Erythropoietin response to anemia among human immunodeficiency virus-infected infants in Malawi

We characterized the erythropoietin response to anemia among 73 HIV-infected and 246 uninfected twelve-month old infants in Malawi. Among HIV-infected and uninfected infants, the fitted regression line was $\log_{10}$ plasma erythropoietin = 2.66 –0.011*hemoglobin, and $\log_{10}$ plasma erythropoietin = 2.90 –0.013*hemoglobin, respectively, and the slope of the regression lines was similar (p = 0.42). There is no evidence that the erythropoietin response to anemia in HIV-infected infants is inadequate compared to that in uninfected infants.

Anemia is common during human immunodeficiency virus (HIV) infection and associated with increased morbidity and mortality.[1] During HIV infection, an inadequate response of erythropoietin to low hemoglobin concentrations has been reported in adults,[1,2] but the response has not been well characterized among infants. We compared the relationship between plasma erythropoietin and hemoglobin in 73 HIV-infected and 246 uninfected infants in Blantyre, Malawi. The study design was cross-sectional within a clinical trial of antenatal vitamin A supplementation for pregnant women.[3] No infants received antiretroviral medications. Twelve-month old infants were tested for HIV infection,[4] and hemoglobin was measured using an automated analyzer (Coulter, Hialeah, FL, USA). Infant length and weight were measured,[5] and growth standards were used as reference.[6] Weight-for-age Z score < -2, weight-for-height Z score < -2, and height-for-age Z score < -2 were considered consistent with underweight, wasting, and stunting.[5] Plasma erythropoietin concentrations were measured using an enzyme-linked immunosorbent assay (ALPCO, Windham, NH, USA).

Comparisons between continuous variables were made using Student's t test with appropriate variable transformations for skewed data. Comparisons of categorical data were made using chi-squared or exact tests. Spearman's correlation was used to examine correlations between variables. A linear regression model was used to compare the relationship between plasma erythropoietin and hemoglobin concentrations among the HIV-infected and uninfected infants using the model $\log_{10}$ erythropoietin = $\beta_0 + \beta_1$hemoglobin + β_2HIV status + β_3HIV status*hemoglobin, where HIV status = 0 or 1 and hemoglobin was expressed in g/L. The characteristics of the HIV-infected and uninfected infants are shown in Table 1. There were no significant differences between HIV-infected and uninfected infants by sex. The mean age of HIV-positive infants was slightly younger than that of the HIV-negative infants. HIV-infected infants had significantly lower mean hemoglobin and were more anemic than uninfected infants. The relationship between $\log_{10}$ plasma erythropoietin and hemoglobin concentrations among HIV-infected infants is shown in Figure 1. Among HIV-infected and uninfected infants, Spearman's correlation between $\log_{10}$ plasma erythropoietin and hemoglobin was -0.385 (p < 0.0008) and -0.526 (p < 0.0001), respectively. Among HIV-infected infants, the fitted regression line was $\log_{10}$ plasma erythropoietin = 2.66 -0.011 (hemoglobin). Among uninfected infants, the fitted regression line was $\log_{10}$ plasma erythropoietin = 2.90 –0.013 (hemoglobin). A linear regression model was used to compare the respective slopes of the regression lines of -0.011 and -0.013 among HIV-infected and uninfected infants (p = 0.42). In an additional linear regression model that adjusted for both age and weight-for-height Z score, the respective slope of the regression lines between $\log_{10}$ plasma erythropoietin and hemoglobin concentrations was -0.010 and -0.013 among HIV-infected and uninfected infants (p = 0.31).

To our knowledge, this is the first study to evaluate the relationship between plasma erythropoietin and hemoglobin concentrations in HIV-infected and uninfected infants. Plasma erythropoietin is produced in a similar manner in response to anemia among HIV-infected and uninfected infants, as the slopes of the regression lines between erythropoietin and hemoglobin in the two groups of infants were not significantly different.[7] However, these findings do not necessarily imply that erythropoiesis is similar among both HIV-infected and uninfected infants, as HIV infection of bone marrow stromal cells or circulating proinflammatory cytokines could potentially impair ery-

Table 1. Characteristics of the twelve-month old infants with and without HIV infection.

Characteristic[1]	*HIV-positive (n = 73)*	*HIV-negative (n = 246)*	*p-value*
Age, days	361±17	366±18	0.024
Sex (% female)	63.0	56.9	0.35
Weight-for-Age Z-score	–1.65±1.29	–0.80±1.09	0.0001
Weight-for-Height Z-score	–0.19±1.01	0.13±1.10	0.021
Height-for-Age Z-score	–2.06±1.33	–1.22±1.09	0.0001
Weight-for-Age Z-score < –2 (%)	35.6	13.4	0.0001
Weight-for-Height Z-score < –2 (%)	2.7	1.2	0.32
Height-for-Age Z-score < –2 (%)	47.9	19.5	0.0001
Hemoglobin (g/L)	98±17	109±18	0.0001
Hemoglobin < 110 g/L (%)	78.1	49.6	0.0001
Hemoglobin < 90 g/L (%)	30.1	13.4	0.0009
Log_{10} erythropoietin (IU/L)	1.62±0.47	1.48±0.43	0.02

[1]*For continuous variables, mean±SD.*

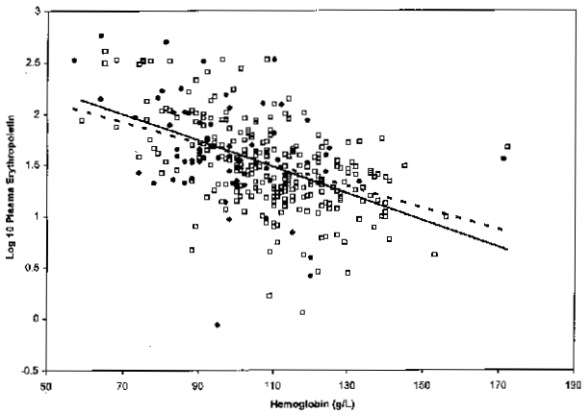

Figure 1. Relationship between $\log_{10}$ erythropoietin and hemoglobin concentrations among HIV-infected infants (circles) and uninfected infants (squares), showing the respective regression lines (broken line for HIV-infected, solid line for uninfected): $\log_{10}$ plasma erythropoietin = 2.66 - 0.011 (hemoglobin) and $\log_{10}$ plasma erythropoietin = 2.90 - 0.013 (hemoglobin).

thropoiesis.[1]

The prevalence of anemia of 78.1% in this study is higher than reported elsewhere, and there is a paucity of data regarding anemia among HIV-infected infants in sub-Saharan Africa. Among HIV-infected infants followed since early infancy in Connecticut, 32.9% were anemic at nine months of age.[8] The present study consisted of infants who were followed from birth and not selected on the basis of symptoms. Studies of symptomatic HIV-infected infants show a higher prevalence of anemia, such as 100% and 92% of symptomatic HIV-infected children with and without opportunistic infections, respectively.[9] About one-half of the anemia among HIV-positive infants in Uganda is due to iron deficiency (Semba RD, unpublished data). A limitation of the present study is that vitamin B_{12} and folate status were not assessed. Other factors might limit erythropoiesis, such as the availability of iron and pro-inflammatory cytokines.[1] Strategies such as micronutrient supplementation, treatment of hookworm infection, and management of malaria need further evaluation in the control of anemia among HIV-infected infants in Africa.[1]

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