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ORIGINAL RESEARCH

Magnitude and Factors Associated with Cytopenia Among Children on Highly Active Antiretroviral Therapy at Hawassa University College of Medicine and Health Science, Sidama Region, Southern Ethiopia

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Background: The most common abnormality in HIV-infected children is cytopenia, a hematological complication characterized by a decline in any of the blood cell lines. It is associated with a higher risk of morbidity and mortality. Therefore, this study aimed to assess the prevalence and associated factors of cytopenia among HIV-positive children on highly active antiretroviral therapy (HAART).

Methods: Hospital-based cross-sectional study design was conducted on HIV-positive children on HAART from July to September 2020. Socio-demographic and clinical characteristics of the study participants' data were collected using a structured questionnaire. Hematological parameters from the blood sample were analyzed using Ruby Cell-Dyne 300 hematology auto-analyzer. The data were analyzed using SPSS version 20. Logistic regression was used to assess the predictors of cytopenia among the study participants. P-values of less than 0.05 are considered statistically significant.

Results: Two hundred seventy-three HAART-experienced children were enrolled in this study, and 50.9% were females. At baseline, 40.7% of children were anemic. The overall magnitude of cytopenia among the study participants was 26.7%. The prevalence of anemia, thrombocytopenia, leucopenia and neutropenia among children was 11.4%, 4.0%, 14.3%, and 18.3%, respectively. Patients with an undetectable viral load (AOR = 0.5, CI = 0.3–0.9) are 50% less likely to report cytopenia. HAART-experienced children living in rural areas are more likely to develop cytopenia (AOR = 2.6, CI = 1.3–5.2) than those living in urban areas.

Conclusion: Hematologic abnormalities are common problems among children on highly active antiretroviral therapy. Therefore, routine investigation of hematological and immunological changes following appropriate therapeutic interventions is recommended.

Keywords: HIV, cytopenia, HAART, children, Ethiopia

Introduction

The human immunodeficiency virus (HIV) remains a global health crisis. According to the USAID 2020 report, 37.7 million people worldwide are living with HIV/AIDS, and 1.7 million of them are children younger than 15 years old.[1] The documented annual rate of new HIV infections globally was 1.5 million; of these, 150, 000 were children younger than 15 years old, and 2800 were from Ethiopia. In addition, 68,000 deaths worldwide were documented from AIDS-related causes; of these, 99,000 were children younger than 15. Ethiopia has a significant pediatric HIV burden, with approximately 2000 children dying from AIDS-related causes.[1]

AIDS is a systemic disease caused by HIV and characterized by severe impairment and progressive damage to both cellular and humoral immune responses. In addition to immunological impairment,[2] hematological defects, particularly cytopenia,

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associated with HIV disease progression, have been identified as strong predictors of mortality and morbidity in HIV-infected individuals.[3] Cytopenia is a decline in any of the blood cell lines, resulting in anemia, leucopenia, and thrombocytopenia.[4]

Anemia and neutropenia are the most common cytopenias among HIV-positive children. The most common causes of anemia and neutropenia are bone marrow suppression caused by HIV infection, mediated by proinflammatory cytokine and chemokine expression, and subsequent alteration of the bone marrow microenvironment.[5,6] Anemia in HIV-infected persons is associated with CD4 cell depletion and progression to AIDS.[7] Neutropenia is recurrently seen in the later phase of HIV infection after developing AIDS. It is also associated with certain antiretroviral treatments (ART).[8] Thrombocytopenia is usually caused by immune-mediated destruction of platelets and inadequate production.[9] HIV infection can also directly decrease the lymphocyte level as the infection progresses, leading to lymphopenia.

Highly active antiretroviral therapy (HAART) initiation has played a critical role in the clinical management of HIV-infected individuals by restoring immune function, preventing morbidity and mortality, improving quality of life, and preventing the transmission of the virus to other uninfected individuals.[10] However, many HIV-infected patients receiving HAART failed to achieve sustained virological suppression by treatment.[11]

Although the range of hematological abnormalities in HIV-infected children is caused by HIV infection, other factors and conditions include opportunistic infection, drugs like zidovudine and Co-trimoxazole, immune mechanisms, and malignancies have also been documented to have the potential to influence all hematopoietic cell lines.[5,12]

A thorough assessment of an HIV patient's blood cell profile is vital to the clinician's informed choice of the correct regimen and overall patient care. Even though some studies on the hematological parameters of HIV patients on HAART have been carried out, hematological studies on HAART-experienced children in our country are scarce. Therefore, this study aimed to determine the magnitude of and factors associated with cytopenia among HIV-infected children on HAART at Hawassa University Comprehensive Specialized Hospital (HUCSH), Sidama Region, South Ethiopia.

Materials and Methods

Study Area and Study Participants

An Institutional-based cross-sectional study was conducted at the HUCSH ART pediatrics clinic from July to September 2020. Two hundred seventy-three HAART-experienced HIV-infected children aged between 6 months and 14 years old who were on follow-up at an ART clinic during the study period were enrolled. Meanwhile, children who are severely sick, on radiation and immunosuppressive therapy for the past 45 days, and who have undergone surgical interventions resulting in massive blood loss were excluded. In addition, children whose information was incomplete or unreadable and who were without a legal guardian or unaccompanied children during the study period were excluded. We included all the registered HAART-experienced HIV-positive children at the ART clinic. Therefore, we did not calculate the sample size. A convenient sampling technique was applied to recruit study participants who met the inclusion criteria.

Socio-Demographic and Clinical Data Collection

A pretested, structured questionnaire was implemented to collect the study participants' socio-demographic characteristics, such as age, gender, and residence of the study participants via face-to-face interviews. Additionally, detailed clinical data of the children, such as WHO HIV disease stage, type of HAART, and duration of HAART, were collected by reviewing the medical records of HIV-infected children. Anthropometric measurements (height and weight) were taken using calibrated equipment, and Z-scores of nutritional indices, such as weight-for-age (WAZ), height-for-age (HAZ), were scored using WHO Anthro (for children aged ≤5 years), and Anthro-plus (for children aged >5 years) software. Two trained pediatric nurses and a pediatric resident were involved in the data collection. The principal investigator strictly supervised the data collection process.

Laboratory Investigation

After collecting 5mL of venous blood in an EDTA tube from each study participant, complete blood count (CBC) results, which include the WBC parameter, RBC parameter, and platelet parameter, were determined with the RUBY Cell-Dyne 3000 hematology auto-analyzer (Abbott Laboratories diagnostics division, USA). The analysis was accomplished within one hour of blood collection at the HUCSH hematology laboratory. HIV viral load was directly determined by an

advanced molecular technique on blood plasma collected from each study participant. The TAQMAN1 AMPLICOR HIV-1 MONITOR (Roche Molecular Systems), an in vitro diagnostic nucleic acid amplification test, was used to quantify HIV-1 RNA in human plasma. Then, the amount of circulating HIV was measured and reported as HIV RNA copies per milliliter (copies/mL) of plasma by well-trained laboratory technologists. The BD FACSCOUNT analyzer (Becton Dickenson and Company, California, and USA) was used to count CD4+ T cells.

The pre-analytical, analytical, and post-analytical factors influencing the laboratory result were controlled and maintained by a senior laboratory technologist at the hematology laboratory. The proper functioning of instruments, laboratory reagents, and the technical performance of the analyzer was also checked by using a quality control (QC) sample before running the study participants' sample. The run will be repeated if the quality control result falls outside the established values.

Hematological abnormalities are defined as follows: leukopenia: white blood cell (WBC) count less than 4000/mm3; leucocytosis: WBC count >12,000/mm3; lymphopenia: lymphocyte count <1500/mm3; platelet count 150,000/mm3 is considered thrombocytopenia; platelet count >450,000/mm3 is considered thrombocytosis. Neutropenia is an absolute neutrophil count (ANC) of <1500/mm3. Anemia was defined as having a hemoglobin concentration of less than 11 g/dl for ages 6–59 months, less than 11.5 g/dl for ages 5–11 years, and less than 12 g/dl for ages 12–14-year-old children.

Data Management and Analysis

The data were cleaned, edited, checked for completeness, entered, and analyzed using SPSS version 20 software. The results were reported as the mean and standard deviation for continuous variables, and categorical variables were reported as percentages. Categorical data were analyzed using Fisher's exact test. Logistic regression analysis was applied to determine the predictor of cytopenia. A P value of <0.05 was used to describe any statistical significance.

Result

Socio-Demographic and Clinical Characteristics of Study Participants

Two hundred seventy-three HAART-experienced HIV-positive children were recruited, of which half (50.9%) were females and 82.1% were urban residents. The mean age and standard deviation (SD) of the study participants were 10.2 ±3.2 years, and the majority (80.6%) of them were above seven years old (Table 1).

Based on the WHO clinical stage of HIV, 98.6% of the participants were in the early WHO clinical stage (stage I or II). 27.5% of the study participants have been on HAART for over ten years. According to the HAART type, 89.4% of study participants were on AZT/3TC/EFV.16.1% of the study participants are on co-medication, and 12% had a CD4 cell count of ≤350 cells/mm^3 (Table 2).

Table 1 Socio-Demographic Characteristics of the Study Participants Attending HUCSH from July to September 2020, Hawassa, Ethiopia (n = 273)

Variables	Category	Sex(N=273)		p-value
		Male	Female	
Age in years	<5	8 (2.9)	8 (2.9)	0.4
	5–11	75 (27.5)	68 (24.9)	
	12–14	50 (18.3)	64 (23.4)	
Residence	Urban	107 (39.2)	117 (42.9)	0.5
	Rural	26 (9.5)	23 (8.4)	
Educational status	Unable to read and write	22 (8.1)	16 (5.9)	0.5
	Primary	104 (38.1)	115 (42.1)	
	Secondary	7 (2.5)	9 (3.3)	

(*Continued*)

Table 1 (Continued).

Variables	Category	Sex(N=273)		p-value
		Male	Female	
Family size	≤3	21 (7.7)	25 (9.2)	0.7
	4–7	93 (34.1)	99 (36.3)	
	>7	19 (7.0)	16 (5.9)	
Primary caretaker	Mother or father	99 (36.2)	114 (41.8)	0.2
	Other	35 (12.8)	26 (9.5)	
Family income (in Ethiopian birr per month)	<1000	58 (21.2)	53 (19.4)	0.4
	≥1000	75 (27.5)	87 (31.9)	

Table 2 Clinical Characteristics of HAART Experienced HIV Positive Children Attending HUCSH (N = 273)

Variables	Category	Sex(N=273)	
		Male	Female
WHO stage	1 and 2	129 (47.3)	140 (51.3)
	3 and 4	4 (1.4)	0
HAART duration(in years)	<10	92 (46.5)	106 (53.5)
	≥10	41 (54.7)	34 (45.3)
Malaria	Yes	0	1
	No	133 (48.7)	139 (50.9)
Temperature C°	≤37	126 (46.2)	135 (49.5)
	>37	7 (2.6)	5 (1.8)
Other medication	No	100 (36.6)	129
	Co-trimoxazole	23 (8.4)	8 (2.9)
	Amoxicillin	3 (2.9)	2 (0.7)
	Augmentin	1 (0.4)	1 (0.4)
	Nutritional supplement	6 (2.1)	0
ART Drugs	AZT/3TC/EVF	120 (44.0)	124 (45.4)
	ABC/3TC/CALETR	9 (3.3)	11 (4.0)
	TDF/3TC/CALETRA	4 (1.5)	5 (1.8)
Co-medication	Yes	100 (43.7)	129 (56.3)
	No	33 (75.0)	11 (25.0)

(*Continued*)

Table 2 (Continued).

Variables	Category	Sex(N=273)	
		Male	Female
CD4 cell cells/mm^3	≤350	23 (8.4)	12 (4.4)
	350–500	16 (5.8)	9 (3.3)
	>500	94 (34.4)	119 (43.6)
Viral load	ND	68 (24.9)	95 (34.8)
	≤150	32 (11.7)	21 (7.7)
	>150	33 (12.1)	24 (8.8)
HAZ	≤-2	49 (18.0)	50 (18.2)
	>-2	84 (30.8)	90 (33.0)
WAZ	<-2	20 (7.3)	7 (2.6)
	≥-2	113 (41.4)	133 (48.7)

Abbreviations: HAZ, Height-Age Z score; WAZ, Weight-Age Z score.

Clinical Characteristics of the Study Participants

98.6% of the study participants are in clinical stages I or II, and 51.3% are females. Regarding ART drug enrollment of the study participants, 89.4% were on AZT/3TC/EFV. 59.7% of the study participants' viral load is not detectable 34.8% of female study participants had no detectable viral load, while 12.1% of male study participants had a viral load of >150 copies. 36.2% of HAART-experienced HIV-positive children have a height-age-z score of ≤-2 (Table 2).

Trends of Hemoglobin and CD4+ T Cell Over Time

40.7% of HAART-experienced HIV-positive children were anemic, and the mean hemoglobin level increased from 12 mg/dl at baseline to 13.1 mg/dl during the study period. The median and interquartile range of CD4+ T lymphocyte cells were 18.4 and 12.3–26.8, respectively, with the majority of study participants (37.3%) having a CD4+ T lymphocyte cell percentage of 15%. The CD4+ T cell median percentage trend increased from 18.4% at baseline to 29.2% during the study period.

The Magnitude of Cytopenia and Its Distribution by CD4+ T Cell and Viral Load

The overall magnitude of cytopenia among the study participants was 26.7%. Neutropenia is the most common (18.3%) cytopenia, followed by leucopenia (14.3%) and anemia (11.4%) (Figure 1).

Distribution of Cytopenia Stratified by Gender

Leucopenia among men (17.2%) is higher than in females (11.5%). Gender-wise variation of all types of cytopenia is not statistically significant ($P > 0.05$) except for neutropenia ($P = 0.01$) (Figure 2).

Distribution of Cytopenia Stratified by Age

Anemia is the most common cytopenia (25%) among children <5 years old, while neutropenia (21.9%), lymphopenia (12.3%), and thrombocytopenia (5.3%) are the most common cytopenias among HAART-experienced children aged 11–14 years old (Figure 3).

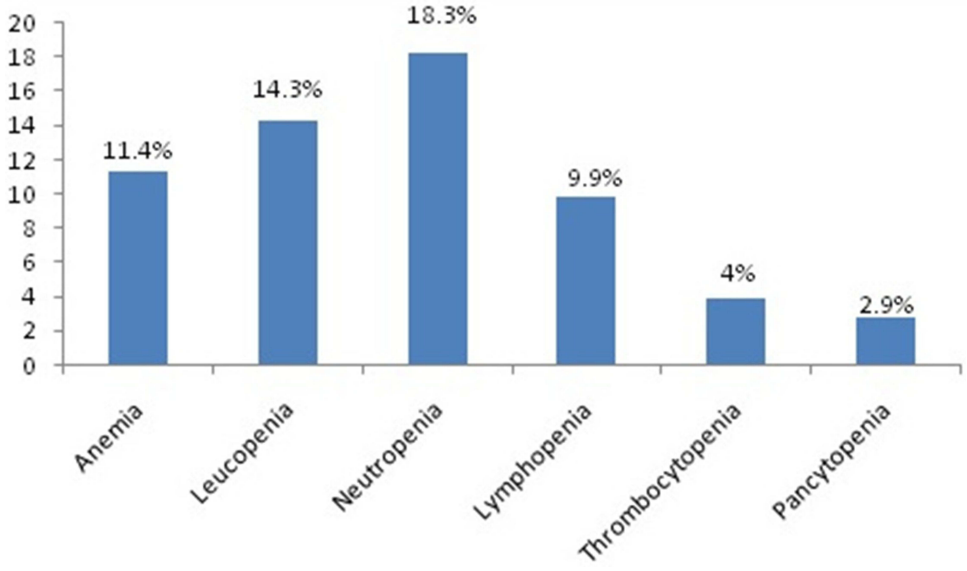

Figure 1 Distribution of cytopenia among HIV positive children on HAART at HUCSH (N = 273).

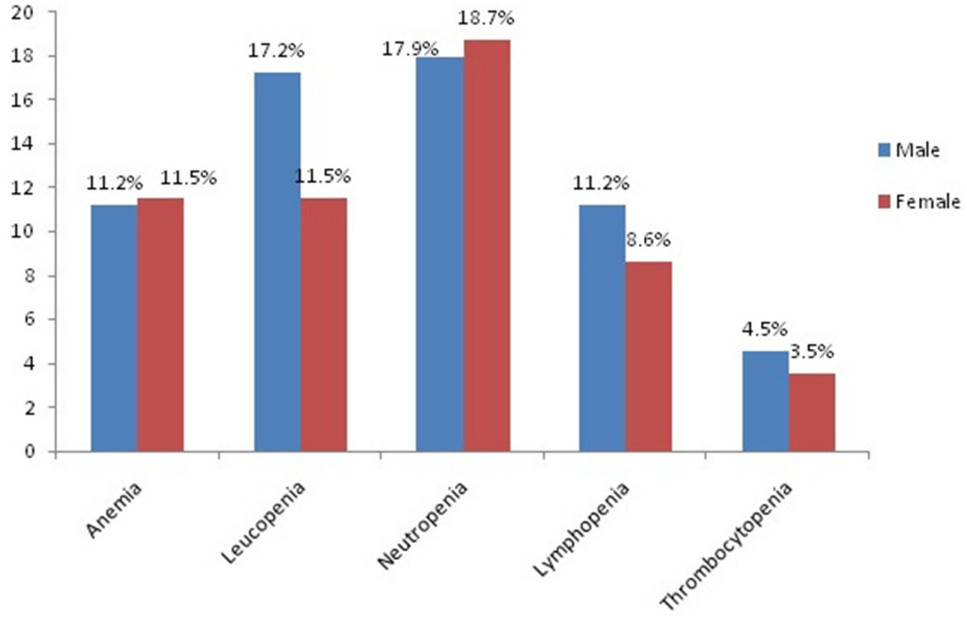

Figure 2 Gender wise distribution of cytopenia among HIV positive children on HAART at HUCSH (N = 273).

Cytopenia Distribution of Study Participants by CD4 Percentage and Viral Load

All types of cytopenia (anemia, leucopenia, leucocytosis, neutropenia, lymphopenia, and thrombocytopenia) were common among HAART-experienced HIV-positive children with a CD4 cell percentage of <15% and among study participants who had >150 viral copies/mm3 (Table 3).

Correlation of Hematological Parameters with a Viral Load of the Study Participants

The viral load of the study participants was negatively correlated with hemoglobin level, lymphocyte count, and platelet count ($p < 0.05$) (Table 4).

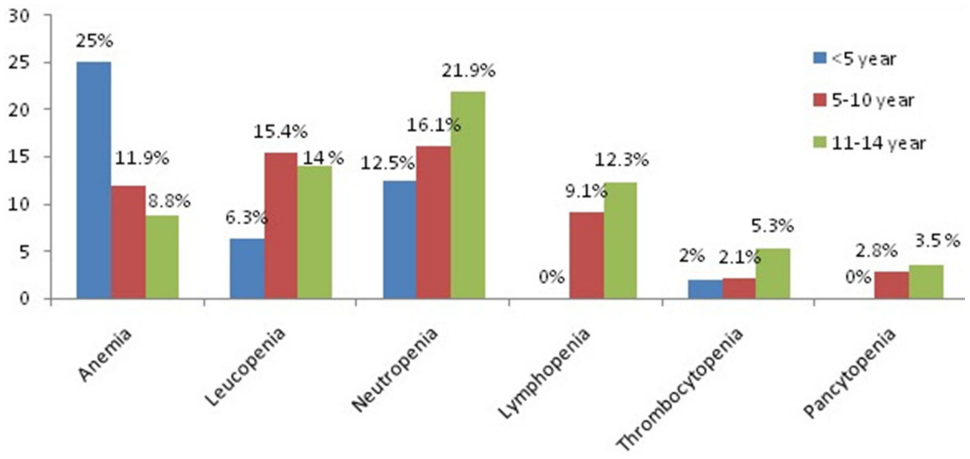

Figure 3 Distribution of cytopenia among HIV positive children on HAART at HUCSH stratified by age (N = 273).

Factors Associated with Cytopenia Among HAART Experienced HIV Positive Children

Independent variables were inserted into a binary logistic regression. On bivariate regression, gender, residence, family size, baseline CD4 percentage, viral load, WHO clinical stage, medication, and HAZ were candidate variables ($p < 0.25$). Residence and viral load were the only statistically significant ($p < 0.05$) variables associated with cytopenia (Table 5).

Discussion

The overall magnitude of cytopenia among study participants was 26.7%. Anemia, thrombocytopenia, leucopenia, and neutropenia were seen in 11.4%, 4.0%, 14.3%, and 18.3% of children, respectively.

The overall prevalence of cytopenia among the study participants was 26.7%, which is lower than the study done in Gonder, Northeast Ethiopia (38.8.%).[13] The observed difference could be attributed to differences in the study participants' HAART duration and regimen type, opportunistic infection, viral load, and nutritional status.

The prevalence of leukocytosis in our study was 4.8%, which is relatively comparable with the study done in North West Ethiopia (4.1%) (16) but lower than the study done in Kenya (6.2%).[14] The prevalence of leukopenia was 14.3%, which is relatively comparable with the study done in northwest Ethiopia (13.5%),[15] but higher than in Bahir Dar, Ethiopia (4.5%).[16]

Table 3 Cytopenia Distribution of Study Participants by CD4 Percentage and Viral Load of HAART Experienced HIV Positive Children at HUCSH (N = 273)

Variables	CD4 Percentage			P-value	Viral Load		
	>25	15–25	<15		ND	<150	≥150
Anemia	18 (10.9)	8 (11.1)	5 (13.9)	0.85	13 (8.0)	4 (7.5)	14 (24.5)
Leucopenia	19 (11.5)	10 (13.9)	10 (27.8)	0.02	18 (11.0)	7 (13.2)	14 (24.5)
Leucocytosis	6 (3.6)	7 (9.7)	0	0.02	6 (3.7)	5 (9.4)	2 (3.5)
Neutropenia	30 (18.2)	13 (18.1)	7 (19.4)	0.9	29 (17.8)	8 (15.4)	13 (22.8)
Lymphopenia	11 (6.7)	6 (8.3)	10 (27.7)	0.001	4 (2.5)	6 (11.3)	17 (29.8)
Thrombocytopenia	5 (3.0)	2 (2.8)	4 (11.1)	0.07	5 (3.1)	1 (1.9)	5 (8.8)
Pancytopenia	5 (3.0)	1 (1.4)	2 (5.5)	0.5	1 (0.01)	1 (1.9)	6 (10.5)

Abbreviations: ND, Not detectable; CD, cluster of differentiation.

Table 4 Correlation of Hematological Parameters with a Viral Load of HAART-Experienced HIV-Positive Children at HUCSH (N = 273)

Hematological Parameter	Mean ± SD/ Median(IQR)	Pearson Correlation, r	P-value
Hb	13.1 (1.5)	−0.2	0.009
RBC	4.1 (0.6)	−0.2	0.01
WBC(Median)	6.4 (4.9–8.4)	−0.1	0.08
Neutrophil	46.0 (35.2–55.0)	0.04	0.5
LYM	41.3 (32.3–51.4)	−0.3	<0.001
Platelet	320 (258–366)	−0.2	0.004

Abbreviations: IQR, Interquartile range; Hb, hemoglobin; LYM, Lymphocyte; RBC, Red blood cell; SD, Standard deviation; WBC, White blood cell.

Table 5 Factors Associated with Cytopenia Among HAART Experienced HIV Positive Children at HUCSH (N = 273)

Variable	Category	COR(95% CI)	p-value	AOR(95% CI)	p-value
Gender	Male	1.4 (0.8–2.4)	0.2*	1.1 (0.6–2.0)	0.8
	Female	1		1	
Residence	Urban	1		1	
	Rural	2.2 (1.2–4.3)	0.02*	2.6 (1.3–5.2)	0.01**
Family size	≥3	1		1	
	<3	1.8 (0.9–3.5)	0.09*	1.8 (0.9–3.7)	0.1
Baseline CD4%	<15	1.9 (0.9–3.7)	0.09	1.5 (0.7–3.2)	0.3
	15–25	1.2 (0.6–2.6)	0.6	1.2 (0.6–2.7)	0.6
	>25	1		1	
Viral	ND	0.5 (0.3–0.8)	0.008*	0.5 (0.3–0.9)	0.03**
	Detectable	1		1	
WHO stage	1 and 2	0.1 (0.01–1.2)	0.07*	0.1 (0.01–1.4)	0.09
	3 and 4	`1		1	
Co-medication	Yes	0.6 (0.3–1.1)	0.1	1.2 (0.2–9.3)	0.8
	No	1		1	
Additional medication	Yes	0.6 (0.3–1.2)	0.1*	0.7 (0.3–1.4)	0.3
	No	1		1	

Notes: *P-value< 0.25; **P-value <0.05.
Abbreviations: CD, Cluster of differentiation; ND, None detectable; WHO, World health organization; HAZ, height- Age-Z score.

Pre-HAART initiation, 40.7% of HIV-positive children at HUCSH were anemic, which aligns with the studies reported from northwest Ethiopia 42.8%,[17] 47.8% in Uganda,[18] and 37.5% in Brazil.[19] However, the current finding was higher than the study done in Addis Ababa, Ethiopia (18.9%)[20] and lower than the study done in India (65.5%).[21] The prevalence of anemia after initiation of HAART was 11.4%, which was in line with the study conducted in Addis

Ababa, Ethiopia (10.4%)[20] but lower than the study done in northwest Ethiopia (18.9%)[15] and Nigeria (54.2%).[22] WHO clinical stage difference, geographic difference, age variation of the study participants, the cut-off value applied, parasitic infection, and nutritional pattern might be the causes for the disparity among the studies.

The most common cytopenia was neutropenia (18.3%), followed by leucopenia (14.3%), anemia (11.4%), lymphopenia (9.9%), and thrombocytopenia (4%) which is in agreement with results documented by different studies.[13,23,24] This is in contrast to the study conducted in northwest Ethiopia (15.3%),[15] Bahir Dar (9.8%),[25] and Addis Ababa, Ethiopia (5.7%).[20] The possible reason for the discrepancies among the studies could be due to the difference in the immunological status of the study participants and the sample size difference. Neutropenia has been widely reported to be associated with some HAART drugs, particularly combination drugs that contain zidovudine. Prophylactic co-trimoxazole, which is frequently used to prevent opportunistic infections in these patients, is thought to cause neutropenia via an unknown mechanism.[26] AZT therapy is probably the most common cause of neutropenia in patients with HIV infection.[27]

In our study, the prevalence of thrombocytopenia was 4%, which was higher than the study reported in Northwest Ethiopia (1.8%)[15] and Lagos, Nigeria (2.5%)[28] but lower than the Jimma, Ethiopia study (7.8%),[29] Addis Ababa, Ethiopia (5.7%),[20] Bahir Dar Ethiopia (6.3%),[25] Zimbabwe (7.2%),[30] Kenya (21%),[31] Kenya (6.5%),[14] Mumbai, India (10%),[32] West Bengal, India (11%),[33] Nepal (17.9%),[34] and Uttar Pradesh, India (29.78%).[35] The difference in prevalence could be due to the difference in sample size, geographical location, and the cut-off value used. Ineffective platelet production and increased platelet destruction by the spleen are the most common mechanisms of thrombocytopenia in HIV infection. In addition, other possible causes of thrombocytopenia in HIV patients are immune-mediated destruction, impaired hematopoiesis, and toxic effects of medications and infections.[27]

This study also showed that a low plasma viral load is less likely to develop cytopenia (AOR = 0.5, CI = 0.3–0.9) than a highly detectable viral load which could be because high plasma viral load causes a decrease in a colony-forming unit of granulocyte, erythrocyte, monocyte, and megakaryocyte (CFU-GEMM) levels, reducing erythropoietin production and increasing erythroid precursor apoptosis by HIV.[36] The suppressive effect is probably mediated by the interaction of viral or virus-associated proteins with the cell membrane of hematopoietic progenitor cells. Different isolates showed different inhibitory activities, so both viral load and biological characteristics of the virus play an important role in suppression. The hematopoietic stem cell is the common progenitor for myeloid and lymphoid lineages. The capacity of HIV to impair the growth of early hematopoietic progenitor cells could contribute not only to the frequent occurrence of anemia, granulocytopenia, and thrombocytopenia in AIDS patients but also to the inability of the bone marrow to reconstitute a functional pool of mature CD4+ T-cells. The result was in agreement with much more previous studies.[37,38]

Conclusion

The prevalence of peripheral cytopenia was 26.7%. Neutropenia was the most common hematological abnormality, followed by leucopenia and anemia. Viral load and residence of the study participants are predictors of cytopenia among HAART experience children. As a result, cytopenia in HIV-infected children, especially those with a high viral load and those living in rural areas, should be investigated and treated with caution. Alternative medications with stronger viral suppression and reduced risk of toxicity concerns should be encouraged.

Limitations of the Study

The main limitation of this study is the nature of its cross-sectional design, which makes relationships between cytopenia and associated factors difficult. Another limitation of this study is that we did not include morphological anemia classification; we did not analyze serum ferritin or perform a bone marrow examination. One of the strengths of this study might be the inclusion of all the available HIV-positive children on HAART at HUCSH.

Data Sharing Statement

Data related to this research can be available with a reasonable request.

Ethical Consideration

Ethical clearance was obtained from the institutional review board (IRB) (Ref.No. JHRPGC/268/12) of Hawassa University College of Health Science. This study also adheres to the codes of the Declaration of Helsinki for Ethical Principles for Medical Research Involving Human Subjects. Then the support letter was taken from the HUCSH clinical and academic director's office. Informed written consent was taken from each study participant before enrollment. The children's parents or caregivers were informed about the purpose of the study, and written informed consent was obtained before the questionnaire was administered. Then the research objective was explained to the study participants, and those who wished to participate were included. To ensure the confidentiality of participants' information, anonymous typing was applied, whereby the name of the participant and any identifier of participants will not be written on the questionnaire. Test results were given to the clinicians working in the pediatric clinic of the hospital for further diagnosis and management.

Acknowledgments

We want to thank those staff working at the pediatric ART clinic of HUCSH and all laboratory staff for their unreserved support. We also want to thank all patients who participated in this study. Test results were given to the clinicians working in the pediatric clinic of the hospital for further diagnosis and management. A preprint has previously been published.[39]

Author Contributions

All authors made a significant contribution to the research done: whether that is in the conception, study design, execution, and acquisition of data, analysis, and interpretation. They also 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.

Disclosure

The authors declare that there are no conflicts of interest.

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