ORIGINAL ARTICLE

RISK FACTORS OF ANAEMIA AMONG ZIDOVUDINE-BASED REGIMEN IN PATIENTS WITH HIV INFECTION- A COHORT STUDY

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Background: Anaemia in patients with HIV infection is commonly multifactorial in origin. Nutritional deficiencies and the presence of opportunistic infections as well as HIV infection itself can cause anaemia. HIV medications like zidovudine can also cause anaemia in patients with HIV infection. This study aimed to study the prevalence and risk factors of anaemia in patients with HIV infection on a zidovudine-based HAART regimen. **Methods**: This hospital-based prospective cohort study was done at the ART (anti-retroviral therapy) centre. All adult patients with HIV attending the ART centre were included in the study. After obtaining written informed consent, the patient's demographic data, risk factors, WHO staging, and body mass index (BMI) were noted. Study population was divided into two groups as patients with or without anaemia and compared using appropriate statistical tests. **Results:** Out of the 202 patients with HIV infection on a zidovudine-based regimen, 52 patients (25.7%) developed anaemia. Anaemia was common in stage 3 or stage 4 of WHO staging (OR-9.94, CI-3.89-25.36) and in patients with low CD4 counts (OR-0.988, CI-0. 982-0.995). Patients with anaemia had significant opportunistic infections. **Conclusion:** Anaemia is common in patients with HIV on zidovudine-based HAART regimen, which is seen as early as less than 8 weeks. WHO staging, and CD4 count were the primary risk factors for anaemia, which a change of treatment regimen and supportive measures can reverse.

Keywords: Anaemia; HIV; Zidovudine; WHO staging; CD4 count

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INTRODUCTION

Haematological abnormalities are common in patients with HIV infection. Prevalence of anaemia varies from 20-95% in patients with HIV infection; which has decreased to 48% by the Highly Active Antiretroviral Therapy (HAART) regimen.[1–3] Anaemia is a major health problem globally with increased morbidity and mortality. Anaemia is associated with disease progression and poor outcomes in patients with HIV infection.[4] Anaemia in patients with HIV infection is commonly multifactorial in origin. Bone marrow infiltration by infection or tumour, myelosuppressive medications, decreased erythropoietin production, haemolysis and HIV infection itself play a role.[5] Moreover, nutritional deficiencies such as iron, folic acid, and vitamin B12 deficiency also cause anaemia. Poor intake, and malabsorption due to secondary infections are the major causes of these nutritional deficiencies.[6] HIV medications like zidovudine can also cause anaemia in patients with HIV infection. Zidovudine is one of the nucleoside reverse transcriptase inhibitors used for the treatment of HIV infection. It is used as a first-line regimen in HAART therapy in developing countries.[7] Zidovudine is associated with anaemia in early high-dose therapy. It can also cause bone marrow suppression which is common in patients with advanced illness and depends on the dose and duration of the therapy. In addition, it causes transient depletion of mitochondrial DNA, depletion of thymidine triphosphate, oxidative stress, and reduction of intracellular l-carnitine or apoptosis of the muscle cells.[8] This study aimed to study the prevalence and risk factors of anaemia in patients with HIV infection on zidovudine therapy.

MATERIAL AND METHODS

This study was hospital-based prospective cohort study. The study was approved by the Institute Ethical Committee, Tertiary care centre, Southern India. It was conducted at ART (anti-retroviral therapy) centre in a tertiary care hospital in Southern India. The participants were chosen by convenient sampling method from patients attending an ART centre who were receiving first-line zidovudine-based HAART therapy. All adult patients with HIV on zidovudine-based HAART therapy as per NACO guidelines were included in the study.[9] Patients with baseline anaemia and haematological illness, on myelosuppressive drugs, anti-tubercular drugs and second-line HAART regimen, co-infection with cytomegalo virus, hepatitis B and C, patients with a history of immune reconstitution inflammatory syndrome, pregnant females, and patients with renal failure

were excluded from the study. The sample size was calculated using the single population proportion formula by considering the formerly reported 14.6% prevalence of anaemia[10], with a 95% confidence interval (CI) and 5% margin of error, which came to be around 192. We have included 202 participants in our study. After obtaining written informed consent, the patient's demographic data, risk factors, WHO staging and body mass index (BMI) were noted. A complete hemogram was done by an automated analyzer. CD4 count was analysed by flow cytometer. Peripheral smear was performed for patients with anaemia. Anaemia was defined as haemoglobin <13gm/dl for men and <12 gm/dl for non-pregnant women as per WHO criteria.[11] The study population was divided into two groups; patients with anaemia and patients without anaemia for comparison and to reduce bias. All patients with anaemia were switched to a tenofovir-based regimen. Nutritional supplements like iron, folic acid, and packed cell transfusion were given depending on the severity of anaemia. Patients were followed for a period eight months. Continuous variables were expressed as mean±SD. Categorical variables were expressed in percentages. An unpaired test was used to assess the difference between continuous variables. Chi-square analysis was done to assess the difference between categorical variables. Binary logistic regression was done to assess the association of risk factors with anaemia. SPSS version 21 was used for the analysis. *p*-value <0.05 was considered significant.

RESULTS

Out of the 202 patients with HIV infection on AZT therapy, 52 patients (25.7%) developed anaemia. The age group was significantly higher in patients with anaemia; the duration of the disease is comparable in both groups. The patients with anaemia were mostly smokers and alcoholics. The patients without anaemia were mostly in the earlier stages of the disease whereas patients with anaemia were in stage 3 or stage 4 of WHO staging. Patients with anaemia had significant opportunistic infections and also had low CD4 counts (Table-1). Among the patients with anaemia, 50% of patients had haemoglobin <6.9 gm%. RBC counts were found to be less than 2 million in about 38% of patients and the Haematocrit was found to be less than 20 in about 34% of patients. MCV was low in 40% of patients and MCH was low in 50 % and this equates well with the 40 % incidence of microcytic hypochromic anaemia in this study population. The second most common pattern was that of macrocytic hypo chromic anaemia in about 23% of patients (Table-2). Most people had developed anaemia after 60 days of zidovudine treatment and females seem to be more prone to it. The improvement in haemoglobin can be found within 60 days after substituting in ART and the maximum number of people got at least 50% increase in haemoglobin. A similar observation can be seen in haematocrit also (Table-3). The haemoglobin can be found to be increased maximum from 50–99% in patients who had Hb <7% and the improvement was significant (Table-4). The multivariable logistic regression analysis adjusted for other significant parameters showed a significant association of WHO staging (OR-9.94, CI-3.89-25.36) and CD4 count (OR-0.988, CI-0. 982-0.995) to zidovudine induced anaemia (Table-5). The females were more affected during the treatment around 60–90 days (Figure-1).

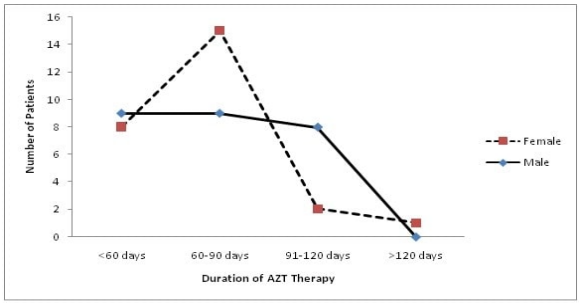

Figure-1: Duration of AZT therapy and number of patients with anaemia in relation to Gender AZT – Zidovudine

Table-1: Characteristics of study population

Parameters	Patient with anaemia (n=52)	Patient without anaemia (n=150)	*p*- value
Age (years)	36.23±9.35	30.87±6.11***	0.000
Gender			0.331
Male	26 (50%)	62 (41.3%)	
Female	26 (50%)	88 (58.7%)	
Duration of HIV since diagnosis (years) mean±SD	2.13±0.53	2.09±0.58	0.599
Duration of ART (days) mean±SD	66.63±23.46	66.4±21.24	0.947
Smoking	12 (23.1%)	11 (7.3%)**	0.004
Alcohol	11 (21.2%)	12 (8%)*	0.02
WHO staging			0.000
Stage 1	0	75 (50%)	
Stage 2	4 (7.7%)	42 (28%)	
Stage 3	15 (28.8%)	30 (20%)	
Stage 4	33 (63.5%)***	3 (2%)	
Opportunistic infections (Total)	14 (26.9%)	6 (4%)***	0.000
Tuberculosis	7 (13.5%)	2 (1.3%)	
Oral candidiasis	3 (5.8%)	2 (1.3%)	
Herpes zoster	3 (5.8%)	2 (1.3%)	
PCP	1 (1.9%)	0	
BMI (kg/m^2) mean±SD	20.06±3.9	20.40±3.89	0.583
CD4 count (cells/mm^3) mean±SD	198±113.2	419±148.4***	0.000
Hemoglobin% mean±SD	6.98±2.18	12.62±0.87***	0.000
* represents *p*-value <0.05, ** represents *p*-value <0.01, *** represents *p*-value <0.001			

Table-2: Haematological parameters of anaemia among zidovudine-based regimen

Parameter	Male n=26	Female n=26	Total n=52	*p*-value
Hemoglobin%				0.2499
<6.9	15(57.7%)	9 (34.6%)	24 (46.2%)	
7-7.9	2 (7.7%)	2 (7.7%)	4 (7.7%)	
8-8.9	6 (23.1%)	5 (19.2%)	11(21.2%)	
9-9.9	2 (7.7%)	6 (23.1%)	8 (15.4%)	
>10	1 (3.8%)	4 (15.4%)	5 (9.6%)	
RBC Count (million)				0.227
<2	13 (50%)	7 (26.9%)	20 (38.5%)	
2-2.9	9 (34.6%)	12 (46.2%)	21(40.4%)	
3-3.9	4 (15.4%)	5 (19.2%)	9 (17.3%)	
>4	0	2 (7.7%)	2 (3.8%)	
Haematocrit (%)				0.033
<20	14 (53.8%)	4 (15.4%)*	18 (34.6%)	
20-29	7 (26.9%)	11 (42.3%)	18 (34.6%)	
30-39	3 (11.5%)	7 (26.9%)	10 (19.2%)	
>40	2 (7.7%)	4 (15.4%)	6 (11.5%)	
MCV (fl)				0.003
<70	12 (46.2%)	0**	12 (23.1%)	
70-79	4 (15.4%)	5 (19.2%)	9 (17.3%)	
80-89	4 (15.4%)	10 (38.5%)	14 (26.9%)	
90-99	3 (11.5%)	6 (23.1%)	9 (17.3%)	
>100	3 (11.5%)	5 (19.2%)	8 (15.4%)	
MCH (Picogram)				0.194
<25	15 (57.7%)	11 (42.3%)	26 (50%)	
25-30	10 (38.5%)	10 (38.5%)	20 (38.5%)	
>30	1 (3.8%)	5 (19.2%)	6 (11.5%)	
Type of Anaemia				0.015
Normocytic normochromic	2 (7.7%)	7 (26.9%)	9 (17.3%)	
Microcytic hypochromic	16 (61.5%)*	5 (19.2%)	21 (40.4%)	
Normocytic hypochromic	3 (11.5%)	7 (26.9%)	10 (19.2%)	
Macrocytic hypochromic	5 (19.2%)	7 (26.9%)	12 (23.1%)	

MCV - Mean corpuscular volume, MCH – Mean corpuscular haemoglobin, MCHC – Mean corpuscular haemoglobin concentration, fl – femtolitre. * represents *p*-value <0.05, ** represents *p*-value <0.01

Table-3: Time to develop anaemia in relation to other parameters

Parameters	<60 days	60-89 days	90-119 days	≥120 days	Total	*p*-value
Age (years)						
<20	0	1	0	0	1	0.386
20-29	5	5	2	0	12	
30-39	6	9	5	0	20	
40-49	4	8	2	0	14	
≥50	2	1	1	1	5	
Gender						
Male	9	9	8	0	26	0.104
Female	8	15	2	1	26	
CD4 count (cells/mm^3)						
<50	1	1	2	0	4	0.675
50-199	9	11	4	1	25	
≥200	7	12	4	0	23	
WHO Stage						
Stage 2	2	1	1	0	4	0.718
Stage 3	6	5	4	0	15	
Stage 4	9	18	5	1	33	
Type of anaemia						
Normocytic normochromic	3	6	0	0	9	0.134
Microcytic hypochromic	7	7	7	0	21	
Normocytic hypochromic	5	3	1	1	10	
Macrocytic hypochromic	2	8	2	0	12	
Hemoglobin% increase after ART modification						0.028
<50%	10	13*	4	0	27	
50-99%	7	7	1	0	15	
100-149%	0	2	2	0	4	
≥150%	0	2	3	1	6	
Hematocrit increase percentage after ART modification						0.081
<50%	10	15	4	0	29	
50-99%	6	7	5	0	18	
≥100%	1	2	1	1	5	

ART- Antiretroviral therapy, * represents *p*-value <0.05, ** represents *p*-value <0.01

Table-4: Multivariable logistic regression for determinants of anaemia among zidovudine-based regimen

Parameter	Odds ratio (95% CI)	*p*-value
WHO staging	9.94 (3.89-25.36)***	0.000
CD4 count	0.988 (0.982-0.995)***	0.000
*** represents *P* value <0.001		

Table-5: Haemoglobin increase percentage when compared with haemoglobin at baseline

Hb% at baseline (gms%)	Hb increase %				Total	*p*-value
	<50%	50-99%	100-149%	≥150		
<7	0	14	4	6***	24 (46.1%)	0.000
7-7.9	3	1	0	0	4 (7.7%)	
8-8.9	11	0	0	0	11 (21.2)	
9-9.9	8	0	0	0	8 (15.4%)	
≥10	5	0	0	0	5 (9.6%)	
Hb – Haemoglobin, % - percentage *** represents *p*-value <0.001						

DISCUSSION

In this study, we have compared the clinical and demographic profiles of HIV patients with and without anaemia. 25.7% of the study population had anaemia which is similar to the study done by Curkendall SM *et al.* and Wubetu M *et al*.[12,13] There was a significant difference in age between the study populations. In our study, the maximum numbers of males were in the age group of 30–40 and females in the age group of 20–29 years. This might be because males in India choose younger female partners and males in their early thirties seek jobs outside and get involved in extramarital sexual affairs hence the chances of acquiring STDs increase.[14] Despite females being (56.4%) common in our study population, there was no gender predilection among the patients with anaemia. In contrast to our study, Agarwal *et al* found that females are prone to zidovudine-induced anaemia.[15]

Anaemia in patients on HAART is commonly observed especially in those who are on zidovudine therapy.[7,16,17] There are so many factors contributing to anaemia in these patients such as body mass index, stage of the disease, presence of opportunistic infections, less CD4 count, and habits like smoking and alcohol consumption. The mean BMI of the patients with anaemia was 20.06±3.9 kg/m^2 which was similar to the patients without anaemia. This is in contrast to the study done by Salli F *et al*, where BMI was the significant risk factor for anaemia.[18] Opportunistic infections were significantly higher in patients with anaemia. Tuberculosis was the most common opportunistic infection in these patients. This may be related to nutritional deficiency and suppressed immunity, as can be evidenced by a low CD4 count. In a study by Harding *et al.* done in the United States, HCV infection was the most common opportunistic infection associated with anaemia.[5]A study done in Ethiopia by Aynalem YA *et al*. had TB as the commonest infection and starting an anti-TB regimen had improved this anaemia.[19] The type of opportunistic infection may be related to the socio-economic status and lifestyle of the people.

Most of the patients having anaemia had habits of smoking and alcohol consumption as observed in other studies.[5,20] Use of alcohol can cause suppression of bone marrow as toxicity to precursor cells. Macrocytosis is the most typical abnormality induced by excessive ethanol consumption, formation of acetaldehyde adducts along with cellular proteins is believed to evoke an immune reaction responsible for the anaemia in alcohol addicts.[21] Though Smoking as such causes an increase in haemoglobin; in our study, the anaemia group had many smokers.[22]

On multivariable logistic regression, WHO staging and CD4 count were the prime determinants of anaemia in our study. In our study, patients with anaemia had predominantly advanced WHO staging and low CD4 count. The stigma to seek treatment for STDs is still present in this country which makes them progress to later stages. Advanced WHO staging and low CD4 count lead to secondary infections, bone marrow suppression, and asthenia causing anaemia in these patients.[23] Curkendall SM *et al.* found out that zidovudine-induced anaemia was significantly common in low CD4 count and in AIDS.[12] CD4 count and low BMI were the significant risk factors for anaemia in a study by Ssali F *et al*.[18]

The most common anaemia observed in the current study was microcytic hypochromic anaemia followed by macrocytic hypochromic anaemia. This was similar to the study done by Getaneh Z *et al*.[24] Panwar A *et al*. and Meidani M *et al.* found normocytic anaemia as the most common type in patients with HIV.[25,26] Microcytic hypochromic anaemia was the commonest in a study by Nyesigire Ruhinda E *et al*. among children with HIV infection.[27] The presence of microcytic hypochromic anaemia in our study may be attributed to iron deficiency, low iron levels, malabsorption, and poor intake. Macrocytic anaemia may be due to folate or vitamin B12 deficiency because of gastric and/or jejunal pathology secondary to infections or other conditions affecting

the gastrointestinal mucosa in HIV. Males were more prone to microcytic hypochromic anaemia in our study, similar to Getaneh Z *et al*. study.[24]

Zidovudine therapy is most commonly associated with anaemia.[28] Zidovudine is a nucleoside-analogue reverse transcriptase inhibitor (NRTIs) commonly used in the treatment of HIV; has been implicated in the inhibition of progenitor blood cells in a time- and dose-dependent fashion. Even though zidovudine anaemia was seen in less than 60 days of treatment in our study; it was common between 60–90 days of treatment and females were more affected. As such females have lesser haemoglobin and on top of its zidovudine therapy would have added to it. Another study demonstrated anaemia starts to develop after 4 weeks of treatment.[29] As zidovudine is known to produce anaemia, reversal of anaemia can also be seen once the regimen is switched over, as observed in our study and other studies.[10,30] After ART substitution with tenofovir regimen, haemoglobin and haematocrit increased significantly more than 50% in those who developed anaemia in 60–89 days; and patients with severe anaemia [Haemoglobin <7 gms%] had a significant rise in haemoglobin in our study.

The limitations of the study were, that we could not collect information regarding nutritional intake and all patients attending ART centre on Zidovudine therapy were not included due to logistic reasons. Since our study involved an Asian ethnic population, the external validity of our study was limited.

CONCLUSION

Anaemia is common in patients with HIV on zidovudine-based HAART regimen, which is seen as early as less than 8 weeks. WHO staging, and CD4 count were the primary risk factors associated with it. This anaemia can be reversed on treatment, new treatment strategies can be designed to alleviate the symptoms of malnutrition and opportunistic infections. Programs must be designed to treat this anaemia and take care of nutritional factors into account for better morbidity and quality of life.

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AUTHORS' CONTRIBUTION

RPK: Conception and design, acquisition of data, or analysis of data. DR: Conception and design, acquisition of data, analysis of data, writing- Original draft preparation. GK: Acquisition of data, analysis of data, writing- Original draft preparation. AG: Acquisition of data, analysis of data, drafting the article or revising. JG: Analysis of data, drafting the article or revising. GS: Acquisition of data, analysis of data, drafting the article. SV: Analysis of data, drafting the article or revising, final approval of the version.

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