa and 148 km from Debre Birhan city, the capital of Amhara Region. The hospital provides comprehensive health-care services including HIV/AIDS diagnosis, treatment and monitoring. Patients were included in this study if they were 18 years and older, and had full blood count results available at baseline before the initiation of ART. Patients with missing data for essential variables, and pregnant women were excluded from the study analysis.

Data Collection and Definitions

The medical records of HIV-infected patients enrolled to receive first-line ART, comprised of at least three drugs from September 2008 and June 2019 were reviewed. Patients' baseline socio-demographic (age, gender, residence, education, weight and height), clinical (WHO clinical stage of disease, CD4+ cell count and presence/history of opportunistic infection), and hematological data (hemoglobin level, total white blood cell count and platelet count) were collected. Serum creatinine results available at baseline were collected and renal function was assessed by estimated glomerular filtration rate (eGFR) calculated using the Modification of Diet in Renal Disease (MDRD) equation.[24] Complete blood count including hemoglobin concentration, total white blood cell count and platelet count (Sysmex KX-21N, Sysmex corporation Kobe, Japan) and CD4 cell count (BD Facscount system, Becton Dickenson, California, USA) were performed as part of a routine evaluation. Anemia was defined in accordance with the WHO guidelines,[25] as hemoglobin concentrations <12.0 g/dL for non-pregnant females and <13.0 g/dL for males. We further classified anemia as mild (11–11.9 g/dL for females and 11–12.9 g/dL for males), moderate (8–10.9 g/dL) and severe (<8 g/dL in both genders). Leucopenia was defined as total white blood cell count $<4.0\times10^3$ cells/µL and thrombocytopenia as platelet count

$<150\times10^3$ /µL.[20] Any cytopenia, bicytopenia and pancytopenia were defined as presence of at least one form of cytopenias (anemia, leucopenia or thrombocytopenia), two forms and all forms of cytopenias, respectively.

Statistical Analysis

Data were entered into an "EpiData version 3.1" and analysed with SPSS version 25 software (SPSS Inc., Chicago, IL, USA). The normal distribution of the data was tested by the Kolmogorov–Smirnov test. Comparisons of continuous variables between groups were carried out using Student's t-test and chi-square (x^2) test was used for categorical variables. A logistic regression analysis was used to identify predictors of anemia, leucopenia, thrombocytopenia and any cytopenia at the initiation of ART. Age, gender, WHO clinical stage of disease, CD4+ cell count, presence/history of opportunistic infections, body mass index (BMI), and eGFR were entered into a univariable model. Variables with P-value <0.25 in the univariable analysis were included in the multivariable models using forward stepwise method. Odds ratio (OR) with 95% confidence interval (CI) was used to measure the strength of statistical association. All tests were two-sided and a $P < 0.05$ was considered to be statistically significant.

Results

Patient Characteristics

A total of 566 HIV-infected adult patients who enrolled in the HIV care from September 2008 through November 2019 were included in this study. The mean age was 36.1 years (standard deviation [SD] ± 9.7) and 324 patients (67.1%) were females (Table 1). The median CD4+ cell count was 264 cells/mm³ (IQR: 192–500), and 439 patients (71.9%) had WHO clinical stage I/II at the time of enrollment. The mean BMI was 20.4 kg/m² (SD ± 3.6). The mean eGFR was 99.2 mL/min/1.73 m² (SD ± 58.2). The mean hemoglobin was 12.7 g/dl (SD ± 2.68), the median total white blood cell count was 5.7×10^3 cell/µL (IQR: 4.5–7.5), and the median platelet count was 240×10^3/µL (IQR: 176–310).

Prevalence and Factors Associated with Cytopenias

Two-hundred and seven patients (36.6%; 95% CI 32.7–40.6%) had anemia, including 92 patients (16.3%) with mild, 85 (15.0%) with moderate and 30 (5.3%) with severe anemia. Advanced clinical HIV/AIDS disease stage (WHO stage III/IV), low CD4+ cell count, history of opportunistic infections, low BMI and low eGFR were associated with anemia in the univariate analysis (Table 2). The multivariable analysis indicated that advanced clinical disease stage (AOR 2.07; 95% CI 1.37–3.18), CD4+ cell count <200 cells/mm³ (AOR 2.00; 95% CI 1.20–3.32), BMI < 18.5 kg/m² (AOR 2.89; 95% CI 1.46–5.69) and low eGFR: <60 mL/min/1.73 m² (AOR 2.41; 95% CI 1.46–3.98) and 60–89.9 mL/min/1.73 m² (AOR 1.92; 95% CI 1.27–2.89) were independently associated with anemia.

Leucopenia was present in 97 patients (17.1%; 95% CI 14.2–20.4%). In univariate analysis, several risk factors met the pre-defined criteria for inclusion in the multivariable model (age, residence, education, WHO clinical disease stage and CD4+ cell count) (Table 3). In the multivariable analysis, only CD4+ cell count <200 cells/mm³ (AOR 1.93; 95% CI 1.22–3.07) was independently associated with leucopenia. Thrombocytopenia was observed in 82 patients (14.5%; 95% CI 11.8–17.6%). The univariate analysis showed a significant association between thrombocytopenia and male sex, education, WHO clinical disease stage, CD4+ cell count and history of opportunistic infections (Table 4). In multi-variable analysis, male sex (AOR 3.22; 95% CI 1.93–5.38), advanced clinical disease stage (AOR 1.72; 95% CI 1.01–2.91) and CD4+ cell count <200 cells/mm³ (AOR 2.07; 95% CI 1.08–3.97) were independently associated with thrombocytopenia.

A total of 301 patients (53.2%; 95% CI 49.1–57.3%) had at least one form of cytopenia, 80 (14.1%; 95% CI 11.4–17.2%) had bicytopenia, and only 3 (0.5%) had pancytopenia. The anemia-leucopenia combination was the most frequent bicytopenia 41 (7.3%), followed by anemia-thrombocytopenia 28 (4.9%) and leucopenia-thrombocytopenia 11 (1.9%). Factors associated with the presence of any cytopenia in multivariable regression were male sex (AOR 1.73; 95% CI 1.20–2.48), advanced clinical disease stage (AOR 1.72; 95% CI 1.10–2.70), CD4+ cell count <200 cells/mm³ (AOR 2.24; 95% CI 1.49–3.37), BMI < 18.5 kg/m² (AOR 1.50; 95% CI 1.02–2.44) and decreased renal function (eGFR: <60 mL/min/1.73 m²) (AOR 2.50; 95% CI 1.52–4.12) (Table 5).

Table 1 Characteristics of the Study Patients at the Initiation of ART (N = 566)

Characteristics	
Age (years), Mean (SD)	36.1 ± 9.7
Age group, n (%)	
18–29 years	156 (27.6)
30–39 years	197 (34.8)
40–49 years	165 (29.2)
≥50 years	48 (8.5)
Gender, n (%)	
Male	242 (42.8)
Female	324 (57.2)
Residence, n (%)	
Urban	356 (62.9)
Rural	210 (37.1)
Education, n (%)	
<High school	452 (79.9)
≥High school	114 (20.1)
WHO stage, n (%)	
Stage I/II	439 (77.6)
Stage III/IV	127 (22.4)
CD4+ cell (cells/mm^3), Median (IQR)	264 (192–500)
<200	160 (28.3)
≥200	406 (71.7)
Opportunistic infections, n (%)	
Yes	149 (26.3)
No	417 (73.7)
Body mass index (kg/m^2), Mean (SD)	20.4 ± 3.6
Estimated glomerular filtration rate (mL/min/1.73m^2), Mean (SD)	99.2 ± 58.2
Hemoglobin (g/dl), Mean (SD)	12.7 ± 2.7
Total white blood cell count (×10^3 cell/μL), Median (IQR)	5.7 (4.5–7.5)
Platelet count (×10^3 cell/μL), Median (IQR)	240 (176–305)

Discussion

In this study, the prevalence of anemia, leucopenia and thrombocytopenia among antiretroviral–naive adult HIV-positive patients enrolled for care and treatment services in Mehal Meda Hospital, central Ethiopia were 36.6%, 17.1% and 14.5%, respectively. About 53.2% of the patients had at least one form of cytopenia (anemia and/or leucopenia and/or

Table 2 Factors Associated with the Presence of Anemia at Initiation of ART

Variables	Anemia		Crude OR (95% CI)	*P*-value	Adjusted OR (95% CI)	*P*-value
	Yes, n (%)	No, n (%)				
Age (years)				0.216		0.199
<35	97 (39.4)	149 (60.6)	1.24 (0.88–1.75)		1.27 (0.89–1.84)	
≥35	110 (34.4)	210 (65.6)	1		1	
Gender				0.252		
Male	95 (39.3)	147 (60.7)	1.22 (0.87–1.73)			
Female	112 (34.6)	212 (65.4)	1			
Residence				0.097		0.153
Urban	121 (34.0)	235 (66.0)	0.74 (0.52–1.06)		0.73 (0.59–1.35)	
Rural	86 (41.0)	124 (59.0)	1		1	
Education				0.776		
<High school	164 (36.3)	288 (63.7)	0.94 (0.62–1.44)			
≥High school	43 (37.7)	71 (62.3)	1			
WHO stage				0.001		0.001
Stage III/IV	63 (49.6)	64 (50.4)	2.02 (1.35–3.01)		2.00 (1.31–3.02)	
Stage I/II	144 (32.8)	295 (67.2)	1		1	
CD4+ cell count (cells/mm^3)				<0.001		0.001
<200	80 (50.0)	80 (50.0)	2.20 (1.51–3.19)		1.90 (1.28–2.81)	
≥200	127 (31.3)	279 (68.7)	1		1	
BMI (kg/m^2)				0.001		0.004
<18.5	76 (47.5)	84 (52.5)	1.90 (1.31–2.76)		1.78 (1.20–2.65)	
≥18.5	131 (32.3)	275 (67.7)	1		1	
Opportunistic infections				0.007		0.339
Yes	68 (45.6)	81 (54.4)	1.68 (1.15–2.56)		1.23 (0.80–1.89)	
No	139 (33.3)	275 (66.7)	1		1	
eGFR (mL/min/1.73 m^2)				<0.001		0.012
<60	56 (53.3)	49 (46.7)	2.35 (1.53–3.61)		1.80 (1.14–2.85)	
≥60	151 (32.8)	310 (67.2)	1		1	

thrombocytopenia). The main factors associated with the presence of any cytopenia were male sex, advanced clinical disease stage, low CD4+ cell count, low BMI, and decreased renal function.

Anemia was the most prevalent cytopenia in this study, occurring in 36.6% of antiretroviral-naive adult HIV-infected patients at initiation of ART. This high prevalence of anemia, already noted by other studies from sub-Saharan Africa,[11,14,20,21,26,27] could be explained by the more advanced immunodeficiency at enrollment as well as the higher prevalence of anemia in the general population in sub-Saharan Africa.[28,29] The presence of anemia prior to the initiation

Table 3 Factors Associated with the Presence of Leucopenia at Initiation of ART

Variables	Leucopenia		Crude OR (95% CI)	*P*-value	Adjusted OR (95% CI)	*P*-value
	Yes, n (%)	No, n (%)				
Age (years)				0.066		0.051
<35	34 (13.8)	212 (86.2)	0.66 (0.42–1.03)		0.63 (0.40–1.01)	
≥35	63 (19.7)	257 (80.3)	1		1	
Gender				0.313		
Male	37 (15.3)	205 (84.7)	0.79 (0.51–1.24)			
Female	60 (18.5)	264 (81.5)	1			
Residence				0.249		0.210
Urban	66 (18.5)	290 (81.5)	1.31 (0.83–2.09)		1.35 (0.84–2.17)	
Rural	31 (14.8)	179 (85.2)	1		1	
Education				0.207		0.173
<High school	82 (18.1)	370 (81.9)	1.46 (0.81–2.65)		1.53 (0.83–2.84)	
≥High school	15 (13.2)	99 (86.8)	1		1	
WHO stage				0.028		0.073
Stage III/IV	30 (23.6)	97 (76.4)	1.72 (1.06–2.79)		1.57 (0.96–2.58)	
Stage I/II	67 (15.3)	372 (84.7)	1		1	
CD4+ cell count (cells/mm^3)				0.004		0.005
<200	39 (24.4)	121 (75.6)	1.93 (1.23–3.05)		1.93 (1.22–3.07)	
≥200	127 (31.3)	279 (68.7)	1		1	
BMI (kg/m^2)				0.375		
<18.5	31 (19.4)	129 (80.6)	1.24 (0.77–1.99)			
≥18.5	66 (16.3)	340 (83.7)	1			
Opportunistic infections				0.380		
Yes	29 (19.5)	120 (80.5)	1.24 (0.77–2.01)			
No	68 (16.3)	349 (83.7)	1			

of combination ART may complicate the treatment of HIV, associated with poor response to ART, treatment failure and clinical disease progression to AIDS and predict decreased survival in HIV-infected patients after ART initiation.[9,14,23] Without intervention, anemia can lead to significant symptoms like fatigue, breathlessness, difficulty in concentration and other effects on functionality and quality of life. Targeted screening for anemia at initiation of ART and modifying the potential risk factors are primary needs to improve disease outcomes in people living with HIV.

We found that advanced clinical HIV disease stage (WHO clinical stage III/IV), low CD4+ count, low BMI and low eGFR are associated with an increased risk of anemia in antiretroviral-naive HIV-infected patients. Worsening parameters of HIV disease, ie, WHO clinical stage III/IV and CD4+ cell count <200 cells/mm^3, are significantly associated with an increased risk of anemia at ART initiation, and this was consistent with findings of previous related studies.[16,19,30,31] We

Table 4 Factors Associated with the Presence of Thrombocytopenia at Initiation of ART

Variables	Thrombocytopenia		Crude OR (95% CI)	*P*-value	Adjusted OR (95% CI)	*P*-value
	Yes, n (%)	No, n (%)				
Age (years)				0.875		
<35	35 (14.2)	211 (85.8)	0.96 (0.60–1.55)			
≥35	47 (14.7)	273 (85.3)	1			
Gender				<0.001		<0.001
Male	56 (23.1)	186 (76.9)	3.45 (2.09–5.69)		3.22 (1.93–5.38)	
Female	26 (8.0)	298 (92.0)	1		1	
Residence				0.917		
Urban	52 (14.6)	304 (85.4)	1.03 (0.63–1.67)			
Rural	30 (14.3)	180 (85.7)	1			
Education				0.026		0.132
<High school	58 (12.8)	394 (87.2)	0.55 (0.33–0.94)		0.65 (0.37–1.14)	
≥High school	24 (21.1)	90 (78.9)	1		1	
WHO stage				0.001		0.042
Stage III/IV	30 (23.6)	97 (76.4)	2.30 (1.39–3.80)		1.72 (1.01–2.97)	
Stage I/II	52 (11.8)	387 (88.2)	1		1	
CD4+ cell count (cells/mm^3)				0.002		0.004
<200	35 (21.9)	125 (78.1)	2.14 (1.32–3.47)		2.07 (1.08–3.44)	
≥200	47 (11.6)	359 (88.4)	1		1	
BMI (kg/m^2)				0.455		
<18.5	26 (16.3)	134 (83.7)	1.21 (0.73–2.01)			
≥18.5	56 (13.8)	350 (86.2)	1			
Opportunistic infections				0.044		0.233
Yes	29 (19.5)	120 (80.5)	1.66 (1.01–2.73)		1.37 (0.82–2.31)	
No	53 (12.7)	364 (87.3)	1		1	

also found evidence that low BMI is associated with an increased risk of anemia prior to ART initiation. Low level of BMI (<18.5 kg/m^2) has been previously found to have significant association with the occurrence of anemia.[19,31] Our results also support findings that impaired renal function is associated with a higher risk of anemia among HIV patients initiating ART.[32] Impaired renal function in HIV infection has a significant impact on lowering hemoglobin levels, resulting in a higher risk of anemia.[33] The multifactorial drivers of anemia in HIV-infected patients prior to initiation of ART require an integrated approach to help ameliorate anemia and its negative health effects while on ART.

The prevalence of leucopenia in our study (17.1%) was comparable with other studies of HIV-infected adults initiating ART in sub-Saharan Africa, ranging between 13.4% and 24.4%.[20,21,26,27,34] A study from India indicated that 18.3% of HIV patients had leucopenia first at the time of presentation,[35] while in the Chinese study, leucopenia was reported in 33.2% of antiretroviral-naive HIV-infected patients.[36] In multivariate analysis, lower CD4+ cell count was independently associated with an increased risk of having leucopenia in HIV-infected antiretroviral-naive patients. This

Table 5 Factors Associated with the Presence of Any Cytopenia at Initiation of ART

Variables	Any Cytopenia		Crude OR (95% CI)	*P*-value	Adjusted OR (95% CI)	*P*-value
	Yes, n (%)	No, n (%)				
Age (years)				0.889		
<35	130 (52.8)	116 (47.2)	0.98 (0.70–1.36)			
≥35	171 (53.4)	149 (46.6)	1			
Gender				0.006		0.003
Male	145 (59.9)	97 (40.1)	1.61 (1.15–2.26)		1.73 (1.20–2.48)	
Female	156 (48.1)	168 (51.9)	1		1	
Residence				0.270		
Urban	183 (51.4)	173 (48.6)	0.83 (0.59–1.16)			
Rural	118 (56.2)	92 (43.8)	1			
Education				0.259		
<High school	235 (52.0)	217 (48.0)	0.79 (0.52–1.19)			
≥High school	66 (57.9)	48 (42.1)	1			
WHO stage				0.004		0.042
Stage III/IV	82 (64.6)	45 (35.4)	1.83 (1.22–2.76)		1.72 (1.10–2.40)	
Stage I/II	219 (49.9)	220 (50.1)	1		1	
CD4+ cell count (cells/mm^3)				<0.001		0.001
<200	112 (70.0)	48 (30.0)	2.68 (1.81–3.96)		2.24 (1.49–3.37)	
≥200	189 (46.6)	217 (53.4)	1		1	
BMI (kg/m^2)				0.009		0.045
<18.5	99 (61.9)	61 (38.1)	1.64 (1.13–2.38)		1.50 (1.02–2.24)	
≥18.5	202 (49.8)	204 (50.2)	1		1	
Opportunistic infections				0.001		0.164
Yes	96 (64.4)	53 (35.6)	1.87 (1.27–2.76)		1.36 (0.88–2.09)	
No	205 (49.2)	212 (50.8)	1		1	
eGFR (mL/min/1.73 m^2)				<0.001		<0.001
<60	77 (73.3)	28 (26.7)	2.91 (1.82–4.65)		2.50 (1.52–4.12)	
≥60	224 (48.6)	237 (51.4)	1		1	

was consistent with other studies that have found HIV patients with low CD4+ cell count to have a higher odds of leucopenia than those with higher CD4+ cell count at the time of antiretroviral-treatment initiation.[20,21,26,34,36]

About 14.5% of our patients had thrombocytopenia at the time of initiation of ART. This was consistent with findings reported from Tanzania,[26] China[36] and India,[35] where thrombocytopenia was found in 14.4%, 15.6% and 15.8% of HIV-infected adult antiretroviral-naive patients, respectively. This was; however, lower than the 18.7% prevalence reported in Northeast Ethiopia,[20] and higher than 5.9% in Northwest Ethiopia[37] and 8.3% in Uganda.[21] These differences could be due to the difference in the study population, sample size, study design and variation in the definition of

thrombocytopenia. Male sex, advanced clinical disease stage and severe immunosuppression (CD4+ cell count <200 cells/mm^3) were independent predictors of having thrombocytopenia in this study. This was consistent with the Ugandan study[21] that has found males to be more likely to have thrombocytopenia than females at initiation of ART. Gender-dependent difference in platelet count, being lower in males than females, could be responsible. However, some of the studies failed to find a significant relationship between sex and thrombocytopenia.[20,26,36,37] This study also confirms the findings of other studies that have shown an association between advanced HIV disease (WHO clinical disease stage III/IV and CD4+ cell count <200 cells/mm^3) and the presence of thrombocytopenia in HIV-infected antiretroviral-naive patients.[20,21,26,35–37]

More than half (53.2%) of the patients had at least one form of cytopenia (anemia and/or leucopenia and/or thrombocytopenia) in this study. In the Northeast Ethiopian study,[20] the overall magnitude of any cytopenia was 63.4% among ART naive HIV-infected patients. In the Ugandan study by Kyeyune et al,[21] 65% of the patients had at least one form of cytopenia at initiation of ART. In the Nigerian study, 59.4% of treatment-naive HIV-infected patients had cytopenia.[38] The factors independently associated with the presence of any cytopenia in this study were male sex, advanced clinical HIV disease stage, low CD4+ cell count, low BMI, and decreased renal function. The Ugandan study[21] reported females were more likely to have at least one form of cytopenia than males at initiation of ART, while other studies did not show any significant association between sex and the presence of any cytopenia.[20,26] Our finding is however in line with the findings of other related studies, which reported a significant association of advanced HIV infection (advanced clinical stages and low CD4+ cell counts) with the presence of any cytopenia.[20,21,26] The present study revealed a significant increase in the odds of anemia with decreasing BMI, which is consistent with the Ugandan study.[21] The association of decreased renal function with any cytopenia may be due to the combined effect of impaired renal function and HIV infection on cytopenia and specifically anemia in this population.[33] However, no studies were available to assess the possible contribution of decreased renal function to the occurrence of cytopenia.

The limitations of this study include its cross-sectional design, which makes determination of temporal relationships between cytopenias and associated factors difficult. We did not assess the various causes of cytopenia and specifically anemia in this population. Well-controlled cohort studies would be appropriate to evaluate the potential impact of cytopenias on clinical outcomes of people living with HIV in our settings.

Conclusions

We detected a substantial burden of cytopenias (anemia, leucopenia and thrombocytopenia) among HIV-infected adult patients enrolled for care and treatment services in resource-limited setting in Ethiopia. The findings indicate that patients with HIV infection should be screened for hematological abnormalities at initiation of ART, with a special attention to be focused on males, patients with advanced disease stages, low CD4+ cell count, low BMI and low eGFR, because of its potential for morbidity and mortality during ART.

Abbreviations

AIDS, acquired immunodeficiency syndrome; AOR, adjusted odds ratio; ART, antiretroviral therapy; BMI, body mass index; CD4, cluster of differentiation; CI, confidence interval; eGFR, estimated glomerular filtration rate; HIV, human immunodeficiency virus; IQR, inter quartile range; MDRD, modification of diet in renal disease; OR, odds ratio; SD, standard deviation; WHO, World Health Organization.

Data Sharing Statement

The data of this study cannot be shared publicly due to presence of sensitive (confidential) participants' information and additional data than that used in this publication. But the data are available from the corresponding author on reasonable request.

Ethics and Consent Statement

Ethical approval of the protocol was achieved from the Institutional Review Board of College of Medicine and Health Sciences, Wollo University. As only routine data were analyzed, informed consent was not required; but patient's

identifiers were removed and only code numbers were used throughout the study. This study was conducted in accordance with the declaration of Helsinki.

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Author Contributions

All authors made a significant 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, revising, or critically reviewing 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 work.

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Disclosure

The authors declare that they have no competing interests in this work.

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