AIDS RESEARCH AND HUMAN RETROVIRUSES
Volume 28, Number 12, 2012

DOI: 10.1089/aid.2011.0373

Prevalence of Anemia and Underlying Iron Status in Naive Antiretroviral Therapy HIV-Infected Children with Moderate Immune Suppression

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Abstract

Anemia is common in HIV-infected children and iron deficiency is thought to be a common cause. This study investigates the prevalence of anemia, thalassemia, and underlying iron status in Thai and Cambodian children without advanced HIV disease to determine the necessity of routine iron supplementation. Antiretroviral (ARV)-naive HIV-infected Asian children aged 1–12 years, with CD4 15–24%, CDC A or B, and hemoglobin (Hb) ≥7.5 g/dl were eligible for the study. Iron studies, serum ferritin, Hb typing, and C-reactive protein were assessed. Anemia was defined as Hb <11.0 g/dl in children <5 years of age or <11.5 g/dl in children 5–12 years. We enrolled 299 children; 57.9% were female and the mean (SD) age was 6.3 (2.9) years. The mean (SD) CD4% and HIV-RNA were 20% (4.6) and 4.6 (0.6) $\log_{10}$ copies/ml, respectively. The mean (SD) Hb and serum ferritin were 11.2 (1.1) g/dl and 78.3 (76.4) μg/liter, respectively. The overall iron deficiency anemia (IDA) prevalence was 2.7%. One hundred and forty-eight (50%) children had anemia, mostly of a mild degree. Of these, 69 (46.6%) had the thalassemia trait, 62 (41.8%) had anemia of chronic disease (ACD), 9 (6.1%) had thalassemia diseases, 3 (2.0%) had iron deficiency anemia, and 5 (3.4%) had IDA and the thalassemia trait. The thalassemia trait was not associated with increased serum ferritin levels. Mild anemia is common in ARV-naïve Thai and Cambodian children without advanced HIV. However, IDA prevalence is low; with the majority of cases caused by ACD. A routine prescription of iron supplement in anemic HIV-infected children without laboratory confirmation of IDA should be discouraged, especially in regions with a high prevalence of thalassemia and low prevalence of IDA.

Introduction

Anemia is a common hematologic problem and is associated with poor prognosis in HIV-infected children.[1] The etiologies of anemia in HIV-infected children are multifactorial, including HIV itself, micronutrient deficiency, particularly iron deficiency anemia (IDA), opportunistic infections, thalassemia, and anemia of chronic disease (ACD).[2] Moreover, the prevalences of anemia and IDA are higher in children in tropical countries than in children in western countries,[1] especially children with advanced HIV disease.[3]

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In the high IDA prevalence countries, iron supplementation for HIV-infected children is common.[4] Although Thailand and Cambodia do not have formal recommendations for routine iron supplementation in HIV-infected children, the use of iron supplements in those with microcytic anemia is not uncommon. However, a Cochrane review reveals that routine iron prescription for anemic HIV-infected children is without proven benefit on morbidity and mortality. [5] Moreover, possible deleterious effects of iron overload have been reported in patients with thalassemia and advanced HIV infection.[6–8]

The prevalence and etiologies of anemia in HIV-infected children are varied, and depend on the stage of disease and geographic area. Most previous reports come from African and western countries, and report on children with varying immune status.[1] Gaps exist as to anemia prevalence and causes in HIV-infected children with mild disease status in Southeast Asian countries where thalassemia is common.[9–11]

We evaluated the iron status, prevalence, and causes of anemia in antiretroviral therapy (ARV)-naive HIV-infected children without advanced HIV infection to determine the necessity of routine iron supplementation.

Materials and Methods

This study analyzed data collected at the baseline visit of children enrolled in the Pediatric Randomized to Immediate versus Deferred antiretroviral Initiation in Cambodia and Thailand study (PREDICT, clinicaltrials.gov identification number NCT00234091). Children were included in PREDICT if they were HIV-infected and ARV-naive, aged 1–12 years old, had a CD4 count between 15% and 24%, and United States Centers for Disease Control and Prevention (CDC) clinical category N (no HIV symptoms), A (mild HIV symptoms), or B (moderate HIV symptoms).[12] The screening laboratory values obtained within 30 days prior to study entry were hemoglobin ≥ 7.5 g/dl, absolute neutrophil count $\geq 750/mm^3$, platelet count $\geq 50{,}000/mm^3$, and alanine transaminase (ALT) < 4 times the upper limit of normal. Children were not allowed to take any supplements that contain iron. This study was approved by local and national ethics committees. All caregivers signed informed consent.

At the baseline assessment, we collected demographic data including age, gender, CDC clinical classification, weight, and height. Complete blood count (CBC), $CD4^+$ T-lymphocyte count, plasma HIV RNA, iron studies [serum ferritin, serum iron (SI), total iron binding capacity (TIBC), transferrin saturation], and C-reactive protein (CRP) were performed. To diagnose thalassemia, the osmotic fragility (OF), dichlorophenolindophenol (DCIP) precipitation, hemoglobin typing, and DNA analysis for thalassemia mutations or deletions were evaluated.

Anemia was defined as hemoglobin < 11.0 g/dl in children < 5 years of age or < 11.5 g/dl in children 5–12 years.[13] IDA[3–15] was defined as anemia with (1) serum ferritin $< 10\ \mu$g/ml if CRP was < 10 mg/liter **or** serum ferritin $< 50\ \mu$g/ml if CRP was ≥ 10 mg/liter[16,17] *and* (2) having at least three of the following five parameters: (1) SI $< 8.8\ \mu$mol/liter, (2) TIBC $> 71.6\ \mu$mol/liter, (3) TS $< 10\%$, (4) mean corpuscular volume (MCV) less than normal age-related values (< 2 years $= 78$ fl, ≥ 2 years $= 81$ fl), or (5) mean corpuscular hemoglobin (MCH) less than normal age-related values (< 2 years $= 23$ pg, 2–5 years $= 24$ pg, and ≥ 6 years $= 25$ pg).[14,15]

Nonthalassemia was defined as having no common thalassemia mutations or deletions of α- and β-genes. Thalassemia traits or diseases were defined based upon information of OF, DCIP, hemoglobin typing, and DNA analysis patterns.[18–20] The interpretation of hemoglobin typing and DNA analysis was performed by a pediatric hematologist at Khon Kaen University, Thailand. Anemia of nonspecific cause or ACD was defined as anemia in the presence of a normal DNA analysis pattern and iron parameters.

Laboratory methods

Serum ferritin levels were determined using the commercially available AxSYM Ferritin (Abbott Laboratories, ABBOTT Diagnostics Division, USA). Reference ranges for normal ferritin levels are 7–140 μg/liter. In addition, CRP levels were determined in all children if they had leftover serum from the ferritin test. CRP concentration was measured using the CRP High Sensitive Assay (Cobas Integra System, Roche Diagnostic Systems, Basel, Switzerland). Reference CRP limits for children were between 0.1 and 2.8 mg/liter.

Serum Iron levels were measured using Vitros Reagent (Ortho-Clinical Diagnostics, Johnson & Johnson Company, USA). The normal range is 9.0–22.0 μmol/liter TIBC. TIBC was assayed by Vitros Reagent (Ortho-Clinical Diagnostics, Johnson & Johnson Company, USA) and reference ranges are 44.8–89.5 μmol/liter.

Transferrin saturation (TS) was determined as (Serum iron concentration $\div$ TIBC) $\times 100$. All laboratories passed quality control standards by Division of AIDS (DAIDS) approved for the Proficiency Testing Program. The OF test and DCIP precipitation test were performed at sites with approved quality control by Safety Monitoring International Laboratory Evaluation (SMILE).

Genomic DNA was prepared from peripheral blood leukocytes using the standard method. Identification of thalassemia (SEA-type) and thalassemia (3.7 kb and 4.2 kb deletions) and Hb Constant Spring (HbCS) mutations were performed using the PCR methodologies described elsewhere.[21,22]

Statistical analysis

Demographics and baseline characteristic of children enrolled in the PREDICT study were characterized by descriptive statistics. Mean and standard deviation or median, interquartile range (IQR) was used to describe continuous data according to their distribution. Frequency percentage distribution was used to describe categorical data.

The prevalence of abnormal iron parameters was calculated using the number of children with an iron parameter less than normal for age-related values by the total number of children; 95% confidence interval (CI) around the prevalence estimate was calculated based on the binomial distribution. The statistical comparison of iron parameters between anemic and nonanemic groups was done by the Chi-square test or Fisher's exact test for proportion of abnormal iron parameters, whereas the mean difference of iron parameters was compared by a *t*-test or Wilcoxon–Mann–Whitney test. Statistical analyses were performed using Stata version 11.1 (StataCorp LP, College Station, TX).

Results

From March 2006 to September 2008, 445 children were screened for the PREDICT study. Two hundred and ninety-nine

Table 1. Baseline Characteristics

Baseline data	*Total* N = *299*
Gender,	
male : female	126 :173
Age (years),	
mean ± SD	6.3 ± 2.9
WAZ,	
mean ± SD	−1.3 ± 1.0
HAZ,	
mean ± SD	−1.6 ± 1.3
WAZ < −2, *n* (%)	78 (26.1)
HAZ < −2, *n* (%)	113 (37.8)
WHZ < −2, *n* (%)	15 (5.0)
CDC clinical classification	
N	5 (1.6%)
A	185 (61.9%)
B	109 (36.5%)
Absolute $CD4^+$ T-lymphocyte (cells/mm^3),	
mean ± SD	700 ± 382
% $CD4^+$ T-lymphocyte,	
mean ± SD	20.0 ± 4.6
Plasma HIV-RNA (log_{10} copies/ml),	
mean ± SD	4.6 (0.6)
Ethnic	
Thai:Cambodian	179:120

WAZ, weight for age *z*-score; HAZ, height for age *z*-score.

children were enrolled and 216 failed screening. One of the failed screening children met the exclusion criterion of hemoglobin <7.5 g/dl. The baseline clinical characteristics are shown in Table 1. The mean (SD) weight for age *z*-score (WAZ) and height for age *z*-score (HAZ) in this study were −1.3 (1.0) and −1.6 (1.3). The WAZ <–2 and HAZ < 2 were 26.1% and 37.8%, respectively (Table 1). The mean CD4% and HIV RNA were 20.0 (4.6)% and 4.6 (0.6) log_{10} copies/ml, respectively. One hundred and thirteen (113) children were age <5 years and 186 were age ≥5 years. Fifty percent (148 of 299 children) had anemia, of whom 60/113 (53.1%) were aged <5 years and 88/186 (47.3%) were age ≥5 years. When classified as having anemia using the Division of AIDS, the United States National Institutes of Health toxicity grading,[23] 71.0% (105/148) of anemic children had not reached grade I toxicity (Hb >10.0 g/dl), 26.4% (39/148) were in grade I (8.5–10.0 g/dl), and 2.7% (4/148) were in grade II (Hb 7.5–8.4 g/dl).

Iron status

One child had no baseline iron assessment at week 0. Eight of 298 children (2.7%) met protocol-defined IDA. The hematologic and iron study parameters are shown in Table 2. Four had serum ferritin <10 μg/liter and CRP <10 mg/liter while four had serum ferritin <50 μg/liter and serum CRP >10 mg/liter. Abnormal iron parameters of at least three of five parameters were found in 86 (28.9%) of 298 children. C-reactive protein results were available in 177 (59.2%) children and 20 (11%) had CRP ≥10 mg/liter (Table 2).

Hemoglobin typing and DNA analysis result

Hemoglobin typing was performed in 296 children. Of the 116 thalassemia trait, 74 had anemia but 42 had no anemia (Table 3). Nine children were diagnosed with thalassemia diseases (seven homozygous hemoglobin E, one hemoglobin H disease, and one hemoglobin H disease with hemoglobin CS). Three of eight children with diagnosed protocol-defined IDA also had hemoglobin E trait. Sixty-five anemic children were nonthalassemic but three children had IDA. Therefore, 62 of 148 anemic children (41.8%) with

Table 2. Hemoglobin, Red Blood Cell Indices, and Iron Studies in HIV-Infected Children

Baseline data	N	*Mean (SD)*	*% Abnormal (95% CI)*
Hemoglobin (g/dl)[a]	299	11.2 (1.1)	49.5 (43.7, 55.3)
Mean corpuscular volume (MCV) (fl)[b]	299	73.4 (7.8)	84.3 (79.7, 88.2)
Mean corpuscular hemoglobin (MCH) (pg)[c]	298	24.1 (3.0)	45.3 (39.6, 51.1)
Serum iron (μmol/liter)	298	11.2 (5.6)	38.3 (32.7, 44.0)
Total iron binding capacity (μmol/liter)	298	53.2 (14.3)	13.8 (10.1, 18.2)
Transferrin saturation (%)	298	22.4 (12.1)	15.1 (11.2, 19.7)
Abnormal ≥3/5 parameters	298	—	28.9 (23.8, 34.4)
Low Hb + abnormal ≥3 parameters	298	—	18.5 (14.2, 23.3)
Low ferritin + low Hb	298	—	1.7 (0.5, 3.9)
Serum ferritin (SF), (μg/liter)	298	78.3 (76.4)	
<10 μg/liter			1.7 (0.6, 3.9)
<50 μg/liter			39.6 (34.0, 45.4)
Serum C-reactive protein (CRP) ≥10 mg/liter	177	—	11.3 (7.0, 16.9)
Iron deficiency anemia (IDA) using			
SF < 10 μg/liter for all	298	4 cases	1.3 (0.4, 3.4)
SF <50 μg/liter for all	298	24 cases	8.1 (5.2, 11.7)
SF <10 μg/liter if CRP <10 mg/liter + SF <50 μg/liter if CRP ≥10 mg/liter		8 cases	2.7 (1.2, 5.2)

[a]Low hemoglobin (Hb) by age: children age <5 years, <11.0 g/dl; age 5–11 years, 11.5 g/dl: age 12–14 years, <12.0 g/dl.
[b]MCV less than normal age-related values (<2 years = 78 fl, 2–5 years = 81 fl, ≥6 years = 81 fl).
[c]MCH less than normal age-related values (<2 years = 23 pg, 2–5 years = 24 pg, ≥6 years = 25 pg).
One child had no iron study at week 0.
IDA, iron deficiency anemia was defined as low Hb + abnormal ≥3 parameters + ferritin criteria below cut-off level.

Table 3. Thalassmia Traits and Diseases by Hb Typing and DNA Analysis Between Anemia and Nonanemia Groups

DNA analysis	*Total*	*Anemia* N = *148*	*Non anemia* N = *151*	p-*value*
Nonthalassemia	174	65 (43.9)	109 (72.2)	< 0.001
Anemia of chronic disease[a]	62	62 (41.8)	0 (0.0)	
Thalassemia trait	116	74 (50.0)	42 (27.8)	
α_1-thalassemia (thal) trait	9	7 (4.7)	2 (1.3)	
α_2-thalassemia trait	31	21 (14.2)	10 (6.6)	
HbCS trait	12	7 (4.7)	5 (3.3)	
HbE trait	47	29 (19.6)	18 (11.9)	
HbE trait + HbCS trait	4	3 (2.0)	1 (0.7)	
HbE trait + α_2-thalassemia trait	10	4 (2.7)	6 (4.0)	
HbE trait + α_1-thalassemia trait	1	1 (0.7)	0 (0.0)	
β-thalassemia trait	1	1 (0.7)	0 (0.0)	
β-thalassemia trait + α_2-thalassemia trait	1	1 (0.7)	0 (0.0)	
Thalassemia diseases	9	9 (6.1)	0 (0.0)	
HbE disease	7	7 (4.7)	0 (0.0)	
HbH diseases[b]	2	2 (1.4)	0 (0.0)	

[a]Anemia of chronic disease (ACD) = 62 cases after excluded three cases of IDA.
[b]One HbA2ABartH and one HbCSA2ABartH.
Eight cases of IDA were in the anemia group (three cases in nonthalassemia, three cases in the HbE trait group, one case in HbE trait + HbCS trait, and one case in α_2-thalassemia trait).

Table 4A. Comparison of Hemoglobin, Red Blood Cell Indices, and Iron Studies Between Anemic and Nonanemic Groups

Parameters	*Anemia* N = *148*	*Nonanemia* N = *151*	p-*value*
Hemoglobin (g/dl), mean (SD)	10.3 (0.8)	12.0 (0.6)	N/A
Mean corpuscular volume (fl), mean (SD)	70.6 (8.5)	76.2 (5.9)	< 0.001
Mean corpuscular hemoglobin (pg), mean (SD)	22.8 (3.5)	25.4 (2.4)[a]	< 0.001
Serum iron (μmol/liter), mean (SD)	9.9 (4.9)	12.5 (5.9)[a]	< 0.001
Total iron binding capacity (μmol/liter), mean (SD)	49.9 (12.2)	56.5 (15.4)[a]	< 0.001
Transferrin saturation (TS%), mean (SD)	21.1 (11.8)	23.6 (12.3)[a]	0.065
Abnormal ≥ 3/5 iron study parameters, *n* (%)	55 (37.16)	31 (20.67)	0.002
Serum ferritin (μg/liter), mean (SD)	82.4 (80.9)	74.2 (71.8)[a]	0.375
Serum ferritin < 10 μg/liter, number (%)	5 (3.4)	0 (0.0)	0.029
Serum ferritin < 50 μg/liter, number (%)	52 (35.1)	66 (44.0)	0.118
Serum ferritin > 140 μg/liter, number (%)	15 (10.1)	16 (10.7)	0.881
WAZ < −2	48 (32.4)	30 (19.9)	0.013
Odd ratio (95% CI)	1.94 (1.14–3.28)		
HAZ < −2	70 (47.3)	43 (28.5)	0.001
Odd ratio (95% CI)	2.25 (1.40–3.64)		

a normal iron study and normal DNA analysis result were classified as having anemia of nonspecified cause or anemia of chronic disease (ACD). By univariate analysis, low WAZ or HAZ (<−2) was significantly associated with the risk of anemia (Table 4A).

Iron status comparing anemic group vs. nonanemic group

Comparing red blood cell indices and iron study parameters between the anemic and nonanemic groups, we found significantly lower MCV, MCH, SI, and TIBC in the anemic group (Table 4A). The mean serum ferritin level was higher in the anemic group (82.4 μg/liter) compared to the nonanemic group (74.2 μg/liter) but did not reach statistical significance. The anemia group was more likely to have at least three of five abnormal iron study parameters (Table 4A).

Iron status comparing thalassemia trait group vs. nonthalassemia group

As this study population had a high prevalence of thalassemia trait, we compared iron study parameters between thalassemia trait and nonthalassemia groups, excluding HbE diseases, HbH diseases, and IDA. We found significantly lower hemoglobin levels, MCV, MCH, and serum ferritin in the thalassemia trait group (Table 4B). The proportion of children with serum ferritin < 50 μg/liter was significantly higher in the thalassemia trait group as compared with the nonthalassemia group ($p = 0.025$) (Table 4B). The thalassemia group was more likely to have at least three of five abnormal iron study parameters.

Discussion

The prevalence of anemia in pediatric HIV ranges from 23% to 48% in high-income countries[24–26] to 78% to 90% in low-income countries.[27–30] In this study, we found that half of ARV-naive Asian children without advanced HIV had anemia. Most anemic children had a mild degree of anemia. The low numbers of moderate and severe anemia were not a result of the exclusion criteria because only one child was excluded during the enrollment period because of very low hemoglobin (Hb <7.5%).

Alteration in iron metabolism, both IDA and iron overload, has been reported in HIV-infected children.[31] Iron deficiency is highly prevalent (18.0–44.3%) in developing countries,[3,29] but not in this study. The high prevalences of IDA in other studies might be the result of the inclusion of children with poorer nutritional status and more severe clinical stage of HIV. Although the mean WAZ and HAZ in this study were low compared to the general population, only 1/4 and 1/3

Table 4B. Comparison of Hemoglobin, Red Blood Cell Indices, and Iron Studies Between Thalassemia Trait and Nonthalassemia Groups

	Thalassemia trait N = *111*[a]	*Nonthalassmia trait* N = *171*[a]	p-*value*
Hemoglobin (g/dl), mean (SD)	11.0 (1.0)	11.5 (1.1)	< 0.001
MCV (fl), mean (SD)	68.8 (5.8)	77.8 (5.3)	< 0.001
MCH (pg), mean (SD)	22.4 (2.2)	25.8 (2.2)	< 0.001
Abnormal ≥ 3/5 iron study parameters, *n* (%)	40 (36.04)	34 (20.00)	0.003
Serum ferritin (μg/liter), mean (SD) (*n* = 116)	63.8 (55.0)	88.4 (82.6)	0.003
Serum ferritin < 50 μg/liter, number (%)	52 (46.9)	57 (33.5)	0.025
Serum ferritin > 140 μg/liter, number (%)	5 (4.5)	25 (14.7)	0.007

[a]Seven HbE diseases, two HbH diseases, and eight IDA were excluded.

MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin.

had WAZ and HAZ < –2, respectively. However, low WAZ or low HAZ < –2 was significantly associated with anemia as in an Indian study.[4] In this study, 28.9% had abnormal (≥ 3 of 5) parameters but were not classified as IDA because few exhibited low serum ferritin levels (Table 2). The most common abnormal parameters were MCV (84.3%), MCH (45.3%), and serum iron (38.3%). The low MCV and MCH values might result from the thalassemia trait in this population while the low serum iron without low serum ferritin values might result from anemia of chronic disease. Abnormal iron release without depletion in iron status can occur in chronic diseases.[32]

Serum ferritin is an acute phase reactant that may be increased in chronic inflammatory diseases such as HIV infection.[31,33] High levels of serum ferritin have been reported in AIDS patients; the more advanced the stage of disease, the higher the serum ferritin level.[34] However, in this study, we enrolled HIV-infected children with moderate immunosuppression, with a generally low incidence of opportunistic infections, and excluded children with acute illness. In addition, we used another acute phase reactant, serum CRP, to reconfirm the presence of inflammatory stage; in cases of high CRP level (> 10 mg/liter), we increased the cut-off level of low serum ferritin from < 10 μg/liter to < 50 μg/liter to define iron deficiency status.[16,17] We found that 11.3% of children (20/177) had high CRP levels (> 10 mg/liter) and thereby identified four more IDA cases. The overall IDA prevalence in this study was 8/299 (2.7%), which was 8/148 (5.4%) in the anemic group. By instituting these controlled conditions and adjusting for the foregoing factors, we believed the serum ferritin levels we reported more reliably represent the iron status and the prevalence of IDA in this HIV population. If we increased a ferritin cut-off level of < 50 μg/liter to define iron deficiency or depletion status for all children, the IDA prevalence was still 24/298 (8.1%). This is consistent with the low IDA prevalence found in a study of school-aged children without HIV infection in the northeast of Thailand (4.6%).[35] However, when comparing the nonanemic group to the anemic group (Table 4A), we found a higher percentage (44.0% vs. 35.1%) of children who had serum ferritin < 50 μg/liter in the nonanemic group. Therefore, the use of this cut-off level to define iron depletion status might not be appropriate.

The current clinical practice of iron supplementation in HIV-infected children is based on weak evidence, comprising observational studies and expert opinion.[5] From this low prevalence of IDA, it appears that iron supplementation should not be routinely prescribed for moderately immunosuppressed HIV-infected children who present with anemia in Thailand and Cambodia. To save the cost of unnecessary investigations for anemia in low IDA prevalent areas, IDA investigations should begin with serum ferritin measurements. Other iron study parameters, such as serum iron, TIBC, and transferrin saturation, should be confirmed only in cases with low serum ferritin levels.

Moreover, hemoglobin E and β- and α-thalassemia appear at high prevalence rates in Thailand and Cambodia.[11,18] Up to 25–35% of Thai and Cambodian people are carriers of α-thalassemia, and up to 60% of Thai and Cambodian people are carriers of hemoglobin E.[11,36] Although the heterozygotes for α-thalassemia 1, β-thalassemia, and HbE typically are asymptomatic, they may cause mild microcytic, hypochromic anemia.[18] In this study, we used the most reliable method (DNA analysis) to detect common thalassemia mutations or deletions of α- and β-genes and found that 125/299 (41.8%) of the study population had underlying thalassemia (Table 3), mainly the thalassemia trait. The thalassemia trait generally does not affect serum ferritin.[10] In contrast; we found significantly lower serum ferritin levels in the thalassemia trait group (Table 4B). Although the reason for this association is unclear, as least it provided reassurance that the underlying trait did not cause high serum ferritin levels, and was therefore not deemed to be a confounding factor in the interpretation of the IDA.

Anemia of chronic disease is common in HIV-infected patients.[2,34,37] In this study, 41.8% of anemic children had no iron deficiency and no thalassemia from DNA analysis, which could be characterized as ACD. The higher serum ferritin levels in the anemic group (Table 4A) provide another piece of supporting evidence for ACD. Other factors such as micronutrient deficiency might also play a role and should be investigated.

We recognize several limitations of this study. First, our results may not be generalizable to countries where IDA is common and for which routine iron supplementation may be indicated. The children were selected based on strict study inclusion criteria and may not represent the general pediatric HIV population. Additionally, this study was designed to explore iron status, and therefore did not investigate other causes of anemia, such as cytokine abnormalities or micronutrient deficiency. We did not measure the soluble transferring receptor, which might help to distinguish between ACD and IDA.

In summary, the prevalence of anemia in HIV-infected children with moderate immune suppression in Thailand and Cambodia was high, but mostly presented in a mild form. ACD is the most common cause. Since the prevalence of iron

deficiency anemia is low, empiric iron supplementation should not be ordered routinely.

PREDICT Trial

The following investigators, clinical centers, and committees participated in the Pediatric Randomized of Early versus Deferred Initiation in Cambodia and Thailand (PREDICT Trial).

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Acknowledgments

We thank the Thailand Research Fund and Office of the Higher Education Commission as the collaborators and partial funder in this substudy. The PREDICT study is sponsored by the National Institute of Allergy and Infectious Disease (NIAID), Grant U19 AI053741, Clinical trial.gov identification number NCT00234091. The study was partially funded by the National Research Council of Thailand. We are grateful to the children and their families for participating in PREDICT. We thank Ms. Amy Markowitz for her editorial help.

The study was presented as poster number P_95 at the First International Workshop on HIV Pediatrics, Cape Town, South Africa, 17–18 July 2009.

Author Disclosure Statement

Antiretroviral drugs for PREDICT were provided by GlaxoSmithKline (AZT, 3TC), Boehringer Ingelheim (NVP), Merck (EFV), Abbott (RTV), and Roche (NFV).

Neither the authors nor member's of the author's immediate families have a financial interest in or arrangement with any commercial organization that may have a direct interest in the subject matter of this article.

KR has received consultating fee or speaker honoraria from GSK and Abbott. KR has also received support through grants HR1161A from the National Research University (NRU) Project of CHE and the Ratchadaphiseksomphot Endowment Fund, Thailand; the Professional Researcher Strengthen Grant from the National Science and Technology Development Agency (NSTDA), BIOTEC; and senior researcher scholar from Thai Research Fund (TRF), Thailand. JA has received consulting and/or speaker's honoraria fees from ViiV Healthcare, Abbott and Gilead. TP has received support through the National Research University Project of Commission of Higher Education and the Ratchadapiseksomphot Endowment Fund (HR 1161A-55). Other authors declare no conflict of interest.

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