



Original Article:

Anemia in Antiretroviral Naïve HIV/AIDS Patients: A Study from Eastern India

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Abstract: Background: Hematological manifestations are common throughout the course of HIV infection. Impact of anemia is the most significant among them. The present study was undertaken to evaluate the etiologies underlying anemia in HIV/AIDS. **Methods** This was a non randomized cross sectional observational study conducted in a tertiary care hospital of India over a period of 2 years. One hundred and fifty HIV patients were screened. Thorough clinical and laboratory evaluation was done in 50 randomly selected anemic cases. **Results:** Proper etiological diagnosis could be reached in 46 patients. Among them correlation between Hb% and CD4 count was statistically insignificant ($p = 0.074$, $r = 0.47$) whereas it was significant with absolute lymphocyte and CD4 count ($p = 0.006$, $r = 0.41$). There was better correlation of bone marrow iron status with percent saturation of transferrin ($p = 0.003$, $r = 0.54$) than with serum ferritin ($p = 0.055$, $r = 0.09$). Bone marrow iron status did not have any relationship with CD4 count. Anemia of chronic disease was the commonest etiology (37%) followed by HIV related myelodysplastic syndrome (31%), iron deficiency anemia (13%), bone marrow suppression due to direct involvement by some infective process (7%). Aplastic anemia, multiple myeloma, Hodgkin's disease, pure red cell aplasia, hemophagocytic lymphohistiocytosis and vitamin B12 deficiency were detected in one case (2%) each. **Conclusions:** Etiologies of anemia in HIV/AIDS are multifactorial with anemia of chronic disease being the commonest. For screening of iron deficiency in this group, percent saturation is a better tool than serum ferritin. Absolute lymphocyte count can sometimes be used as a surrogate marker of immunological status in antiretroviral naïve HIV patients, particularly in resource poor areas.

Key Words: HIV; AIDS; Anemia; MDS; India

Introduction:

HIV/AIDS is the major health challenge in the modern world and causing devastation in the resource poor south-east Asian countries. It involves almost all the systems in human body. Disorders of hematopoietic system including lymphadenopathy, anemia, leucopenia and/or thrombocytopenia are common

throughout the course of HIV infection. Studies have unequivocally demonstrated that anemia is associated with quality of life decrements, decreased survival and increased disease progression in adults with HIV infection.[1-3] While generally mild, anemia can be quite severe and may require repeated blood transfusion. It is supposed to have multifactorial etiology [4]; drug toxicities (e.g. zidovudine, dapsone, trimethoprim/sulfamethoxazole, ganciclovir, interferon α etc.), systemic fungal and mycobacterial infection, nutritional anemia (malabsorption and anorexia induced by HIV/AIDS), anemia of chronic disease being the major causes. Apart from them, Parvo virus B-19 infection, HIV induced myelosuppression and HIV associated myelodysplastic syndrome (MDS) are some other etiologies. Vitamin B-12 level may be depressed in HIV/AIDS patients as a consequence of achlorhydria or malabsorption, though folate levels are usually normal. Autoimmune hemolytic anemia is rare, although 20% of patients may have a positive direct antiglobulin test as a consequence of polyclonal B cell activation.[5]

There is wide variation in the prevalence of anemia among HIV/AIDS patients in different studies all over the world and dearth of information in India addressing this issue. There is hardly any data available from the eastern part of the country. The present study was planned to evaluate the etiologies underlying anemia in HIV/AIDS.

Methods

The study was conducted at the HIV Clinic and the Medicine Department, in collaboration with the Hematology Department of a tertiary care hospital of eastern India. This was a non randomized cross sectional observational study undertaken over a period of 2 years. During this period, we screened 150 patients documented as seropositive for HIV at any Integrated Counseling and Testing Center (ICTC) of India, who were not on any anti-retro viral therapy (ART). Patients with pregnancy, known malignancy or hematological disorders like thalassemias, hemophilia etc were excluded from study along with those undergoing treatment for anemia. Also excluded were patients suffering from medical conditions known to

cause anemia, like chronic renal failure, hypothyroidism etc. Informed consent was taken from all the patients. The study received clearance from Institutional Ethical Committee.

All the patients underwent evaluation initially by detailed history taking (including duration of HIV seropositivity, drug history and history of opportunistic infections) and thorough clinical examination with special reference to hematopoietic system and signs of opportunistic infections. Initial laboratory investigations included a complete hemogram, CD4 count, random blood sugar, urea, creatinine, liver function test, chest x-ray, ultrasonography of whole abdomen, sputum for AFB and urine for routine examination. Anemia was defined as hemoglobin level less than 12g/dl in women and 13g/dl in men [6, 7]. Further evaluation was carried out on 50 randomly selected anemic patients for the etiological diagnosis. All of them were subjected to assessment of serum ferritin, serum iron, TIBC, bone marrow aspiration for morphology and iron store. Selected patients were put on investigations like trephine bone marrow biopsy and cytogenetic study; Ziehl-Neelsen (Z-N) stain for acid fast bacilli (AFB), fungal stain and bactec culture (Bactec 460 System) of bone marrow aspirate; serum vit-B12 and folic acid level; direct Coomb's test, stool for ovum parasite cyst, occult blood test, upper gastro intestinal endoscopy and colonoscopy; lymph node fine needle aspiration cytology/biopsy.

HIV was diagnosed by Rapid ELISA test kit (HIV Comb, Tri-dot), CD4 count was documented by a FACS Counter (Becton-Dickinson) by fluochrome-conjugated antibody to CD4. Complete blood count was performed on a fully automated 5 part differential cell counter (SYSMEX SS 300) from EDTA blood. Reticulocyte slides were stained with methylene blue (supra vital stain). Serum iron and total iron binding capacity (TIBC) estimation was done by FERROZINE method (reference value for serum iron: adult male 60-160 µg/dl, adult female 35-145 µg/dl and for TIBC: 250-400 µg/dl) and serum ferritin assay was done by ELISA method (reference value was 18-270 ng/ml for men and 18-160 ng/ml for women). Bone marrow aspirates were taken from posterior iliac crest with Salah's bone marrow aspiration needle & bone marrow biopsy when required was done with Jamshidi bone marrow biopsy needle. Marrow aspirate staining was done by Leishman stain. ZN staining of bone marrow aspirate was done in selected cases. Special fungal staining and culture of bone marrow aspirate was done in selected cases. Bone marrow iron was stained by Perl's reagent. Bone marrow trephine biopsy was stained by hematoxylin and eosin (H-E) stain. Folic acid was estimated from serum sample (reference range 5.4-18 ng/ml) and serum vitamin B12 assay was done by chemiluminescence immunoassay (Architect, Abbott with reference range – normal: 189-883 pg/ml, borderline: 125-189 pg/dl and deficient: < 125 pg/dl).

Results were tabulated in Microsoft office excel worksheet and expressed as mean (\pm standard deviation) for continuously distributed variable, and in absolute numbers and percentages for discrete variables. Standard statistical tests were applied and p values less than 0.05 were considered statistically significant.

Results:

Most common hematological abnormality in the 150 initially screened patients was anemia, present in 74.7% cases. It was followed by leucopenia (38%), thrombocytopenia (23.33%) and pancytopenia (16%). Among the anemic 23.2% had severe anemia (<7g %). Mean CD4 count was 188 cells/µL (range 12 to 504 cells/µL).

From the cohort of anemic patients, 50 cases were randomly selected for further evaluation, after taking proper consent. A proper etiology could not be detected in four patients. Final diagnosis of anemia could be reached in 46 patients. There were 32 male and 14 female among them. All the 46 patients had AIDS. They had a mean CD4 count of 133.7 cells/µL

(± 79.9) and the mean hemoglobin was 7.2 g/dL (± 1.9). No statistical significant correlation was detected in between Hb% and CD4 count ($p = 0.074$, $r = 0.47$). Majority belonged to normocytic normochromic group (63%), followed by microcytic hypochromic anemia (28%). Macrocytic anemia was seen in 9% patients. The mean MCV (mean corpuscular volume) was 85.8 fL (± 10.6). The mean WBC, absolute lymphocyte and platelet counts were 4.2×10^3 cells/mm³ (± 2.98), 0.76×10^3 cells/mm³ (± 0.6) and 150.1×10^3 cells/mm³ (± 0.98) respectively. The correlation of absolute lymphocyte and CD4 count was statistically significant ($p = 0.006$, $r = 0.41$).

Bone marrow examinations revealed hypercellular marrow in most of the cases (63.04%). Hypocellular marrow was detected in 19.57% cases. Erythropoiesis was suppressed in 36.96%. Most important bone marrow finding of our study was very high prevalence of dysplastic changes (Figure 1). Though trilineage dysplasia was seen in 6.5%, dysplastic changes involving isolated cell lines were ranging from 13.1 to 45.7%, most prevalent being dysmegakaryopoiesis followed by dyserythropoiesis and dysgranulopoiesis. Increased numbers of plasma cells were found in a significant proportion of cases (23.9%). Erythrophagocytosis was seen in 6.52% cases. Bone marrow granuloma was detected in one patient. Z-N staining revealed acid fast bacilli in two patients. Histoplasma was evidenced as clusters of budding yeast cells in bone marrow trephine biopsy of one patient and as budding yeast cells within macrophages in bone marrow aspirate of another patient (Figure 2). Marrow iron was adequate in majority except a few cases of iron deficiency anemia. The correlation of bone marrow iron status was far better with percent saturation of transferrin ($p = 0.003$, $r = 0.54$) than serum ferritin ($p = 0.055$, $r = 0.09$). There was no correlation in between bone marrow iron status and CD4+ count ($p = 0.713$, $r = -0.07$). Relationship of bone marrow iron status with different variables is shown in Table 1.

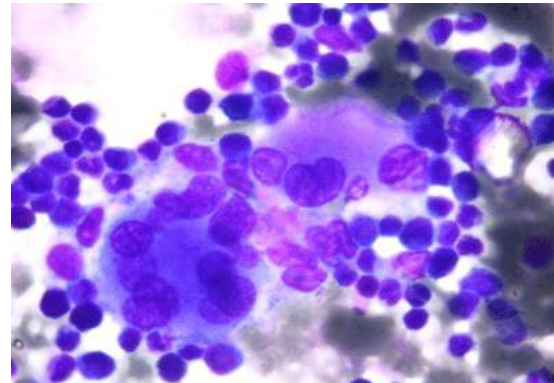


Figure 1: Dysplastic changes involving bone marrow.

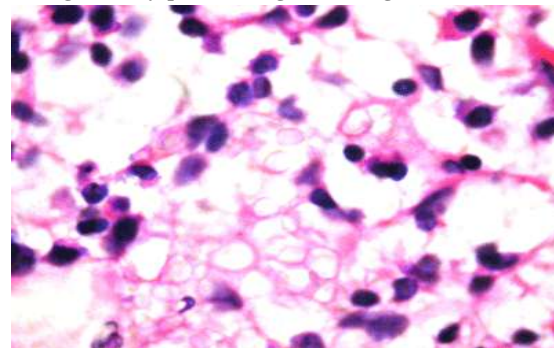


Figure 2: Histoplasma in bone marrow.

The Leishman stained bone marrow aspiration slide showed myelodysplastic changes.(Fig. 1)

Bone marrow trephine biopsy specimen stained with hematoxylin and eosin showed clusters of budding yeast cells of *Histoplasma capsulatum*.(Fig. 2)

Parameters	Mean	Standard deviation (± SD)	Coefficient of correlation with BM iron status (r value)	Statistical significance (p value)
CD4 count (cells/ μ L)	133.7	79.9	-0.17	0.713
Hb% (g/dl)	7.3	1.9	-0.11	0.569
Serum ferritin (ng/dl)	226.1	324.5	0.09	0.055
Serum iron (μ g/dl)	97.6	34.8	0.43	0.012
Percent saturation (%)	42.6	20.4	0.54	0.003

SD = standard deviation, BM = bone marrow, Hb% = hemoglobin level. Statistically significant positive correlation of bone marrow iron was detected with serum iron and percent saturation of transferrin, stronger for the later. Negative correlation was seen with CD4 count, but it was statistically insignificant.

Diagnosis		Age (years)	CD4 (cells/ μ L)	Hb% (g/dl)	MCV (fL)	WBC (cells $\times 10^3$ /mm ³)	Platelets (cells $\times 10^3$ /mm ³)	Iron (μ g/dl)	Percent saturation (%)	Ferritin (ng/dl)
ACD	Mean	36.9	136.3	7.9	83.4	5.3	201.2	101.2	42.8	343.9
	SD	9.7	82.3	1.7	9.4	4.1	82.6	36.7	21.9	458.8
MDS	Mean	43.5	144.8	7.4	91.5	4.2	151.4	110.1	46.7	123.2
	SD	12	88.6	1.9	8.9	1.8	93	29	15.6	15.6
IDA	Mean	34.7	176.8	7	76.7	4.1	175.8	46.8	36.5	88.2
	SD	8.2	34.4	1.1	9.8	2	82.2	17.7	17.1	134.6
BS	Mean	46	40.7	5.9	80	1.9	18.7	93	51.1	554.7
	SD	7.9	50	1.3	12.5	0.5	12	19	36.1	471.9
AA		35	224	5.9	87	1.9	6	87	43.9	77
MM		61	104	3.2	94.9	1.2	10	110	12.3	142
HD		19	12	6.4	85.8	3.1	20	87	11.9	150
PRCA		43	46	4.8	92	3.4	106	105	55	117
HLH		50	88	4	80	3.6	22	82	66	122
B12D		28	152	6.7	108	1.2	88	112	17.7	149
Total (n = 46)	Mean	39.5	133.7	7.3	85.8	4.2	150.1	97.6	42.6	226.1
	SD	11.1	79.9	1.9	10.6	3	98.4	34.8	20.4	324.5

MCV = mean corpuscular volume, WBC = white blood cell, St Dev = standard deviation. ACD - anemia of chronic disease, MDS- HIV related myelodysplastic syndrome, IDA- iron deficiency anemia, BS- bone marrow suppression due to direct involvement of marrow by some infective process, AA- aplastic anemia, MM- multiple myeloma, HD- Hodgkin's disease, PRCA- pure red cell aplasia, HLH- hemophagocytic lymphohistiocytosis, B12D- vitamin B12 or cyanocobalamin deficiency anemia.

■ ACD ■ MDS ■ IDA ■ BS ■ AA ■ MM ■ HD ■ PRCA ■ HLH ■ B12DA

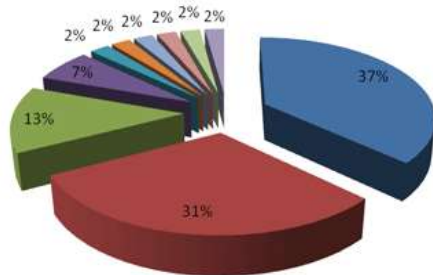


Figure 3: Contribution of different etiologies in the final diagnosis of anemia (n = 46)

ACD - anemia of chronic disease, MDS- HIV related myelodysplastic syndrome, IDA- iron deficiency anemia, BS- bone marrow suppression due to direct involvement of marrow by some infective process, AA- aplastic anemia, MM- multiple myeloma, HD- Hodgkin's disease, PRCA- pure red cell aplasia, HLH- hemophagocytic lymphohistiocytosis, B12D- vitamin B12 or cyanocobalamin deficiency anemia.

Anemia of chronic disease (ACD) was seen as the most common etiology, responsible in 37% cases, followed by HIV related myelodysplastic syndrome (MDS) in 31%. Next common etiology was iron deficiency anemia (IDA) in 13% cases. Bone marrow suppression (BS) due to direct involvement of marrow by some infective process was responsible in 7% cases. Aplastic anemia (AA), multiple myeloma (MM), Hodgkin's disease (HD), pure red cell aplasia (PRCA), hemophagocytic lymphohistiocytosis (HLH) and vitamin B12 or cyanocobalamin deficiency (B12D) anemia were each responsible in 2% (1 cases each, see Figure 3). All of the patients with bone marrow suppression as well as the later mentioned diagnosis had pancytopenia in peripheral blood, whereas 12%, 36% and 17% patients with ACD, MDS and IDA respectively had pancytopenia. Lymphopenia was noted in 71% of ACD, 64% of MDS, 33% of IDA and 100% of patients diagnosed with bone marrow suppression due to some infective process in marrow. Absolute neutropenia was a comparatively uncommon finding in the study. Table 2 shows the distribution of different parameters among the etiologies diagnosed. Figure 4 depicts distribution of mean CD4 count in different etiologies.

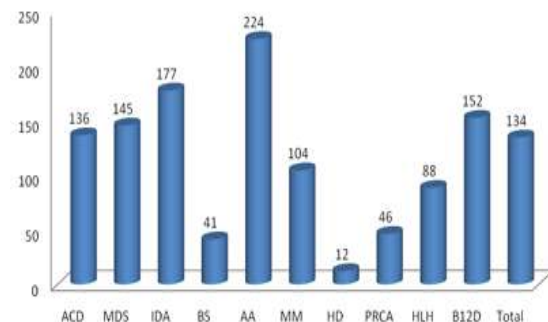


Figure 4: Distribution of mean CD4 count in different etiologies (n = 46)

ACD - anemia of chronic disease, MDS- HIV related myelodysplastic syndrome, IDA- iron deficiency anemia, BS- bone marrow suppression due to direct involvement of marrow by some infective process, AA- aplastic anemia, MM- multiple myeloma, HD- Hodgkin's disease, PRCA- pure red cell aplasia, HLH- hemophagocytic lymphohistiocytosis, B12D- vitamin B12 or cyanocobalamin deficiency anemia.

Anemia of chronic disease was the most commonly encountered diagnosis (in 31% of cases), followed by HIV related myelodysplasia.

The lowest CD4 count was encountered in the patient with diagnosis of Hodgkin's disease.

Common presenting symptoms included weight loss, generalized weakness, fever etc. They were not specific for the etiologies diagnosed. Among the examination findings lymphadenopathy (26%) and oral candidiasis (24%) were the most prominent, followed by splenomegaly (21%).

Discussion:

In HIV/AIDS, International literature reveals that prevalence of anemia is widely variable. They not only depend upon the stage of the disease, but socio-demographic factors also have a huge impact. In our study, among the initial 150 patients, the prevalence of anemia was comparable with other studies (approximately 70%) but we found lower number of leucopenic and thrombocytopenic patients compared to other series (approximately 50% and 40% respectively) [8-11]. The reason behind this variation is largely unexplained.

Though in most series the correlation of Hb% and CD4 count is linear [12-14], there are studies in which a weak correlation similar to our study was observed between CD4 cell count and Hb% (SM Alavi et al - $r = 0.451$, $p = 0.056$) [15]. It was postulated that, apart from immunological status and virus load, other factors might play major roles in the pathogenesis of anemia. Detecting normocytic normochromic morphology as the major type of anemia was in tune with the existing data.[4] Despite conflicting reports worldwide, in few studies strong correlation ($r = 0.645$, $p = 0.001$) has been shown in between absolute lymphocyte and CD4 count.[15] Our study revealed similar statistically significant correlation. So, absolute lymphocyte count can sometimes be used as a surrogate marker of immunological status in ART naïve HIV patients, particularly in resource poor areas.

In the present study, we found anemia of chronic disease (ACD) as the most common etiology, responsible in 37% cases. In 35% of cases diagnosed as ACD, no infection other than HIV was identified. This fact highlights the possibility of the role played by human immuno-deficiency virus itself in the production of anemia similar to ACD. Next common etiology of anemia in our study was HIV related MDS, responsible for 31% of the cases. They were characterized by long standing anemia often requiring blood transfusion and having predominantly normocytic blood picture (79%) with mean MCV of 91.5 fl. They had pancytopenia or bicytopenia in peripheral blood in a significant proportion of cases (36% each) apart from the classical dysplastic changes involving the bone marrow. As per the information available, this HIV related MDS is not totally identical to the MDS that is commonly diagnosed in non-HIV population; because the former variety often responds to antiretroviral therapy and the chances of transforming into acute leukemia is also negligible.[16-19] Bone marrow changes in long-term HIV patients have different characteristics from primary MDS and constitute the entity for which the name HIV-myelopathy has been proposed in the literature.[20]

Iron deficiency anemia was detected in only 13% of patients, in the contrary to the common belief that they are responsible for the production of anemia in a large proportion of cases even in HIV, in this part of the world. Most of them presented with microcytic hypochromic blood picture (83%). On further investigation one patient was found to have stool parasite on routine testing, another patient was detected with esophageal erosion on esophago-gastro-duodenoscopy though biopsy reported to be nonspecific. One more Hepatitis B co-infected patient with chronic liver disease was detected with esophageal varices. Endoscopic evaluations of the other patients were within normal limit. The diagnosis of IDA was

made on the basis RBC indices, serum ferritin, serum iron, TIBC, percent saturation of transferrin and bone marrow iron status.[21,22] There was almost no correlation between serum ferritin and bone marrow iron as already specified. This probably reflects high prevalence of concurrent inflammation in HIV infected patients resulting in rise of ferritin as an acute phase reactant. So, it was postulated that for screening of iron deficiency in HIV infected persons, assessment of percent saturation of transferrin would be a better option than assessing serum ferritin. No statistically significant correlation was detected between iron status and immunological status (CD4 count) in the present study, similar to the study conducted among the HIV-infected pregnant women in Malawi by Semba et al.[23]

Peripheral blood pancytopenia and grossly hypocellular bone marrow were detected in four patients in the study. Among them two were detected to have budding yeasts of *Histoplasma* species in trephine biopsy or aspirate, one had bone marrow tuberculosis as evidenced by multiple acid fast bacilli on ZN staining. In the remaining one patient no infective process or dysplastic changes could be documented in marrow aspirate or biopsy. So a provisional diagnosis of aplastic anemia was made. It remains to be determined whether this was due to the direct effect of HIV infection as reported in other studies.[24] We found multiple myeloma in one of our patients. Multiple myeloma is shown in some series to occur with greater frequency in HIV-infected patients.[25,26] Although multiple myeloma is of rare occurrence in HIV-infected individuals[27], bone marrow plasmacytosis is a relatively common finding. In our study, around 24% patients had marrow plasmacytosis. Also worth mentioning is the occurrence of Hodgkin's disease in one patient. Although HD does not represent an AIDS-defining condition, recent evidence consistently indicates that HIV infected people have a significantly increased risk of developing HD.[28] HIV-related HD is characterized by the preponderance of aggressive histological subtypes, advanced stage at diagnosis, and malignant clinical course [28]. In bone marrow biopsy of one patient giant pronormoblasts were detected, who was later diagnosed to be a case of pure red cell aplasia. Another rare disorder which we found in one of our patients was hemophagocytic lymphohistiocytosis. Hemophagocytic lymphohistiocytosis has been diagnosed with increasing frequency in patients infected with HIV.[29,30] Hemophagocytosis is commonly found, to varying degrees, in the bone marrow of HIV-infected individuals without an underlying diagnosis of HLH, which raises the possibility of a sub clinical form of HLH.[31] Vitamin B12 deficiency anemia, which is a well documented entity in HIV infection, was diagnosed in one patient.

Conclusion:

Anemia is the most common hematological abnormality in antiretroviral naïve HIV disease. It is in majority normocytic and normochromic in morphology. Etiologies of anemia are multifactorial among this population, anemia of chronic disease being the commonest. It is followed by HIV associated MDS, iron deficiency anemia and other rare causes. For the screening of iron deficiency, percent saturation of transferrin is a better tool compared to serum ferritin. Absolute lymphocyte count can sometimes be used as a surrogate marker of immunological status in antiretroviral naïve HIV patients, particularly in resource poor areas.

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