Original Article

Impact of Anemia on Outcome of HIV-Infected Pediatric Patients: A Prospective Observational Study

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Abstract

Introduction: Anemia has been widely reported to predict a poorer prognosis for HIV-infected patients, both in terms of progression to AIDS and in survival. This study aimed to determine the etiology of anemia and its immunological correlation in HIV-infected children. **Materials and Methods:** Four hundred and eighty-nine HIV-infected children were screened, of which 86 HIV-infected children with anemia were enrolled. Standard WHO definitions were used for anemia, HIV staging, and growth parameters. Chi-square test, *t*-tests, and univariate and multivariate logistic regression analyses were used to analyze the data. **Results:** Anemia was present in 17.58% (86/489) of HIV-infected children, including 84.6% with moderate anemia, 11.5% with severe anemia, and 2.32% with mild anemia. The mean hemoglobin (Hb) among patients with CD4 count <350 cell/mm^3 was lower (7.90 g%) (standard deviation 1.48) compared to those having CD4 >350 cell/mm^3 ($P = 0.02$). Children with severe immunological stage had a significantly lower mean Hb (adjusted estimate: −1.61, 95% confidence interval: −2.65, −0.56) compared to those who had normal immune status. No statistically significant differences in mean Hb at baseline when compared to various demographic and clinical characteristics were observed in unadjusted and adjusted regression models. **Conclusion:** Hb is an easy and inexpensive tool to measure and can be used for monitoring disease progression in a resource-limited setting.

Keywords: CD4 count, Hemoglobin, HIV

Introduction

Globally, the HIV epidemic remains a serious challenge and continues to take its toll, particularly on vulnerable populations – our children. In 2009 alone, globally, 370,000 children under the age of 15 years were newly infected, i.e., approximately 1000 a day and 260,000 children died, the majority under the age of five.[1,2]

In patients with HIV, anemia is a commonly encountered hematologic abnormality that has a significant impact on clinical outcomes and quality of life (QOL). Resolution of HIV-related anemia has been shown to improve QOL, physical functioning, energy, and fatigue in individuals with HIV. More recently, the use of highly active antiretroviral therapy (ART) has also been associated with a significant increase in hemoglobin (Hb) concentrations and a decrease in the prevalence of anemia.[3]

In recent studies, viral load has been shown to be highly prognostic for AIDS and death, but the prognostic value of Hb level in addition to the information provided by CD4 lymphocyte count and viral load has yet to be determined. Earlier studies have tended to concentrate on a single measurement of Hb and CD4 lymphocyte count, and few have used serial measurements of both markers to determine their joint prognostic value.[4] There is also no long-term data on the impact of ART on anemia and the follow-up Hb levels later. This prompted us to do a study on anemia etiologies and its immunological correlation in our pediatric ART clinic.

Materials and Methods

A prospective cohort study was conducted in the pediatric ART clinic at a tertiary care hospital from January 2009 to December

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2009. Prior Institutional Review Board approval was taken for the study. Written informed consent was obtained from parent/guardian. Four hundred and eighty-nine HIV-infected children were screened during the study period, of which 86 HIV-infected children with anemia were enrolled. Children with HIV infection at 18–24 months of age confirmed by ELISA and having anemia confirmed as per the WHO criteria were included in the study. Children with infection, who are febrile, or who had blood transfusion within 6 weeks prior to the study were excluded.

The children were categorized into types of anemia as per WHO 2001 standard. History, examination, and investigative parameters were documented in a predesigned pro forma. Hb, absolute CD4 count, and percentage were done at baseline and at 3 months of follow-up. Fixed-dose combination ART was started in children who fulfilled clinical and/or immunological criteria as per the NACO guidelines.

Statistical analysis

The means and standard deviations (SDs) for Hb across various demographic and clinical characteristics were calculated. The means across groups were compared using *t*-tests and ANOVA.[5] Linear regression models were used to estimate the mean differences in Hb across various demographic and clinical characteristics. A multivariate regression model was used to estimate the differences in Hb and adjust for confounding variables. The multivariate random effects (RE) model was used for the analysis of longitudinal data. We had information on the outcomes and covariates in these individuals for two time points. Estimates from RE models accounted for both the within-subject and between-subject correlations.

Results

Eighty-six of the 489 (17.58%) HIV-infected children had anemia. Among the 86 children, 86.04% (n = 74) had moderate anemia, 11.62% (n = 10) had severe anemia, and 2.32% (n = 02) had mild anemia. There were 35 (40.70%) children with isolated iron deficiency anemia, 13 (15.12%) with iron deficiency anemia with a co-infection such as tuberculosis, 23 (26.74%) with anemia of chronic infection, 7 (8.14%) with zidovudine-induced anemia, 8 (9.30%) with varied causes for anemia (two children had nutritional megaloblastic anemia and three had pancytopenia of which two cases were of septran induced and one case was of HIV-induced myelosuppression) [Figure 1]. We also had two cases of stavudine-induced pancreatitis with anemia, three cases of bicytopenia, one case of immune thrombocytopenia with anemia, and two cases of malignancies – Burkitt's lymphoma and non-Hodgkin's lymphoma.

Patients on ART had a mean Hb value of 8.38 (SD 1.28). Those patients who were on zidovudine-based ART regimen had lower mean Hb 8.19 g% (SD 1.76) compared to those who were on lamivudine, efavirenz, nevirapine, and stavudine regimen (P = 0.42). Patients with severe immunodeficiency had the lowest mean Hb 7.79 g% (SD 0.98) among the three immunological classifications (normal, mild/moderate, and severe).

Majority of the patients in our study population had a moderate-to-severe anemia with an advanced immunological state CD4 count <500 cells/mm^3. It was observed that, as the anemia improved, an improving trend in the CD4 count was seen, thereby suggesting that increasing Hb levels were associated with better immunological status [Figure 2]. In correlation with CD4 count, mean Hb among patients having CD4 count <350 cell/mm^3 was lower (7.90 g%) (SD 1.48) as compared with those having CD4 >350 cell/mm^3, this was statistically significant (P = 0.02).

There were no significant differences in mean Hb at baseline according to various demographic and clinical characteristics such as age, sex, immunization status, nutrition and clinical WHO staging, presence of opportunistic infections, and type of ART regimen, as observed in our unadjusted and adjusted regression models. However, children who were classified as severe immunological stage had a significantly lower mean Hb (adjusted estimate: −1.61, 95% confidence interval [CI]: −2.65, −0.56) compared with those who had normal immune status. Similarly, those classified as mild/moderate immunological stage had a lower mean Hb (adjusted

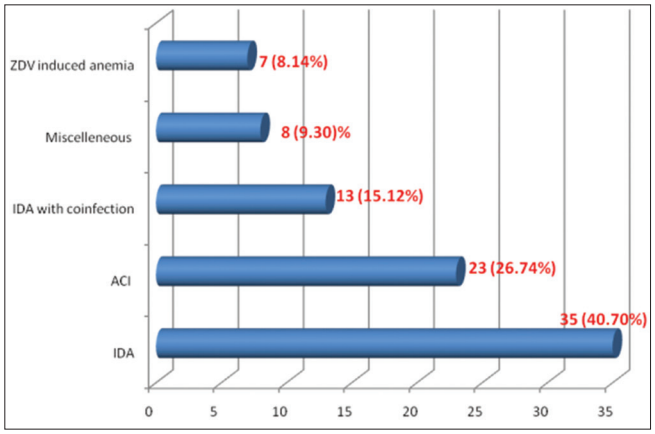

Figure 1: Etiologies of Anemia among sample (n = 86)

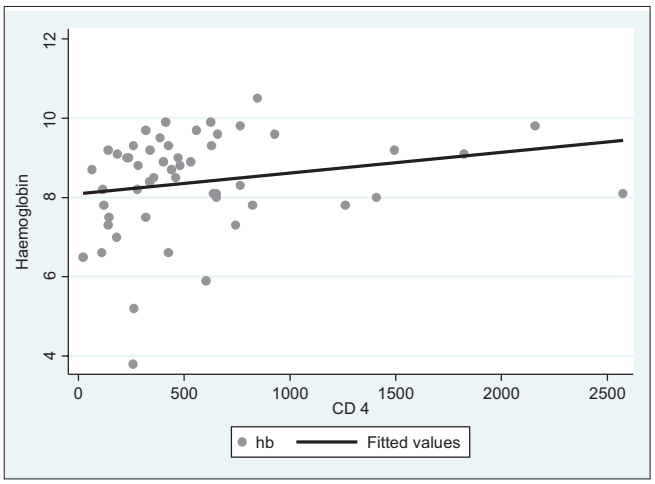

Figure 2: The distribution of hemoglobin and CD4 cells

estimate: −0.82, 95% CI: −1.58, −0.05) compared with those classified as normal.

On multivariate analysis, after adjusting for various demographic and clinical characteristics as shown in Table 1, it was found that the mean Hb was lower by 1.43 in HIV-infected children with a CD4 count of 0–349 cells/mm^3 compared with those with a CD4 count >350 cells/mm^3; this mean difference was statistically significant (95% CI: −2.24, −0.62).

In the longitudinal analysis (RE models), after adjusting for other covariates such as age, sex, and clinical stage of the disease, the mean Hb was lower by 1.28 in HIV-infected children with CD4 count 1–349 cells/mm^3 compared to those with CD4 count >350 cells/mm^3; this difference was statistically significant (95% CI: −2.02, −0.54) [Table 2].

We did not find any statistically significant differences in mean Hb in ART-naive HIV-infected children classified according to various characteristics such as malnutrition, clinical stage, immunological stage, immunization status, opportunistic infection, or drug therapy in this study.

Discussion

In our study, the overall prevalence of anemia was 17.58%, which was much lower than the study by Shet *et al*. where the prevalence was 66%.[6] One of the reasons for low prevalence in our study group could be that our population was from an urban setting and anemia prevalence as per the National Family Health Survey-3 report is higher among the rural children. Recent longitudinal studies show that anemia is an independent predictor of mortality among children with HIV infection.[7]

Clinical features in HIV-infected children in our study had some similarities and few differences from the previous Indian studies.[8-10] Tuberculosis was encountered in 38.37% cases in various forms such as pulmonary (66.66%) and extrapulmonary and abdominal type (33.34%). Merchant *et al*.[8] had also reported 29.4% of cases. Dermatological manifestations were common in our study; most were infectious and postinfections skin lesions. Shah *et al*. also reported similar findings.[9] Nonspecific findings such as hepatosplenomegaly, lymphadenopathy, failure to thrive, diarrhea, and recurrent fever were often the presenting features in these HIV-infected patients.[8,11-13]

In our study, moderate anemia was the most common type (86.04%) followed by severe anemia (11.5%) and mild anemia (2.32%). Hence, the mean Hb was 8.38 g%, which was lower in the study by Shet *et al*.,[6] which could be explained by the fact that we had higher incidence of severe clinical disease. We found 40.69% of normochromic normocytic anemia followed by 38.33% of hypochromic microcytic anemia and 20.09% of hypochromic macrocytic anemia. Pancytopenia was present in three children: the first one was HIV-induced myelosuppression and the other two had transient drug-induced myelosuppression secondary to cotrimoxazole therapy. Bicytopenia was present in two children with malignancies such as Burkitt's lymphoma in one case and non-Hodgkin's lymphoma in the other case.

Due to economic constraints, detailed investigation such as serum iron, serum ferritin, soluble transferrin levels, serum total iron-binding capacity (TIBC), serum Vitamin B12, red blood cell folate levels, and bone marrow examination could not be performed. However, on detailed clinical and peripheral smear examination, the diagnosis could be ascertained in almost all the cases.

CD4 counts are used to assess the immunological status of an HIV-infected child. The CD4 count is done at baseline and then at every 6 month or more frequently if required. Although % CD4 is more significant in our study, absolute CD4 count was taken for statistical analysis; this may be a potential limitation of this study. We had a higher number of children with mild-to-moderate immunosuppression (42.30%), and this finding was similar to a study done by Shet *et al*.[6]

Table 1: Multivariate analysis in 86 HIV-infected children

Characteristics	Unadjusted
CD4 count	
≥350	Reference
0-349	−1.43 (−2.24, −0.62)
Age (years)	
2-5	Reference
5.1-15	0.97 (0.14, 1.81)
Sex	
Male	Reference
Female	0.35 (−0.39, 1.09)
Zidovudine	
No	Reference
Yes	−0.65 (−2.82, 1.53)

Table 2: Regression estimates from longitudinal analysis in 86 HIV-infected children

Characteristics	Unadjusted
CD 4 count	
≥350	Reference
0-349	−1.28 (−2.02, −0.54)
Age (years)	
2-5	Reference
5.1-15	0.33 (−0.45, 1.12)
Sex	
Male	Reference
Female	0.06 (−0.68, 0.79)
Clinical stage	
Stage 1/2	Reference
Stage 3/4	0.45 (−0.21, 1.11)
Zidovudine	
No	Reference
Yes	−1.01 (−2.57, 0.54)
Intraclass correlation	0.23

On further detailed analysis of an ART cohort (n = 52), interesting insights were gained. The mean Hb was 8.38 g% (SD 1.28); hence, the baseline prevalence was 33.6%, which is lesser as compared to the study by Rajasekaran *et al*. which demonstrated a prevalence of 66%. Because all our patients were from an urban setting, it is known that they have better Hb than the rural background.[6,14]

Anemia has been widely reported to predict a poorer prognosis in HIV-infected patients both in terms of progression to AIDS and in survival.[15] Majority of patients had a moderate-to-severe anemia with CD4 count <500 cells/mm^3, i.e., advanced immunological state, and it was observed that the Hb levels on follow-up after 3 months improved with a simultaneous improving trend in the CD4 counts, thereby suggesting that good immunological status is associated with better Hb levels. This finding is similar to the study by Shet *et al*.[6] and Morfeldt-Månson *et al*.[16] The finding that HIV-infected children with pulmonary tuberculosis were three times more likely to have anemia indicates that co-infection with tuberculosis is a potent risk factor for anemia, particularly severe anemia.[17] Severe immunodeficiency had the lowest mean Hb 7.79 g% (SD 0.98) in the three immunological categories (normal, mild/moderate, and severe). The mean difference across these three groups was statistically significant (P = 0.05); this has also been quoted in various studies.[6] In correlation with CD4 counts, the mean Hb among patients having CD4 count <350 cell/mm^3 was lower (7.90g %) (SD 1.48) as compared to those having CD4 >350 cell/mm^3, which was statistically significant (P = 0.02). Our finding is similar to the study done by Shet *et al*.[6] The mean Hb at baseline did not significantly differ according to various demographic and clinical characteristics such as age, sex, immunization status, nutrition and clinical WHO staging, presence of opportunistic infections, and type of ART regimen, as observed in our unadjusted and adjusted regression models. However, in the same models, we found that children who were classified as severe immunological stage had a significantly lower mean Hb (adjusted estimate: −1.61, 95% CI: −2.65, −0.56) compared with those who were classified as normal in the immunological staging. On multivariate analysis, it has been found that the mean Hb was lower by 1.43 in HIV-infected children with CD4 count 1–349 cells/mm^3 compared to those with CD4 count >350 cells/mm^3; this mean difference was statistically significant (95% CI: −2.24, −0.62).

In the longitudinal analysis after adjusting for other covariates such as age, sex, and clinical stage of the disease, the mean Hb was lower by 1.28 in HIV-infected children with CD4 count 1–349 cells/mm^3 compared to those with CD4 count >350 cells/mm^3; this difference was statistically significant (95% CI: −2.02, −0.54). The varied etiologies of anemia as described extensively by Calis JC *et al*[18] is well known. Common causes include nutritional deficiencies, HIV induced myelosuppression, drug effects, opportunistic infections and HIV associated malignancies. We found all these etiologies in our study. In our resource-challenged setting, identifiable nutritional deficiencies such as iron, folic acid, and Vitamin B12 were present. However, definite diagnosis of these with extensive laboratory investigations was beyond the scope of our study. Iron deficiency anemia is an interesting finding as several studies with an HIV-uninfected control group did not clearly suggest the increased prevalence of iron deficiency among HIV-infected children with uninfected children.[19,20] In fact, there are serious concerns that indiscriminate iron supplementation may adversely affect the progression of HIV.[21,22] We observed a large number of children of anemia of chronic inflammation, with the most common co-infection being tuberculosis and opportunistic infections such as cytomegalo virus, cryptococcosis, pneumocystis pneumonia (PCP), and chronic parotitis. Treatment of the underlying condition along with ART led to a dramatic increase in Hb levels.

There are limited data analyzing the effect of preexisting anemia on disease progression among children with HIV. Our data suggested that immunological staging was the single-most independent covariate which affected the baseline Hb in children on ART, and the Hb levels improved with the rise in CD4 counts significantly. We, therefore, postulate that the Hb levels can provide prognostic information regarding the progression of HIV infection.

The study highlights the need for further large-scale study to know the correlation of anemia and immunological stage of HIV in children to plan appropriate interventions in resource-limited settings.

Conclusion

Hb is an easy and inexpensive tool to measure and can be used for monitoring for disease progression in a resource-limited setting. It can be a red flag to the clinician alerting him/her to patients who require intensive and regular clinical follow-up.

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Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Antiretroviral Therapy (ART) Guideline-NACO, 14 I Pediatrics Guidelines 13. Available from: http://naco.gov.in/sites/default/files/Pediatric_14-03-2014.pdf. [Last accessed on 2018 Dec 30].
2. Guidelines for HIV Care and Treatment in Infants and Children. Available from: http://apps.who.int/medicinedocs/documents/s18022en/s18022en.pdf. [Last accessed on 2018 Dec 30].
3. Belperio PS, Rhew DC. Prevalence and outcomes of anemia in individuals with human immunodeficiency virus: A systematic review of the literature. Am J Med 2004;116 Suppl 7A: 27S-43S.
4. Villamor E, Misegades L, Fataki MR, Mbise RL, Fawzi WW. Child mortality in relation to HIV infection, nutritional status, and socio-economic background. Int J Epidemiol 2005;34:61-8.
5. Hamilton LC. Statistics with Stata. Stata Version 10. Hamilton CA, USA: StataCorp, College Station TX, USA, Brooks/Cole-Thomson Learning; 2004.

6. Shet A, Mehta S, Rajagopalan N, Dinakar C, Ramesh E, Samuel NM, *et al.* Anemia and growth failure among HIV-infected children in India: A retrospective analysis. BMC Pediatr 2009;9:37.
7. Totin D, Ndugwa C, Mmiro F, Perry RT, Jackson JB, Semba RD, *et al.* Iron deficiency anemia is highly prevalent among human immunodeficiency virus-infected and uninfected infants in Uganda. J Nutr 2002;132:423-9.
8. Merchant RH, Oswal JS, Bhagwat RV, Karkare J. Clinical profile of HIV infection. Indian Pediatr 2001;38:239-46.
9. Shah SR, Tullu MS, Kamat JR. Clinical profile of pediatric HIV infection from India. Arch Med Res 2005;36:24-31.
10. Lodha R, Upadhyay A, Kabra SK. Antiretroviral therapy in HIV-1 infected children. Indian Pediatr 2005;42:789-96.
11. Udgirkar VS, Tullu MS, Bavdekar SB, Shaharao VB, Kamat JR, Hira PR, *et al.* Neurological manifestations of HIV infection. Indian Pediatr 2003;40:230-4.
12. Abuzaitoun OR, Hanson IC. Organ-specific manifestations of HIV disease in children. Pediatr Clin North Am 2000;47:109-25.
13. Dhurat R, Manglani M, Sharma R, Shah NK. Clinical spectrum of HIV infection. Indian Pediatr 2000;37:831-6.
14. Rajasekaran S, Jeyaseelan L, Ravichandran N, Gomathi C, Thara F, Chandrasekar C. Efficacy of antiretroviral therapy program in children in India: Prognostic factors and survival analysis. J Trop Pediatr 2009;55:225-32.
15. Mocroft A, Kirk O, Barton SE, Dietrich M, Proenca R, Colebunders R, *et al.* Anaemia is an independent predictive marker for clinical prognosis in HIV-infected patients from across Europe. EuroSIDA study group. AIDS 1999;13:943-50.
16. Morfeldt-Månson L, Böttiger B, Nilsson B, von Stedingk LV. Clinical signs and laboratory markers in predicting progression to AIDS in HIV-1 infected patients. Scand J Infect Dis 1991;23:443-9.
17. Swaminathan S, Padmapriyadarsini C, Sukumar B, Iliayas S, Kumar SR, Triveni C, *et al.* Nutritional status of persons with HIV infection, persons with HIV infection and tuberculosis, and HIV-negative individuals from Southern India. Clin Infect Dis 2008;46:946-9.
18. Calis JC, van Hensbroek MB, de Haan RJ, Moons P, Brabin BJ, Bates I. HIV-associated anemia in children: A systematic review from a global perspective. AIDS 2008;22:1099-112.
19. Miller MF, Humphrey JH, Iliff PJ, Malaba LC, Mbuya NV, Stoltzfus RJ, *et al.* Neonatal erythropoiesis and subsequent anemia in HIV-positive and HIV-negative Zimbabwean babies during the first year of life: A longitudinal study. BMC Infect Dis 2006;6:1.
20. Buskin SE, Sullivan PS. Anemia and its treatment and outcomes in persons infected with human immunodeficiency virus. Transfusion 2004;44:826-32.
21. Andrews NC. Anemia of inflammation: The cytokine-hepcidin link. J Clin Invest 2004;113:1251-3.
22. de Monyé C, Karcher DS, Boelaert JR, Gordeuk VR. Bone marrow macrophage iron grade and survival of HIV-seropositive patients. AIDS 1999;13:375-80.