

Research Article

## A Study of Prevalence of Anemia among HIV Patients and its Correlation with Clinical Stage of Aids, Cd4 Count and Antiretroviral Therapy

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### ABSTRACT:

Anaemia is an important clinical problem in patients with HIV infection and those with AIDS. The causes of anaemia in HIV infection are multifactorial. HIV per se causes decrease in production of RBCs and other bone marrow elements, as it has direct effect on bone marrow stromal cells and cause cytokine secretion. The elevated level of cytokines and Tumour necrosis factor further inhibit haematopoiesis in HIV. There is also evidence of increased risk of anaemia in association with zidovudine use, CD4 cell counts of <200 cells/ $\mu$ l and high viral load. This study was conducted to find out the incidence of anaemia among patients with HIV and its association with WHO clinical staging, CD4 count and Anti- Retroviral Therapy (ART). The study was conducted at department of medicine of a tertiary care teaching hospital in western Maharashtra from July 2015 to September 2016.

A total of 316 patients (106 Outpatients and 214 indoor patients) were included in the study. Significantly high prevalence of anaemia was seen in patients in WHO stage II-IV, with the highest prevalence in stage III. Although anaemia was seen in all levels of CD4 counts, anaemia prevalence 89.5% was significantly high in patients with CD4 count < 200 cells/ $\mu$ l. The patients not on ART had higher prevalence of anemia than those who were receiving ART, regardless of whether the regimen was AZT containing or not. The study highlights that advanced disease, low CD+ count and non-exposure to ART are adverse risk factors for development of anemia among HIV patients.

**Key Words:** HIV, AIDS, ANEMIA, CD4 COUNT, ART

### INTRODUCTION

Anaemia is an important clinical problem in patients with HIV infection and those with AIDS. In 1998, the Anaemia in HIV Working Group issued a consensus statement addressing the impact of anaemia on HIV-infected individuals, as well as treatment strategies and future research directions. The Anaemia in HIV Working Group reconvened in 2002 to evaluate the then available data and to determine the implications of those data for patient management.<sup>1</sup>

The causes of anaemia in HIV infection are multifactorial.<sup>2</sup> HIV per se cause decrease in production of RBCs and other bone marrow elements, as it has direct effect on bone marrow stromal cells and cause cytokine secretion. The elevated level of cytokines and Tumour necrosis factor further inhibit haematopoiesis in HIV. Treatment of HIV and reduction of virus load by the use of highly active antiretroviral therapy (HAART) may improve haematopoiesis.<sup>3</sup>

Individuals with HIV infection who are significantly more likely to develop anaemia include women and African American persons. There is also evidence of increased risk of anaemia in association with zidovudine use, CD4 cell counts of <200 cells/ $\mu$ l and high viral load.<sup>4</sup>

Zidovudine treatment is associated with bone marrow suppression and an increased risk of developing anaemia.<sup>6,7</sup> In one of the study, it was stated that before 1996, anemia was associated with use of zidovudine but another study conducted after 1996, it stated that use of zidovudine was not significantly associated with anaemia. It documented that the presence of anaemia (defined as a hemoglobin level of <12 g/l) in 41.6% of subjects receiving zidovudine therapy, compared with 34.3% of those not receiving zidovudine, P value < 0.01.<sup>4,5</sup>

Patients with HIV may also acquire chronic parvovirus B19 infection of bone marrow, resulting in profoundly decreased numbers of RBCs. In addition, anaemia may result from the indirect effects of HIV infection, such as adverse reactions to medications such as zidovudine, opportunistic infections, neoplasms, or nutritional abnormalities stemming from anorexia, malabsorption or metabolic disorders. Although many drugs used to treat HIV-related disorders are myelosuppressive, severe anaemia is most often related to the use of zidovudine.<sup>5</sup>

Low CD4 cell counts (<200 cells/μl) and higher HIV-1 RNA levels in plasma have each been independently associated with an increased risk of anaemia in multivariate analyses.<sup>8, 9</sup> In study by Voth R.S et al they reported the main immunological complication and hallmark of HIV infection is cellular CD4 T-lymphocyte depletion for which various mechanisms are involved: HIV induced cytolysis; deregulations of cytokines; cytotoxic T-lymphocyte responses and HIV induced autoimmune reactions which are not mutually exclusive have been suggested.<sup>10</sup>

There has been an independent correlation between decreased survival regardless of Cluster of differentiation (CD4+) T-lymphocyte count and anaemia and plasma HIV Ribonucleotide analogue (RNA) concentration and that anaemic HIV-infected patients who recover from anaemia have better survival rates as compared to those who do not recover.<sup>11</sup>

**AIMS & OBJECTIVES:** This study was conducted to find out the incidence anaemia among patients with HIV and its association with WHO clinical staging, CD4 count and ART.

**MATERIALS AND METHODS**

This was a hospital based descriptive cross-sectional study. This study was conducted at department of medicine of a tertiary care teaching hospital in western Maharashtra between July 2016 and September 2016.

**Inclusion Criteria** - All consented HIV infected patients aged 18 years and older admitted at VIMS medicine wards and patients attending OPD at the time of study were included in the study.

**Exclusion Criteria** - Pregnant and lactating women, patients under 18 years, as well as patients known to have chronic kidney disease, patients with known sickle cell disease and thalassemia and patients who received blood transfusion within three month before the study were excluded from the study.

A structured questionnaire was used to collect information regarding medical and past medical history including detailed drug use apart from ART. Information on ART types and duration was obtained from patients ICTC card number for patients on ART. Gynaecological history was taken for all enrolled women. Suspected pregnancy i.e. last normal menstrual period (LNMP) longer than 1 month had UPT done.

WHO clinical staging was done to all recruited patients after a thorough history and clinical examination according to standard clinical examination methods. Revised WHO clinical staging of HIV for resource-constrained settings were used. Clinical stages are categorized as 1 to 4, progressing from primary HIV infection to advanced HIV/AIDS.<sup>12</sup> Patients were investigated aseptically for determination of CD4 count, which was done using FACS calibre. All the results were finally compiled and significance calculated using t test.

**RESULTS**

From July 2015 to September 2016 a total of 1025 HIV infected patients visited the outpatient department or were hospitalised in Medicine Wards. 829 patients aged 18 years and above attended the outpatient clinic and 196 known HIV were admitted to the Medicine wards. Out of 829 out patients 230 were willing to participate in study. Of the 230 patients, 5 patients were excluded from the study because 2 had Chronic kidney disease (CKD), 2 were pregnant and 1 had sickle cell disease therefore from Clinic 225 patients entered final analysis. Of the 196 known HIV admitted patients 69 were not willing to participate in study. 127 were interviewed. 29 had blood transfusion within 3 month, 4 had been backed out and 3 had CKD therefore 91 patients entered final analysis, making a total of 316 patients

**Association between anaemia and Clinical stage of HIV**

Out of 316 patients, 103 (60.6%) of stage 1 and 14 (29.2%) of stage 4 had no anemia. Among patients with stage 4 disease 33.3% had severe anaemia while severe anaemia was seen in only 1.2% of stage 1 patients. Severity of anaemia increased with advanced stage of HIV infection and this was statistically significant (P 0.0001) (Table 1).

**Table 1: Association between anaemia and WHO clinical stage of HIV**

Variable	Anaemia			Total (N=316)	P value
	Normal HGB	Non severe anaemia	Severe anaemia		
Clinical stage of HIV					
Stage I	103(60.6%)	65(38.2%)	2(1.2%)	170(100%)	0.0001
Stage II	23(47.9%)	23(47.9%)	2(4.2%)	48(100%)	
Stage III	12(24%)	25(50%)	13(26%)	50(100%)	
Stage IV	14(29.2%)	18(37.5%)	16(33.3%)	48(100%)	

**Association between anaemia and CD4 count**

CD4 count ranged from 5 to 1288 cells/μl, with mean CD4 of 77.84 ± 243.9 cells/μL. Out of 316 patients, 80(25.3%) had CD4 less than 200 cells/μl. Anaemia was seen in all levels of CD4, of the patients with CD4 above 500cell/μl 31(36.5%) had anaemia while 64(80%) of patients with CD4 of less than 200cells/μl had anaemia. 28(35%) of patients with CD4 of less than 200 cells/μl had severe anaemia while only 2(2.4%) of patients with CD4 above 500 cells/μl had severe anaemia. Low CD4 count was significantly associated with anaemia (P 0.0001) (Table 2).

**Table 2: Association between Anaemia and CD4 count**

Variable	Anaemia			Total (N=316)	P value
	Normal HGB	Non severe anaemia	Severe anaemia		
CD4 count					
500+	54(63.5%)	29(34.1%)	2(2.4%)	85(100%)	0.0001
349-499	41(64.1%)	21(32.0%)	2(3.1%)	64(100%)	
200-<349	41(47.1%)	45(51.7%)	1(1.1%)	87(100%)	
<200	16(20%)	36(45%)	28(35%)	80(100%)	

**Association between anaemia and ART** Anaemia was more prevalent in ART naive patients [30/44 (68.2%)] than in those on ART, regardless of the type. Anaemic patients constituted 97/177 (54.8%) of patients on AZT containing regimen while there were 45/95 (47.4%) of anaemic patients among patients on non-AZT containing regimen. Non- severe (43.2%) and severe (25%) anaemia were more prevalent in ART naive patients than it was in patients on ART. Among patients on ART, severe anaemia was more prevalent among patients on AZT containing regimen (14.1%) than among patients on non-AZT containing regimen (13.7%) (P 0.0001) (Table 3).

**Table 3: Association between Anaemia and Type of ART Regime**

Variable (Type of ART Regime)	Anaemia			Total (N=316)	P value
	Normal Hemoglobin	Anaemia Not severe	Anaemia Severe		
Not on ART	14(31.8%)	19(43.2%)	11(25.0%)	44(100%)	0.0001
AZT containing regimen	80(45.2%)	72(40.7%)	25(14.1%)	177(100%)	
Non AZT containing regimen	50(52.6%)	32(33.7%)	13(13.7%)	95(100%)	

**Mean Haemoglobin among Indoor vs Outdoor Patients**

The patients recruited from medical wards had significantly lower mean haemoglobin (9.67±3.00) than were patients recruited from the outpatient clinic who had mean haemoglobin of 12.11 ± 1.95 (P value <0.0001). This difference is obviously because the indoor patients are more serious and have some acute additional problem as compared to outdoor patients (Table 4).

**Table 4: Comparison of mean Haemoglobin among Indoor and Outdoor Patients**

Place (Indoor or Outdoor)	Number (%) (N=316)	Haemoglobin Mean(±SD)	*P value
Medical wards	91(28.8%)	9.67(±3.001)	<0.0001
Outpatient Clinic	225(71.2%)	12.11(±1.952)	

**DISCUSSION**

**Association between anaemia and WHO clinical stage of HIV**

Significantly high prevalence of anaemia were seen in patients in WHO stage II-IV, with the highest prevalence in stage III.<sup>13</sup> Unexplained anaemia of < 8 g/dl is used to stage patients into WHO stage III<sup>13</sup> and can partially explain the highest prevalence in Stage III. Todd S. Wills et al also reported higher prevalence of anaemia in patients with advanced HIV disease.<sup>14</sup>

**Association between anaemia and CD4 count among HIV patients**

Although anaemia was seen in all levels of CD4 counts, anaemia prevalence 89.5% was significantly high in patients with CD4 count < 200 cells/µl. A study in Mexico on risk factors and correlates for anemia in HIV treatment-naïve infected patients concluded that a CD4+ Cell Count <200 cells/mm<sup>3</sup> was associated with an increased risk of anemia after having observed that there is a positive correlation between hemoglobin and CD4+ cell count without use of ART.<sup>15</sup> The study by Todd S et al titled “Anaemia Prevalence and Associated Risk Factors in a Single-Centre Ambulatory HIV Clinical Cohort” showed that 38.6% patients with CD4+ cell count of less than 200/µl, had an Haemoglobin level of less than 13 g/dl, compared with only 12.2% of patients with a CD4+ cell count of 500 or more/µl (P 0.0001).<sup>14</sup> These findings suggest that low CD4+ count is a risk factor for developing anaemia among HIV patients.

**Association between Anaemia and type of ART regimen among HIV patients**

The patients not on ART had higher prevalence of anemia than those who were receiving ART, regardless of whether the regimen was AZT containing or not. No ART would mean more opportunistic infections, low CD4 counts and advanced stage of HIV; the factors that are known to cause anaemia.<sup>7,15</sup> These findings suggest that HIV infection by itself is a risk for anaemia as evidenced by results from our study. Among patients on ART those on AZT containing regimen had higher prevalence of anaemia which is similar to observation from previous studies.<sup>7,16</sup>

**CONCLUSION**

This study showed that risk factors for anaemia among HIV patients are multifactorial and these include advanced WHO stage of HIV, CD4 count less than 200 cells/mm<sup>3</sup>, non-

exposure to ART and using AZT based regimen. Anaemia is common problem among HIV patients and admitted patients had higher prevalence of severe anaemia compared to patients seen at outpatient clinic this would mean anaemia contributes to burden of HIV care as it is associated with increased morbidity among these patients. ART naive patients had higher prevalence of anaemia regardless of ART regimen that and ART treatment was associated with improvement of Haemoglobin. Furthermore, AZT containing regimen are associated with higher prevalence of anaemia compared to non- AZT regimen.

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