ORIGINAL ARTICLE

Effect of ART on anemia in Children living with HIV attending tertiary care hospitals of New Delhi

D Verma[1], A S Acharya[2], D Bachani[3], A Seth[4], A Hemal[5]

[1]Resident, [2]Professor, [3]Director Professor, Department of Community Medicine, [4]Professor, Dept. of Pediatrics, Lady Hardinge Medical College & Associated Hospitals, New Delhi, [5]Professor, Dept. of Pediatrics, Dr. Ram Manohar Lohia Hospitals, New Delhi

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Corresponding Author

Address for Correspondence: D Verma, Resident, Department of Community Medicine, Lady Hardinge Medical College, New Delhi
E Mail ID: dr.deepshikha.vrma@gmail.com

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Abstract

Background: Globally in 2012, an estimated 35.3 (32.2–38.8) million people were living with HIV (PLHIV) including 3.2 million children. India has the third largest number of PLHIV with estimated number of 2.09 million (2011). Estimated number of children living with HIV (CLHIV) is 1,45,000 and 25,739 such children are on antiretroviral therapy (ART). The prevalence of anemia in these children has a wide range (57% - 100%) as reported by number of researchers. Screening for anemia before initiating ART is recommended as it helps in deciding the composition of the first line ART regimen (Zidovudine based regimen avoided in anemia) and in treatment of anemia. **Objectives:** To study the clinico-social profile and anemia in Children living with HIV and to assess the effect of ART on anemia. **Material & Methods:** The study was part of follow up study of children seeking ART in Delhi undertaken between November 2012 and March 2014 in Kalawati Saran Children Hospital and Dr. Ram Manohar Lohia Hospital. It involved a retrospective case review and one year follow up of 55 children between 11 months to 13 years of age living with HIV and attending the pediatric ART clinic. Information on demographic and clinical profile including anemia in CLHIV were studied before and one year after the start of ART. **Results:** Majority (61.8%) of CLHIV comprised of boys. Fourteen (25.5%) children were orphans. Both parents of CLHIV were found to be positive in 69.1% while mother was found to be positive in 76.4%. Before the start of ART anemia was seen in forty five (81.8%) children out of which thirty four were having moderate to severe anemia, while after one year of ART anemia was seen in twenty (36.3%) children out of which eleven were moderately anemic and no one had severe anemia. There was a significant reduction in prevalence and severity of anemia in children following ART (p=0.00). **Conclusion:** HIV positive children should be screened for anemia before initiation of ART and should be closely followed up for anemia during ART. There is evidence of reduction in prevalence of anemia following ART.

Key Words

AIDS; Anemia; CD4 Count; Immunodeficiency; Opportunistic infections

Introduction

Acquired Immunodeficiency Syndrome (AIDS) is a fatal illness caused by a retrovirus known as Human immunodeficiency virus (HIV) which breaks down body's immune system, leaving the victim vulnerable to life threatening opportunistic infections, neurological disorders or unusual malignancies. AIDS refers only to the last stage of HIV infection and is one of the most urgent threats to global public health. Globally in 2012, there are an estimated 35.3 (32.2–38.8) million people living with HIV (PLHIV) including 3.2 million children. India has the third largest number of PLHIV with estimated number of 2.09 million (2011). Estimated number of CLHIV in India is 1,45,000 and of these 25,739 children are on antiretroviral therapy (ART). Globally in 2012,

647,000 children under 15 years of age were receiving ART. HIV treatment coverage for children [34% (31%-39%)] remained half of coverage for adults [64% (61%-69%)] in 2012. In priority countries, including India only 3 in 10 eligible children receive HIV treatment (1).

High prevalence of anemia is well known amongst HIV infected children (2), moreover these children may also have co-morbidities and nutritional deficiencies. Also, other pathologies like myelosuppression interact significantly to worsen the condition (3). Studies have also demonstrated that anemia is associated with decreased survival (4-6), increased mortality (7) and poor quality of life (8). Initiating Highly Active Antiretroviral drugs (HAART) has been shown to improve the clinical stage, nutritional status and quality of life of these children (9, 10).

Studies in younger cohorts are essential to understand better the full spectrum of treatment responses in the developing world. In India, limited studies have been conducted to demonstrate the effect of HAART on anemia in HIV positive children.

Objectives

1. To identify factors associated with anemia in children living with HIV.
2. To assess response of ART on anemia in HIV positive children seeking treatment in Delhi.

Material and Methods

The current study was a follow up study, undertaken between November 2012 to March 2014 in Delhi at Kalawati Saran Children Hospital and Dr. Ram Manohar Lohia Hospital on 55 children of 11 months to 13 years of age living with HIV on HAART and attending the pediatric ART clinic. Enrolment of the study subjects was done till March 2013. Thereafter, the subjects were followed-up for one year after initiation of ART. For those children who had already initiated ART before the start of the study but had not completed one year of ART, were also included. In these children a retrospective case review with collation of data from medical records was undertaken and follow up was done till completion of one year period from ART initiation. Ethical approval from local Institutional Review Boards of both the institutions was obtained prior to the beginning of the study. All consecutive, ambulant, not acutely ill, residents of Delhi were eligible for inclusion in the study if their caregivers gave consent and study subjects who were more than 7 years gave assent. Relevant information on demographic and clinical profile including baseline hemoglobin among CLHIV was obtained before and one year after initiating HAART. Eligibility for initiation of ART was based on clinical and immunological criteria outlined in the current NACO guidelines (11). The first line ART regimen comprised of two nucleoside reverse transcriptase inhibitors (zidovudine and lamivudine), and one non-nucloside reverse transcriptase inhibitor (neverapine). Efavirenz replaced nevirapine if a child was on concurrent treatment for tuberculosis with rifampicin. Stavudine replaced zidovudine if a child had Hemoglobin <8gm/dL. Specific information on use of iron supplements was also recorded.

WHO clinical staging was used to classify children living with HIV. For analysis WHO clinical stages I and II were described as early disease, while WHO clinical stage III and IV as advanced disease. CD4 count and CD4 percentage were used to categorize the immunological status of each CLHIV, based on WHO classification. Anemia was defined and graded based on age-appropriate WHO classification of anemia (6-59 months, <11g/dl; 5-11years, <11.5g/dl; 12-14years, <12g/dl) (12).

Data was entered into SPSS statistical software version 12. Results were expressed in terms of mean ± SD. Means were compared with student t-test or paired t-test while proportions and ratios were compared using Pearson Chi squared test. All analysis was done taking confidence interval of 95% and p-values of < 0.05 were considered as significant

Results

Clinico-social profile of CLHIV: In all 55 children were recruited in the study out of which 32 were from KSCH and rest (23) from RML hospital. Out of the children recruited, 61.8 % (34) were males. The mean age was 6 years (SD = 3.9 years; range 11 months to 13 years). In the present study 67.3% of the study subjects belonged to upper lower socio-economic status according to modified Kuppuswami scale CPI 2013, majority (52) were Hindus while only 3 were Muslims.

Mode of HIV transmission in young children is primarily perinatal or is transfusion acquired. The present study has shown similar results, where mother to child transmission was the most common route of transmission seen in 76.4% of the study subjects followed by transfusion of blood and blood products (12.7%). Majority (69.1%) of the children

had advanced stage of HIV infection (WHO Clinical Stage 3 and 4). Early disease was present in 16 (29.1%) CLHIV while only one child was asymptomatic. Severe, moderate and mild immunodeficiency was observed in 49.1%, 30.9% and 12.7% children, respectively, while only 4 (7.3%) children were not immunodeficient.

In 76.4% of the study subjects, mothers were HIV positive while father was found to be positive in 69.1%. Both parents were found to be HIV positive in nearly three fourth (69.1%) of the study subjects, while in 13 CLHIV both of the parents were HIV negative. At the time of study both parents were alive in almost three fourth of the study subjects (74.5%), 12 (21.8%) CLHIV were single orphan while 2 were double orphans.

Anemia in CLHIV: Before the start of HAART, overall prevalence of anemia in CLHIV was 81.8% (45 children) out of which 12.7% were severely anemic. After taking HAART for one year the prevalence of anemia decreased to 36.4% and none of the study subject was having severe anemia (Table 1). There was significant rise in mean hemoglobin after initiation of HAART by 1.7 gram/dL and this increase was found to be statistically significant (p<0.001).

Before the start of HAART, the prevalence of anemia in early and advanced clinical stage was 58.8% and 86.8% and the difference was found to be statistically significant (p=0.03). After one year of HAART, most of the study subjects shifted to early stages where the prevalence was found to be 40% while only 5 of the study subjects remained in advanced stage (all in clinical stage III) and none of them were having anemia (Table 2). Before starting HAART, hemoglobin level was significantly lower among those with advanced clinical stage as compared to those in early stage (9.6gm/dL vs. 10.6gm/dL; p = 0.01) while after one year of HAART the difference was not found to be statistically significant (12.6gm/dL vs. 11.5gm/dL; p = 0.3)

With respect to immunological stage before initiation of HAART 92.8% of study subjects were immunodeficient out of which mild, moderate and severe immunodeficiency was present in 13.7%, 33.3% and 52.9% children, respectively. After taking one year of HAART immunodeficiency was present in only 17 children (30.9%) out of which 52.9%, 29.4% and 17.6% were mild, moderate and severe immunodeficient respectively (Table 3). Before initiation of HAART hemoglobin level was significantly lower among those with moderate to severe immunodeficiency compared to those in no to mild immunodeficient stage (9.7gm/dL vs. 10.5gm/dL; p = 0.02) while after one year of HAART the difference was not found to be statistically significant (10.7gm/dL vs. 11.7gm/dL; p = 0.7)

Discussion

Our study found high prevalence of anemia among HIV-infected pediatric patients majority of them were moderately anemic. The prevalence of anemia was 81.8% which is comparable to the other studies done in India (13), Nigeria (14), Lagos (15), South Africa (16) and Malawi (17) (66%-78%). These studies have observed prevalence of anemia as a significant predictor of growth failure, morbidity and mortality among HIV infected children (3,7,14,18-20). In a study review by Calis et al on the global prevalence of HIV associated anemia reported that prevalence of anemia was seen in 50%-90% of CLHIV2. The beneficial effect of ART on anemia has also been demonstrated previously (21,22,23). In this study similar results were seen, with a baseline mean hemoglobin of 9.9gm/dL (SD = 2.0) which increased to 11.6gm/dL (SD = 1.6) after one year of ART initiation and this rise was found to be statistically significant (p = 0.00). In fact the prevalence of anemia also showed a significant association between progressive clinical severity and progressive increase in immunodeficiency affecting 86.8% of study subjects in advanced clinical stage and in 77.3% in moderate to severe immunodeficiency at baseline. These findings are similar to the studies conducted in other parts of India (18, 24), Nigeria (14), South Africa (16) and Uganda (19). In this study, 33/43 (76.7%), of those with anemia were in advanced clinical stage (clinical stage III or IV) while 34/43 (79.1%) were in moderate to severe immunodeficiency. As expected in previous studies (25,26) most of the CLHIV showed significant clinical response (p = 0.00), as well as significant immunological response (p = 0.00) to ART, including those with advanced HIV disease or moderate to severe immunosuppression.

Anemia in these study subjects may be attributed to its multifactorial nature. Nutritional deficiencies may get magnified in these settings. Advanced HIV disease in children may be associated with deficiencies of other micronutrients like iron, folic acid, vitamin B12, zinc and Vitamin A which is thought to have a role in erythropoeisis as well as iron transport (27). Although anemia has been

frequently reported in HIV infected population, but when compared with HIV uninfected population as a control group did not clearly suggest increase prevalence of iron deficiency among HIV infected children (28,29). Other factors like parasitic infections, opportunistic infections, chronic inflammation, cytokine induced myelosuppression and HIV infection of bone marrow stroma (3,30) are some of other reasons causing increase losses and depressing erythropoeisis and thus worsening the disease progression.

Regardless of the cause, recognition of anemia at ART initiation could be useful alert for clinicians in treatment of CLHIV, in selection of ART drugs (Zidovudine based regimen avoided in anemia), monitoring response to drugs or treatment failure. Moreover, correction of anemia improves prognosis, and thus monitoring of hemoglobin levels during ART also helps to identify those not responding to treatment and may be useful in deciding further investigations and specific treatment to correct anemia.

Conclusion

This study on HIV infected children in Delhi has shown high prevalence of anemia. Frequency of anemia was associated with worsened clinical and immunological stage. Treatment with HAART improved anemia in most of the HIV infected children so much so the after one year of HAART none of the children was severely anemic. A thorough search for correctable causes of anemia may need to be applied to HIV infected children whose anemia does not improve following HAART.

Recommendation

Anemia is one of the common morbidity found among the children living with HIV. Timely diagnosis and treatment of HIV and its co-morbidities helps in improvement of not only anemia, but also results in better clinical outcome and immunity. However, other factors like adherence to ART and nutritional interventions need to be further studied.

Limitation of the study

There are some limitations to this study. Firstly the exact type and cause of anemia in these study subjects were not determined. Secondly results of this study in limited setting in Delhi cannot be generalized. Thirdly other predictors of anemia like under nutrition and virological response to HAART have not been studied. However, association of anemia and ART response warrants further longitudinal studies in larger cohort.

Relevance of the study

The study would be useful in managing children living with HIV in a more comprehensive manner by giving due attention to anemia and other co-morbidities.

Authors Contribution

First author was the main researcher for data collection, basic analysis and preliminary manuscript. All other authors contributed in the study design, supervision, in-depth analysis, interpretation and finalizing the manuscript.

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Tables

TABLE 1 DISTRIBUTION OF STUDY SUBJECTS ACCORDING TO ANEMIA (N=55)

Anemia	Before starting HAART		After 1 year of HAART	
	Number	%	Number	%
No Anemia	10	18.2	35	63.6
Mild	11	20.0	9	16.4
Moderate	27	49.0	11	20.0
Severe	7	12.7	0	0
Total with anemia	45	81.8	20	36.4
Mean (SD) hemoglobin gm /dL	9.9 (±2.0)		11.6 (±1.6)	
P-value	< 0.001			

TABLE 2 DISTRIBUTION OF STUDY SUBJECTS BASED ON THEIR CLINICAL STAGE AND ANEMIA (N=55)

WHO Clinical Stage	N	Before starting HAART		N	After 1 year of HAART	
		Anemia			Anemia	
		Present n (%)	Absent n (%)		Present n (%)	Absent n (%)
Early stage (Stage I + II)	17	10 (58.8)	7 (41.2)	50	20 (40.0)	30 (60.0)
Advanced stage (Stage III + IV)	38	33 (86.8)	5 (13.2)	5	0 (0)	5 (100)
Total	55	43	12	55	20	35

TABLE 3 DISTRIBUTION OF STUDY SUBJECTS BASED ON THEIR IMMUNODEFICIENCY STATUS AND ANEMIA (N=55)

Immunodeficiency	N	Before starting HAART		N	After 1 year of HAART	
		Anemia			Anemia	
		Present n (%)	Absent n (%)		Present n (%)	Absent n (%)
No to mild immunodeficient	11	9 (81.8)	2 (18.2)	47	15 (31.9)	32 (68.1)
Moderate to severe immunodeficient	44	34 (77.3)	10 (22.7)	8	5 (62.5)	3 (37.5)
Total	55	43(78.2)	12 (21.8)	55	20 (36.4)	35 (63.6)