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Baseline Hematological Indices among HIV-1 Infected Children at Kenyatta National Hospital

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Abstract: **HIV infected children experience a range of hematological complications including anaemia, neutropenia and thrombocytopenia. The objective of the study was to describe the haemoglobin levels, red cell morphology, white blood cells and platelets of Antiretroviral (ARV) naïve HIV -1 infected children. It was a retrospective study done in the period between September and November 2008. During this period medical records of children attending the paediatric HIV comprehensive care clinic (CCC) at Kenyatta National hospital were reviewed daily. HIV infected children were enrolled into the study if they were aged 5-144 months, and results of haematological assessment at baseline were available. Standard tools were used to abstract pre-HAART haematological parameters as well as anthropometric measurements from individual patient medical records. By the end of the study medical records of 337 children meeting enrollment criteria were reviewed. The median age of the children was 63 months with a male to female ratio of 1:1. The prevalence of anemia at baseline was 35.9% with 7% having hemoglobin levels of less than 8gm/dl. Thrombocytopenia was noted in 21% of the study population and leucopenia in 10%. WHO stage 3 and 4 was associated with a ten-fold increased likelihood of anaemia OR=10.6 (95% CI 3.6, 36.3). Chronic malnutrition WAZ < -2SD was associated with anaemia (p=0.04) but wasting and immunologic staging were not. The study concluded that haematological abnormalities are common among HIV infected ARV naïve children and anemia was the commonest hematological abnormality with almost half of the study population having microcytic hypochromic picture of anemia.**

Keywords: **Paediatric HIV, Haematological Abnormalities.**

I. INTRODUCTION

Haematological complications of human deficiency virus infection (HIV) which include cytopenias of all major cell lines were recognized shortly after the first description of AIDS cases (1). Unexplained anaemia defined as hemoglobin of less than 8gm/dl, neutropenia <1000 cells/mm^3 or thrombocytopenia less than 30000 platelets/mm^3 persisting for more than one month are currently classified as WHO stage 3 disease (2).

Anaemia, the most common abnormality causes chronic fatigue, affects cognitive function and influences the choice of ART and opportunistic infection (OI) medications (3). In published literature prevalence of anaemia among HIV-1 infected children varies from 16% to 94%, increases with advancing stage of HIV disease, but also varies with sex, age and the definition of anaemia used (4-9). A 2008 meta-analysis that included 15 previously published studies and representing over 2000 HIV infected children shows a prevalence of mild [haemoglobin (Hb) 10-12.0] and moderate anaemia (Hb 8.0-9.9) to be 22-94% and 3-82% respectively (9). The prevalence of mild and moderate anaemia in western settings ranged from 22-94% and 11-82% respectively while in tropical settings it was 50-91% for mild anaemia and 3-

38% for moderate anaemia (9). Neutropenia is present in approximately 10% of patients with early, asymptomatic HIV infection, and more than half of individuals with more advanced HIV-related immunodeficiency (4,5,10). Thrombocytopenia which is frequently asymptomatic occurs in 20% to 33% of paediatric patients with HIV with the prevalence increasing with duration of illness and development of Aids (4,5,8, 10, 11).

The pathophysiological mechanisms responsible for HIV related haematopoietic abnormalities can be broadly classified into factors that interfere with bone marrow function and those related to blood loss. So far the most important cause of anaemia is insufficient production of erythrocytes caused by ineffective erythropoiesis, reduced erythropoietin production, associated infections, neoplasia, medications and micronutrient deficiencies. A key mechanism for HIV associated decreased production of all haematological elements is low levels of CFU-GEMM or HIV itself blunting production of erythropoietin (1). Laboratory studies have shown that HIV causes apoptosis of erythroid pre-cursors while infection of the auxillary cells interferes with cytokine and erythropoietin response. Infiltration of the bone marrow with non – Hodgkin lymphoma particularly non-cleaved cell lymphoma has also been described as a cause of anaemia in the HIV infected child, (10). Bacterial infections with Mycobacterium tuberculosis, Mycobacterium Avium complex (MAC) and non-typhoidal salmonella infections are associated with severe anaemia. Viral infections with hepatitis C, cytomegalovirus and Epstein-Barr virus and parvovirus both associated with anaemia (1, 10). .

The most common observed peripheral morphology is microcytic, hypochromic red blood corpuscles. One study that has compared the mean cell volume (MCV) and mean cell haemoglobin (MCH) of HIV infected and control children found them to be similar in the first 2 years of life (7). Further 11-20% of children with HIV infected children have a pancytopenia with no differences between children from the West and tropical regions respectively (10). The research was therefore aimed at describing the haematological parameters in Kenya HIV-1 HAART naïve children

II. MATERIALS AND METHODS

This retrospective cohort study was carried out at Kenyatta National Hospital comprehensive care centre. During the study period September and November 2008, a total 337 medical records of children were evaluated. Children were enrolled into the study if they were age 5 to 144 months, confirmed to be HIV positive by rapid tests for those aged over 18 months and PCR DNA for those aged less than 18 months, attending the Kenyatta National Hospital comprehensive care center. Currently on first line regimen of ART for at least six months, available complete medical records and parents/guardians provided informed consent. Standard study tools were used to abstract data from the medical records of enrolled children and included demographic characteristics, clinical stage Pre ART estimates of, absolute CD4, CD4%, haemoglobin level, total white blood cells count, absolute lymphocyte counts, granulocyte counts, and platelets counts were recorded in an abstract form. Ethical clearance to conduct the study was obtained from the department of Pediatrics and Child Health and the KNH ethical review Committee.

Data entry and analysis were done using SPSS version 16.0. The WHZ scores, HAZ scores and WAZ scores were computed using the nutrition software of Epi Info 3.2. Mean and median values of Baseline haematological parameters were determined. Differences in associations and relationships were taken as significant where P was less than 0.05.

III. RESULTS

Baseline characteristics of the study participants

A total of 337 children who satisfied the inclusion criteria were recruited into the study, among them 53.4% female and 46.6% male giving a female to male ratio of 1.1:1, and a median age of 63 months (range of 5 months to 144 months) as shown in the table 1. WHO clinical stage at ART initiation was 189 (56.4%) stage III, 48 (14.3%) stage IV, while 77 (23%) and 21(6.3%) patients were in stage II and I respectively.

Baseline hematological parameters

At baseline 121 (35.9%) of the study population had anemia (Hb <10gm/dl) with a mean and median of 10.6gm/dl. Twenty four (7%) of the patients had Hb less than 8gm/dl .One hundred and four children 104 (31%) had an MCV of less

than 70 fl and only one had an MCV of above 100fl. MCH had a mean of 24.4pg with 154 (46.7%) having an MCH of below 24pg as shown in table 2

The platelets had a mean of 275×10^3 mm^3 with a median of 255×10^3 mm^3 and an interquatile range of 159-352 $\times10^3$ mm^3. Thrombocytopenia was found in 65 (21%) of the study population with platelet counts of below 150 $\times10^3$/mm^3.

At baseline, the mean WBC counts was 9.4×10^3 mm^3 and a median of 8.7 $\times10^3$ mm^3 .Thirty three children 33 (10%) had levels of below 4 $\times10^3$ mm^3 and 97 (27%) having levels above 11×10^3 mm^3. Granulocytes had a median of 2.8×10^3 mm^3 with 22 (6.5%) having levels below 1 $\times10^3$/mm^3. The total lymphocytes had a mean of 5.3×10^3 mm^3 and median of 5.2×10^3 mm^3 as shown in table 3

Factors associated with low baseline haemoglobin level

In a stratified analysis the 216 (64.1%) and 121 (35.9%) children with Hb above and below 10gm/dl respectively were compared to determine demographic and clinical characteristics associated with anaemia. Children in WHO stage 3 and 4 were more likely to have Hb of less than or equal to 10gm/dl compared to children in WHO stage 1 and 2 OR=10.6 (95% CI 3.64, 36.3) (P<0.001). Children with WAZ greater than -2SD had significantly reduced likelihood of having Hb of less than 10gm/dl OR= 0.62 [(95% CI 0.38, 1.01) P=0.04] as shown in table 5.

IV. DISCUSSION

The main findings of this study conducted in an outpatient Paediatric HIV clinic was the high prevalence of pancytopenias. Anaemia was the commonest haematological abnormality. The median level of haemoglobin was 10.6gm/dl was similar rates to Hb of 10.3gm/dl in a cohort of ARV naïve Zambian children (12). The prevalence of anaemia (Hb less than 10gm/dl) of 35.9% in this study was lower than the 44% found among Jamaican children (13). Elsewhere in Africa reported prevalence of anaemia among HIV infected children is much higher, 90.9% in Uganda 74% in South African and 84% in Zimbabwe (6, 7, 15). Similarly high prevalence is reported among hospitalized children at Kings county hospital in New York where the rate of anaemia was 92% (8). These regional variations in the prevalence of anaemia are most likely related to differences in study populations with higher rates reported among in-patients (8). Use of higher cut-off points for anaemia also contributes to higher reported prevalence of anaemia. The Ugandan and South African studies used a Hb of less than 11gm/dl as the cut-off point for anaemia (6,7). In this study few children had Hb of below 8gm/dl and none with levels below 5gm/dl. In published studies including a meta-analysis on markers of predicting mortality in HIV infected and untreated children, baseline Hb of less than 8gm/dl was associated with higher mortality (12,14).

Mean corpuscular volume (MCV) and MCH are a reasonable surrogate measure of iron deficiency anaemia. In this study half of the study participants had MCV of less than 70 fl and MCH $\leq$ 24 pg comparable to findings of researchers' in Zimbabwe who found that 40% of the HIV infected children included in their study had hypochromic microcytic anaemia (15). The findings may be comparable to the prevalence of iron deficiency anaemia in a study done by Totin et al in Uganda (6). The above picture could be attributed to the nutritional deficiencies common in HIV -1 infected children.

In tandem with other published studies, anaemia was correlated with HIV diseases status (5, 6). In this study anaemic children had a ten-fold increased risks of being in WHO HIV clinical stage 3 and 4. Similar to other studies there was no significant relationship between the haemoglobin levels and immunological stage of the (6, 7). In our study low weight for age was significantly associated with hemoglobin levels and also with age. This is similar to findings in adults where there was a significant association between low hemoglobin level, lower body mass index and sex (4). We found male sex to be significantly associated with low Hb as compared to the adult studies which have reported female sex to be more associated with low Hb possibly because most of the adult studies have been performed in female population.

Prevalence of thrombocytopenia was comparable to that documented in studies using similar reference cut-off points. The proportion of study participants who had platelet counts of less than 150×10^3/mm^3 was found to be similar to the findings of Suarez et al in their study in New York (8). Lower levels were reported by Adetifa et al in Nigeria and Pryce C et al in Jamaica who reported rates of 2.5% and 10% respectively (6,13). Difference in the prevalence rate would be attributed to the different reference range of $<100\times10^3$ mm^3 as used by Adetifa et al (5).

In our study, leucopenia was found in 33 (10%) of the study population and was not associated with W.H.O staging of the disease, sex or WAZ. The prevalence was found to be higher than found by Adetifa et al of 17.5% although the reference range used was 3×10^3 mm^3compared to ours of 4×10^3 mm^3 (5). Elsewhere Suarez et al found a higher rate of 43% in children admitted with AIDS (8). Prevalence of granulocytopenia was 22 (6.5%) which was reported to be almost similar to the findings in the Italian study where the rate was found to be 7.8% (4). In contrast higher rates were found in Nigeria with neutropenia being reported in 17.5% but were also found more in severe disease (5). The lower rates of leucopenia and Granulocytopenia in this study could have resulted from higher incidences of infection in children that might have caused leucocytosis and high granulocyte levels before initiation of HAART.

Study limitation

1) Records on social demographic were not available and these could have been used in determining whether there were social factors associated with haematological abnormalities in poor resource setting.
2) Due to the retrospective nature of the study the data available from the medical records were not confirmed.

V. CONCLUSION

Haematological abnormalities are common among HIV infected ARV naïve children. Anemia was the commonest hematological abnormality with almost half of the study population having microcytic hypochromic picture of anemia. Anaemic children had a ten-fold increased risks of being in WHO HIV clinical stage 3 and 4 and low weight for age was significantly associated with hemoglobin levels. Leucopenia was not associated with W.H.O staging of the disease, sex or WAZ.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

All authors conceptualized the study and wrote the proposal. Dr Kibaru carried out the data collection, Professor Nduati, Dr Wamalwa; Dr Nyambura Kariuki supervised the work. All the four authors participated in data analysis and wrote the manuscript.

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APPENDIX – A

Table 1: Baseline demographic characteristics of the study participants

Variable	Frequency (n=337) number,(%),or median
Female	179 (53.4%)
Male	156 (46.6%)
Age (months) Median	63
IQR	36-97
Weight for Age Z score	
SD >-2	130 (39%)
SD -3 to-2	95 (28%)
SD < -3	112 (33%)
Weight for Height Z score	
SD>-2	229 (88%)
SD-3 to -2	22 (6.5%)
SD<-3	15 (4.4%)
Height for Age Z score	
SD >-2	85 (25%)
SD-3 to -2	53 (16%)
SD<-3	198 (59%)
CD4 count Median (1QR)	456 (171.0-753)
CD4 percent Median (1QR)	9.9 (5.0-14.0)

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Table 2: Baseline hemoglobin levels, MCV, MCH and RBC

	Mean (SD)	**Median (IQR)**
Hemoglobin (gm/dl) Hb <10gm/dl Hb <8gm/dl	10.6 (1.8) 121 (35.9%) 24 (7%)	10.6 (9.4-11.7)
MCV(fl)	75.9 (11.0)	76.5 (68.0-82.4)
MCH(pg)	24.4 (4.4)	34.3 (21.5-27.5)
RBC	4.4 (0.8)	4.3 (3.8-4.9)

Table 3: Baseline total WBC, granulocytes and lymphocytes

Parameters	**Mean (SD)**	**Median (IQR)**
WBC $\times 10^3 mm^3$	9.5 (4.9)	8.7 (6.2 – 11.5)
Granulocytes $\times 10^3 mm^3$	3.7 (3.2)	2.8 (1.8-4.3)
Lymphocytes $\times 10^3 mm^3$	5.3 (3.2)	5.2 (2.9 -6.7)

Table 4: Factors associated with hemoglobin of less than 10gm/dl

Hb grades	**Hb ≥ 10** **N = 216 (64.1%)**	**Hb ≤ 10** **N = 121(35.9%)**	**P**
CD4 (median)	9.0	10.8	0.2
Sex Female Male	109 (50.5%) 107 (49.5%)	47 (38.8%) 74 (61.2%)	**0.04**
Age in years	6.5	4	0.3
WHO stage 1and 2 Stage 3 and 4	76 (35.2%) 140 (64.8%)	4 (8.2%) 80 (81.8%)	**0.01**
WHZ <-2 >-2	26 (12.0%) 190 (88.0%)	17 (14.2%) 103 (85.8%)	0.58
WAZ <-2 >-2	124(57.4%) 92 (42.6%)	83 (68.6%) 38 (31.4%)	**0.04**
HAZ <-2 >-2	157(73.0%) 58 (27.0%)	93 (76.8%) 28 (23.2%)	0.4