Original Article

Anemia and Iron-Deficiency Anemia in Children Born to Mothers with HIV in Western Kenya

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Abstract

The objective of this study was to determine and compare anemia and iron-deficiency anemia (IDA) rates in young Kenyan children who are HIV infected (HI), HIV exposed, uninfected (HEU), and HIV unexposed (HU). Questionnaires, anthropometrics, and blood samples were collected from HI, HEU, and HU aged 18 to 36 months. Descriptive statistics, Fisher's exact tests, and linear regression were used for analysis. Of 137 total participants, HI (n = 18), HEU (n = 70), and HU (n = 49), 61.1%, 53.6%, and 36.7%, respectively, were anemic, with mean hemoglobin levels highest in HU ($P = .006$). After adjusting for covariates, HI ($\beta = -9.6$, 95% CI:−17.3 to −2.0) and HEU ($\beta = -7.4$, 95% CI: −12.9 to −1.9) had lower hemoglobin levels compared with HU. The proportion of children with IDA did not differ significantly across groups ($P = .08$). HEU have rates of anemia and IDA similar to HI. Anemia risk is generally higher in HEU than HU, even after adjusting for covariates.

Keywords

HIV, anemia, sub-Saharan Africa, children, Kenya

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Introduction

Anemia is a global problem, affecting approximately 43% of children younger than 5 years of age.[1,2] Anemia disproportionately affects children who live in low- and middle-income countries (LMICs). From 2003 to 2012, surveys estimated anemia rates in children aged 6 to 59 months in the United States to be 3.4%; in sub-Saharan Africa, anemia rates were as high as 58% to 91%.[3,4] The most common cause of anemia is iron deficiency, which is challenging to measure in LMICs. A study of children in Kenya found the prevalence of anemia among children aged 6 to 35 months to be 45.9% and the prevalence of iron-deficiency anemia (IDA) to be 26.9%.[5] Children who are anemic and who have IDA are at risk for poor growth and developmental outcomes, which may be persistent if not identified early and appropriate interventions are provided.[6-8]

Children living with HIV may be at particularly high risk for anemia and its sequelae. Studies of children who are HIV-infected (HI) in Ethiopia and Uganda found anemia rates of 54.4% and 85%, respectively.[9,10] However, few studies directly compared the prevalence of anemia and IDA among children with and without HIV living in the same community. Furthermore, while some studies have found that children who are HIV-exposed and uninfected (HEU) are vulnerable to infections, growth impairments, development delays, and mortality at higher rates than their HIV-unexposed (HU) peers,[11-15] research on anemia and iron deficiency among this population has been sparse. Most related research focuses primarily on

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children who are HI, employing those who are HEU as a socially similar comparator group.

This cross-sectional study aimed to describe and examine the rates of anemia and IDA among children who are HI, HEU, and HU in Kenya to address knowledge gaps in the relationship between anemia and HIV status. As secondary aims, we assessed the relationship between HIV status, serum ferritin (SF), and mean corpuscular volume (MCV), and explored the sensitivity of MCV, a parameter routinely available from CBC analyses, as an alternative to SF for assessment of iron deficiency.

Methodology

Study design and population: This was a descriptive cross-sectional analysis nested within a larger study assessing neurodevelopment among young children in Kenya (NeuroDEV) as part of the Academic Model Providing Access to Healthcare (AMPATH) consortium. The AMPATH HIV care program, born from a 20-year partnership between Indiana University School of Medicine, Moi University School of Medicine, and the Moi Teaching and Referral Hospital (MTRH) in Eldoret, Kenya, has enrolled over 160 000 patients and currently provides care for approximately 15 000 children who are HIV-positive and HIV-exposed in 65 clinics in western Kenya.[16,17] The children and their caregivers were recruited for the NeuroDEV study from the MTRH and AMPATH Module 4 pediatric clinics between 12/2017 and 9/2019. Children who were HI were recruited from the AMPATH pediatric HIV outpatient clinic located in MTRH. Children who were HEU or HU were recruited from the MTRH well-baby clinic. Eligible children were 18 to 36 months of age at the time of enrolment. A sample of blood was taken at enrolment to evaluate blood indices and SF as biological factors that could affect development (results reported elsewhere[18]).

Data Collection, Sample Collection, and Laboratory Analysis

Each child's caregiver participated in a standardized interview to collect demographic information and medical history, including birth history and HIV status (mother's and child's). The caregiver also provided information on household wealth and possessions, maternal education, water/sanitation, and income using the Wealth-Assets-Maternal Education-Income (WAMI index[19]). Each child's body mass and standing height was measured.

Three 4 mL blood samples were collected from each child using EDTA vacutainer tubes (Becton Dickinson, San Jose, CA, USA). The first tube was collected for a CBC, conducted using the Coulter ACT 5diff analyzer (Beckman Coulter, France). Output measurements included white blood cell count, hemoglobin concentration (Hgb), hematocrit, MCV, mean cell hemoglobin, mean cell hemoglobin concentration, red cell distribution width, and platelet count. Blood from the second tube was used to assess SF levels using the COBAS INTEGRA 400 plus analyzer (Roche Diagnostics, Switzerland). Because some children were resistant to the blood drawing procedure, insufficient blood volumes were obtained to complete all labs in some children. As such, SF results were not as complete as CBC results. Because laboratory assays were performed in the United States long after sample collection, the results of the blood tests were not communicated back to medical personnel in Kenya or participants.

Study data were collected and managed using REDCap electronic data capture tools hosted at Indiana University.[20]

Definitions

Anemia. WHO guidelines classify a child aged 6 to 59 months as anemic if their hemoglobin falls below 110 g/L.[21] However, because children attending clinics in and near Eldoret live at altitudes over 2000 m above sea level, we classified a child as having anemia if their hemoglobin concentration measured less than 118 g/L, based on a WHO-published algorithm.[21] Those with anemia were further classified as having mild (108-118 g/L), moderate (78-108 g/L), or severe ($<$78 g/L) disease.[17] Sensitivity analyses using the 110 g/L cut-off were also conducted.

Iron-deficiency anemia. Iron deficiency may be diagnosed with several models, including levels of serum ferritin (SF), levels of soluble transferrin receptor, and multiple-criteria indicators including the soluble transferrin receptor/ferritin index.[5,22,23] However, each of these requires additional studies beyond the standard complete blood count (CBC), and in many low-resource settings, these studies are either unavailable or prohibitively expensive.

For this study, children with SF concentrations below 12 µg/L were considered to have ferritin deficiency, and, when coupled with the threshold for anemia, were categorized as IDA. For the analysis comparing sensitivity and specificity of MCV in detecting IDA, children with MCV below 72 fL were considered to have low MCV, which was then coupled with the threshold for anemia to qualify as IDA.

Statistical Analysis

Data were analyzed using R 4.0.0 (www.r-project.org). For all analyses, results were considered statistically significant if $P < .05$. Data related to socioeconomic status (water, sanitation, income, maternal education, and possessions) were summarized individually and in the WAMI index, a composite measure of socioeconomic status.[19] Body mass and standing height were converted to Z-scores based on the child's age and mass-to-height ratio using growth charts created from the WHO Multicentre Growth Reference Study.[24] Comparisons across groups were made using analysis of variance (ANOVA) for continuous variables, the Kruskal-Wallis rank-sum test for skewed continuous and ordinal variables, and Fisher's exact test for categorical variables.

Laboratory variables were treated as continuous and summarized by their means and standard deviations, except for SF, which exhibited significant positive skew and was summarized using its median and interquartile range. Differences in distribution across all groups were assessed using ANOVA; differences between 2 groups were assessed using a two-sample t-test.

To better understand the relationship between HIV status and hemoglobin concentrations, linear regression models adjusting for age, sex, anthropometric measurements, WAMI, and socioeconomic variables contributing to WAMI were evaluated. Hemoglobin concentration was used to define anemia as a binary (anemia/no anemia) and categorical (none/mild/moderate/severe) variable. HIV status was evaluated as a risk factor for lower hemoglobin concentrations using multivariate linear regression. WAMI, components of WAMI, the child's age, anthropometric measurements, and gender were also evaluated as potential effect modifiers.

Fisher's exact test was used to identify differences in the frequency of low MCV and ferritin deficiency by HIV exposure group. Among children who were anemic, the sensitivity and specificity of low MCV as a surrogate for ferritin deficiency was evaluated.

All caregivers provided written informed consent for their child's participation in this study, and the study was approved by institutional review boards at Indiana University School of Medicine in Indianapolis, USA (1601531540) and Moi University (IREC/2016/09) in Eldoret, Kenya.

Results

Of the 187 children seen between November 21, 2017 and August 26, 2019 in the main study, 137 (73.3%) had both interview data and at least partial laboratory results available. Fifteen of the children excluded from the study did not complete the main study, and thus could not be compared to included children. Among the remaining 35 excluded children with demographic data but no lab data, excluded children were more often HI (71.4% vs 35.8%) and less often HEU (11.4% vs 51.1%). Excluded and included children did not differ with respect to age (excluded: 23.5 months, vs included: 23.0 months) or WAMI (excluded: 0.69, vs included: 0.64). Of included children, 18 children were HI (35.8%), 70 were HEU (51.1%), and 49 were HU (13.1%). Demographic and socioeconomic characteristics of these children are summarized in Table 1. The 3 groups of children differed from each other with respect to age and WAMI but did not differ with respect to the child's sex, birth history, or anthropometric measurements (Table 1).

Among variables contributing to the WAMI, HIV exposure groups differed significantly from each other with respect to maternal education and to some household assets (having a separate kitchen, a bank account, a television or a chair) (Table 1). At the time of enrolment, caregivers were asked whether their child was currently taking any medications, and those answers were screened for medications that might affect ferritin or hemoglobin concentrations. One HEU child was taking an iron supplement, and 2 HEU children were taking antimalarial medications. About Sixteen HI children (88.9%) were taking antiretroviral medications, although the specific drugs were not documented.

Anemia

Haemoglobin levels and anaemia severity differed across the three groups of children (Table 2). Relative to children who were HU, mean haemoglobin levels were 7.5 g/L lower for children who were HI (95% CI: –12.6 to –2.4 g/L, $P = 0.005$) and 9.7 g/L lower for children who were HEU (95% CI: –17.2 to –2.1 g/L, $P = 0.013$). Within our study population, 4.1% of HU, 28.9% of HEU, 38.9% of HI experienced moderate or severe anaemia (Table 2). When anaemia was defined as haemoglobin below 110 g/L, anaemia was present in 38.9%, 33.3%, and 12.2% of HI, HEU, and HU children, respectively. In addition to HIV status, only one covariate, living in a home with a separate kitchen (β=6.65, 95% CI: 1.35 to 12.0), appeared statistically related to haemoglobin levels. These variables minimally altered the statistical effects of HIV infection (β=-9.6, 95% CI: –17.3 to –2.0) or exposure (β= –7.4, 95% CI: –12.9 to –1.9) on haemoglobin levels. The statistical effects of HIV infection and HIV exposure on haemoglobin did not differ significantly ($P = 0.53$).

Table 1. Sociodemographic and Health Characteristics of Children Surveyed.

	HIV exposed, N = 70	HIV infected, N = 18	HIV unexposed, N = 49	*P*-value
Mean age, standard deviation (SD)	21.8 (3.6)	26.7 (6.0)	23.3 (4.8)	<.001*
Male (%)	32 (45.7%)	11 (61.1%)	30 (61.2%)	.20
Socioeconomic indicators				
Mean WAMI (SD)	0.59 (0.20)	0.57 (0.20)	0.74 (0.19)	<.001*
Primary water source	68 (97.1%)	18 (100%)	49 (100%)	.63
Primary sanitation facilities	41 (58.6%)	7 (38.9%)	34 (69.4%)	.076
Possessions				
Separate kitchen	29 (41.4%)	8 (44.4%)	33 (67.3%)	.018
Bank account	25 (35.7%)	1 (5.6%)	23 (46.9%)	.004
Mattress	63 (90%)	15 (83.3%)	46 (93.9%)	.4
Refrigerator	10 (14.3%)	5 (27.8%)	11 (22.4%)	.3
Television	36 (51.4%)	11 (61.1%)	41 (83.7%)	<.001
Table	60 (85.7%)	15 (83.3%)	45 (91.8%)	.44
Chair	58 (82.9%)	16 (88.9%)	48 (98%)	.021
Mean years of maternal education (SD)	9.3 (4.2)	9.4 (2.9)	12.5 (3.5)	<.001*
Median people in household per room (IQR)	3 (3–4.8)	3 (2.2–4)	3 (2–4)	.16**
Household income (Kenyan Shillings)	17 (24.3%)	5 (27.8%)	6 (12.2%)	.17**
0–1959	10 (14.3%)	2 (11.1%)	4 (8.2%)	
1960–3539	10 (14.3%)	2 (11.1%)	2 (4.1%)	
3540–5424	9 (12.9%)	1 (5.6%)	4 (8.2%)	
5425–7979	9 (12.9%)	3 (16.7%)	8 (16.3%)	
7989–10164	4 (5.7%)	3 (16.7%)	7 (14.3%)	
10165–15209	6 (8.6%)	2 (11.1%)	11 (22.4%)	
15210–22064	5 (7.1%)	0 (0%)	7 (14.3%)	
>22065	17 (24.3%)	5 (27.8%)	6 (12.2%)	
Health and medical history				
Birth history: preterm (%)	9 (13.4%)	1 (6.2%)	3 (6.1%)	.5
Mean height-for-age Z-score (SD)	–1.3 (1.4)	–0.9 (1.9)	–1.2 (1.4)	.53*
Mean weight-for-age Z-score (SD)	–0.3 (1.1)	–0.1 (0.8)	–0.2 (1.1)	.79*
Mean weight-for-height Z-score (SD)	0.4 (1)	0.4 (1.4)	0.6 (0.9)	.69*

**P*-value calculated by ANOVA. ***P*-value calculated by Kruskal–Wallis test. All others calculated by Fisher's exact test.

Iron Deficiency Anemia

Among children with anemia, 32/51 (62.7%) had iron deficiency as assessed by low SF, and this proportion did not differ significantly across HIV exposure groups (HI = 55.6% [5/9], HEU = 76.9% [20/26], HU = 43.8% [7/16], $P = .08$, Fisher's exact test). Median serum ferritin also did not differ significantly across the groups ($P = .11$), nor did the proportion of children with low serum ferritin ($P = .11$) (Table 2).

Among children with anemia, 44/66 (66.7%) had iron deficiency as assessed by MCV. The distribution of MCV varied significantly across the 3 groups ($P = .02$), with HU children having the highest mean MCV (75.2 fL) and HEU children having the lowest (70.5 fL) (Table 2). However, the proportion of children with anemia who had low MCV did not differ significantly across HIV exposure groups (HI = 72.3% [8/11], HEU = 75.7% [28/37], HU = 44.4% [8/18], $P = .08$, Fisher's exact test). The prevalence of iron deficiency among anemic children also did not differ significantly between MCV and serum ferritin definitions ($P = .81$, two-sample test for equality of proportions).

Ferritin versus MCV for IDA

Figure 1 shows the distribution of serum ferritin values relative to MCV values for children with no, mild, and moderate anemia. Of note, no severe anemia cases are shown because the sole child with severe anemia did not have serum ferritin levels available. Treating serum ferritin as the gold standard for iron deficiency, the sensitivity of MCV for iron deficiency among anemic children was 0.78, and the specificity was 0.53.

Discussion

Within this study, we observed that children who are HEU or HI have lower hemoglobin levels compared with children who are HU. Overall rates of anemia did

Table 2. Anemia and Iron Deficiency Anemia, by HIV Status.

	Total	HIV exposed, N = 70	HIV infected, N = 18	HIV unexposed, N = 49	*P*-value
Hemoglobin, g/L, standard deviation (SD)		114.1 (16.6)	112 (12)	121.7 (10)	.006*
Median serum ferritin, interquartile range (IQR)		8 (4.3–17.6)	12.6 (4.7–17.6)	14.9 (7.4–21.8)	.11**
Mean corpuscular volume (MCV) (SD)		70.5 (10.6)	74.8 (9.9)	75.2 (5.8)	.02*
Any anemia		37 (53.6%)	11 (61.1%)	18 (36.7%)	.1
Anemia severity					
Mild anemia		17 (24.6%)	4 (22.2%)	16 (32.7%)	.004
Moderate anemia		19 (27.5%)	7 (38.9%)	2 (4.1%)	
Severe anemia		1 (1.4%)	0 (0%)	0 (0%)	
Iron deficiency anemia, using ferritin		33 (60%)[a]	7 (46.7%)[b]	18 (39.1%)[c]	.11
Iron deficiency anemia, using MCV		31 (44.8%)	9 (50%)	13 (26.5%)	.08

[a]N = 55.
[b]N = 15.
[c]N = 46.
*Compared using ANOVA. **Compared using the Kruskal-Wallis test. All others compared by chi-square test.

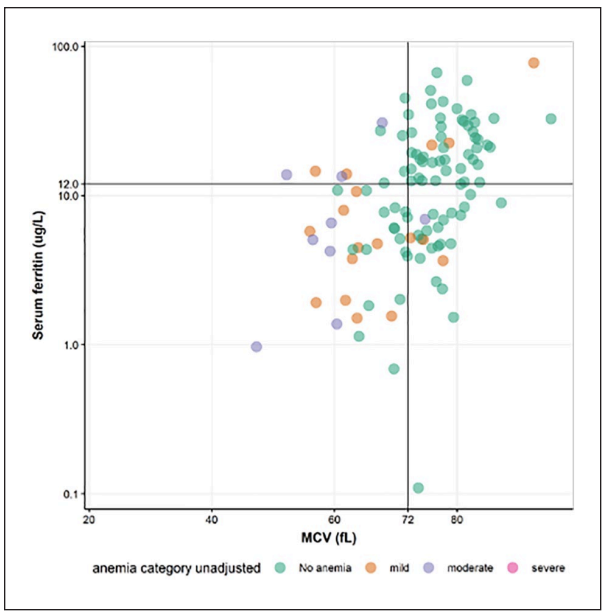

Figure 1. Log-linear scatterplot of serum ferritin levels and MCV. Lines at 12.0 μg/L and 72 fL indicate critical values for low serum ferritin and low MCV, respectively.

not differ statistically across our HIV exposure groups; however, rates of moderate and severe anemia were much higher in children who were HI or HEU compared with those who were HU, and point estimates of anaemia prevalence were higher among HEU and HI relative to HU. The hemoglobin levels of HEU and HI children did not significantly differ from one another. Within settings that lack access to ferritins or other specific measures of IDA, using the MCV is a moderately sensitive proxy marker for IDA within children with anemia.

Anemia is a prevalent complication of pediatric HIV infection and is associated with poor prognosis.[25,26] Less is known about children who are HEU, but our study demonstrates that children who are HEU have similarly high anemia and IDA rates. The mechanism for this is unclear. Controlling for maternal education and sociodemographic information had minimal effects on the association of HIV status with anemia. We do not have access to maternal HIV or antiretroviral therapy information, so further delineation by viral load or medication regimen is not possible. However, for the nearly 15 million children who are HEU globally, more research is necessary to understand the clinical impact of anemia and IDA on health, growth, and development.[27]

Because of Eldoret's high altitude, we adjusted the cut-offs for anemia as recommended by the WHO for populations residing 2000 m above sea level. However, adjusting hemoglobin cut-offs in this manner is not universally accepted as the degree to which hemoglobin increases with altitude varies by population.[28] Although adjustment does not change our conclusions regarding the differences between HI, HEU, and HU children, it significantly alters the measured prevalence of anemia. Other studies in lower-altitude Kenyan communities have reported the prevalence of anemia to be 45.9% overall,[5] 68.8%[29] in HEU children, and 90.5%[29] in HI children, all in the 6- to 35-month age range. These findings are similar to our adjusted anemia prevalence, leading us to believe that the adjustment is appropriate.

Despite the high rates of anemia and IDA within our study population, only 1 child was taking iron supplementation. To aid in the prevention of anemia and IDA, the World Health Organization (WHO) recommends daily iron supplementation in children 6 to 59 months of age who live in regions where anemia prevalence is greater than 40%.[30-32] However, the regional prevalence of anemia is not always known, and iron is not administered until clinical anemia has been diagnosed. With the

elevated rates of anemia found within our study, we propose that daily iron supplementation treatment should be considered within HIV programs monitoring infants born to HIV-infected mothers.

Our analysis also suggested that MCV, a measure readily available from most CBC assays, is a moderately sensitive, but not specific, marker for iron deficiency among anemic children. Although additional iron studies would have been useful to characterize the underlying pathophysiology of anemia in these children, in our study, SF levels cost approximately $7 U.S. dollars per test, and this cost may be prohibitively expensive within our clinical context. Other studies have also highlighted the need for inexpensive iron status assays.[5]

In summary, HI and HEU children both experience lower hemoglobin levels relative to their HU peers, even after adjusting for socioeconomic and demographic covariates. This raises the possibility that exposure to HIV or to interventions for the prevention of mother-to-child HIV transmission may place HEU children at an increased risk for anemia. Additionally, our data suggest that there may be an unrecognized burden of anemia in our high-altitude study population and that increased availability of diagnostic tests and iron supplementation may improve the health of these children.

This analysis is strengthened by the inclusion of HU children, who represent the underlying risk of anemia in this community in the absence of HIV infection or exposure. However, although we statistically controlled for differences in socioeconomic status, we acknowledge that unrecognized confounders or contributors to anemia may exist and explain some of the apparent effects of HIV exposure on hemoglobin levels. These include parasitaemia[33,34] and lingering effects of, or ongoing exposure to, antiretroviral drugs,[35,36] and additional measures of socioeconomic status. Additionally, because the children invited to participate in this study were not randomly sampled from the population of children in Eldoret, it is not possible to say what the true prevalence of anemia is in this population. Further investigation is warranted to determine whether these children might benefit from an iron supplementation program.

Conclusions

Children who are HEU and HI have lower hemoglobin level compared to children who are HU, and high proportions of HEU and HI children have moderate to severe anemia. Within settings that do not have access to additional lab markers for IDA, the MCV is a moderately sensitive proxy marker. Programs that monitor children born to mothers with HIV should consider providing daily iron supplementation, as rates of anemia are high within this population and may lead to poor clinical outcomes.

Author Contributions

MSM and EO conceptualized and sought funding for this study. Study design also informed by RCV. AOR oversaw data collection activities and data management processes. ZY and AR completed all statistical analyses with significant input from MSM. EO completed the first draft of this manuscript, with the support of AR and MSM. All authors contributed substantially to revising this article critically for important intellectual content. All authors contributed to the final manuscript and approved submission for publication.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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