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The Pattern of Haematological Changes in the Baseline Blood Cell Counts and the CD4+ T Lymphocyte Levels among Antiretroviral Therapy Naïve Adult HIV Positive Patients in a Nigerian Hospital

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Abstract

Background: Haematological abnormalities are strong independent predictors of morbidity and mortality in HIV infection. **Objectives of the Study:** This study was carried out to assess the pattern of the changes in the baseline peripheral blood cell counts among adult HIV positive patients. To also determine the CD4+ T cell levels and its correlation with the changes in the baseline cell counts of the patients using HIV negative blood donors as controls. **Methods:** This was a case controlled prospective study. The subjects were antiretroviral therapy naive adult HIV positive patients and HIV negative blood donor controls. Five milliliters (5 mls) of venous blood was collected from the cubitus of every consecutive consenting subject. Blood sample was analysed for baseline complete blood cell counts and the CD4+ T lymphocyte levels using Sysmex and Cyflow R Counter autoanalysers respectively. Obtained data was analysed with the statistical package for the social scientist (SPSS version 20.0). The Erythrocyte sedimentation rate of subjects was measured by the manual standard Westergreen method. **Results:** Of 300 subjects, there were 139 (46.3%) males and 161 (53.7%) females in the study. Anaemia was found in 72 (29.2%), leucopenia in 20 (8%) and thrombocytopenia in 6 (2.4%) of the patients. The mean erythrocyte sedimentation rates of the subjects were 81.88 mm/hr and 9.46 mm/hr ($p = 0.000$) for the patients and the controls respectively. The mean CD4+ T lymphocyte cell counts were 293 cells/μl and 750 cells/μl ($p = 0.000$) for the patients and controls respectively. **Conclusion:** Anaemia, leucopenia and thrombocytopenia were more

prevalent among the studied HIV positive patients.

Keywords

Haematology, Complications, HIV Infection, Nigeria

1. Introduction

Human immunodeficiency virus (HIV) infection causes acquired immune deficiency syndrome (AIDS) which is a late stage disease [1]. HIV attacks the body's immune system; specifically the $CD4^+$ T lymphocyte cells or T cells which naturally help the body immune system fight off infections [2]. Over time in infection, HIV destroys many of these T cells so that the body can't fight off infections and diseases. Untreated HIV reduces the number of T cells in the body which results in opportunistic infections or cancers that take advantage of a very weak immune system resulting in AIDS [2]. In 2018, UNAIDS reported the HIV prevalence among the adult general population in Nigeria as 1.5% [3]. An estimated 1.9 million people are living with the virus in this country [4]. In Sub-Saharan Africa, Nigeria has one of the highest rates of new infections and is reportedly the second largest HIV epidemic in the world [4].

In HIV infection, changes in the peripheral blood cells counts result in haematological abnormalities which are documented as strong independent predictors of morbidity and mortality [5] [6]. These abnormalities reportedly involve all three blood cell lineages and may be attributable to direct and indirect effects of the virus [7] [8]. The haematological abnormalities in peripheral blood cell counts are reportedly more frequent and severe with disease progression [5] [8]. The range of haematological abnormalities associated with HIV infection include ineffective haematopoiesis, invasive disease of the bone marrow, peripheral destruction of blood cells secondary to splenomegaly, malignancies, immune-mediated cytopenias and altered coagulation mechanisms [8]. Haematological abnormalities in HIV infection are reportedly among the most common non-immunosuppressive complications and frequently present as cytopenias in the treatment naïve patients [9]. Anaemia has been found to be the most commonly encountered haematological abnormality in HIV infections and an important indicator of progression to AIDS [10] [11].

Previous studies have reported leucopenia and neutropenia in HIV infection [10] [11] [12] [13]. Leucopenia is known to increase the incidence of opportunistic infections while neutropenia makes HIV patients susceptible to bacterial infections [8] Lymphopenia and low total lymphocyte count are reportedly common in HIV infection [13] [14] [15]. Previous researchers have documented high prevalence of thrombocytopenia in asymptomatic HIV positive patients [12] [13] [15]. Thrombotic thrombocytopenic purpura and venous thromboembolism are well documented haematological complications of HIV infection and have been recorded in 1% - 5% and 2% of affected patients respectively

[16] [17]. The Erythrocyte Sedimentation Rate (ESR) is an old surrogate marker and screening test which is widely used in clinical practice for evaluating the inflammatory or acute response, infection, trauma, autoimmune and malignant diseases [18]. Previous studies have reported the ESR as an important predictor of the development of AIDS [8] [12].

The absolute $CD4^+$ T cell count of an individual is of immense value in the evaluation of the body immune system [19]. It is an important surrogate marker for assessing the risk of progression to AIDS or developing certain opportunistic infections in HIV infected individuals [20]. Low $CD4^+$ T cell counts have been documented in HIV positive patients in previous studies [5] [8].

HIV infection is documented to be accompanied by marked haematological changes that complicate health as well as care and treatment of the patients. Therefore to ensure a holistic care and treatment with improved quality of life of HIV infected patients, it is important to be knowledgeable about the haematological peripheral blood cell changes in this cohort in our environment. This proposed study aims to assess the changes in the peripheral blood cell counts and the absolute $CD4^+$ ve T cell levels among HIV positive patients in a Lagos tertiary hospital, Nigeria.

Objectives of the study

1) To determine the pattern of the changes in the baseline peripheral blood cell counts and the $CD4^+$ T lymphocyte levels in HIV positive patients.

2) To determine the relationship of any changes in the baseline peripheral blood cell counts with absolute $CD4^+$ ve T lymphocyte levels.

3) To make recommendations based on observed haematological changes in HIV positive patients, so as to improve the holistic care, treatment and the quality of life of people living with HIV (PLHIV).

2. Participants and Methods

This prospective case controlled study was carried out from January to May 2018 at the HIV clinic of the Lagos State University Teaching Hospital (LASUTH), a tertiary and referral health care facility in Nigeria. This hospital which has over one thousand bed spaces serves an estimated population of about 22 million residents in Lagos, the commercial capital city of Nigeria. The study protocol was approved by the hospital research and ethics committee and informed consent was obtained from subjects. Two hundred and fifty (250) antiretroviral therapy naïve consecutive and consenting adult HIV positive patients were recruited at enrolment into care and treatment. Also, fifty (50) sex and age matched HIV negative blood donor control subjects were recruited from the blood donors' clinic. Inclusion criteria of the patients for this study were age ≥ 18 years, confirmed for HIV infection, antiretroviral therapy naïve while the exclusion criteria were age ≤ 18 years, unconfirmed for HIV and being antiretroviral therapy experienced. HIV diagnosis was made by testing capillary blood of the patients and the prospective blood donors for antibodies to the virus after pretest counseling and posttest was also done. Rapid HIV testing was performed

according to the WHO approved Nigerian National serial testing algorithm with Determine TM HIV-1/2, Unigold and Stat-Pak rapid kits. Two screening rapid test kits; Determine TM HIV-1/2 and Unigold were sequentially used to test for HIV antibodies in the serial algorithm of serologic testing. A reactive sample to Determine TM HIV-1/2 was confirmed using the Unigold rapid kits and Stat-Pack, a tie breaker in inconclusive tests. After an informed consent, 5 milliliters of whole venous blood was collected from the cubital vein of every HIV confirmed consecutive patient into a Potassium-ethylenediaminetetra acetic acid (K-EDTA) containing vacutainer collection tube. The same volume of venous blood was collected into K-EDTA bottles from healthy blood donor controls who were HIV negative. Blood samples from the patients and the control blood donors were analysed within six (6) hours of collection on a daily basis for absolute $CD4^+$ ve T cell counts using Cyflow R Counter (Partec, Germany). Complete blood cell count which included haemoglobin (Hb) levels, haematocrit (Hct), total white blood cell (WBC) and platelet counts were carried out on the same sample using Sysmex Kx-2IN Haematology autoanalyser (Sysmex Corporation, Japan) while following the manufacturer's instructions. The erythrocyte sedimentation rate (ESR) of the samples was performed manually by the standard Westergreen method according to the standard operating manual. Obtained data were analysed with statistical package for the social scientist software (version20.0; SPSS, Chicago, IL). The statistical tests used in this current study included mean, median, mode and t-test. Obtained results were presented in simple tables with frequencies, percentages and mean values. The P-value ≤ 0.05 was adopted for the limit of statistical significance of group comparisons.

3. Results

The subjects in this study were 300 comprising 139 males and 161 females. The mean ages were 37.86 and 32.28 years (p = 0.000) for HIV positive patients and blood donor controls respectively as in Table 1. The majority of the patients 107 (42.8%) were in the age group 29 - 39 years while among the blood donors controls, <40 years of age were most highly represented 42 (84.0%), p = 0.000 in Table 1.

At a cut off value of Hb < 10.0 g/dl, 72 (29.2%) and 0% of the patients and controls had anaemia respectively (p = 0.000) in Table 2. Twenty (8%) of the patients and 0% of the controls had leucopenia (at WBC of <2.0/nl) P = 0.030. Of 250 patients, 6 (2.4%) and 0% of the controls (p = 0.260) had thrombocytopenia (at platelet count cut off <100/nl) in Table 2. The minimum absolute $CD4^+$ T cell counts of the patients was 4 cells /µl and 255 cells/µl among the controls (p = 0.000). The maximum absolute $CD4^+$ T cell count was 1324 cells/µl and 1736 cells/µl in patients and controls respectively (p = 0.000). The mean absolute $CD4^+$ ve Tcell counts were 293 cells/µl and 750 cells/µl for the patients and controls respectively (p = 0.00, Table 3). In Table 4, most 110 (44%) of the HIV positive patients had absolute $CD4^+$ Tcell count < 200 cells/µl, while 96 (38.4%)

Table 1. Age and gender distribution of study subjects.

Variables	HIV positive patients n = 250 n (%)	Blood Donor Controls n = 50 n (%)	P-value
Age group (years)			
18 - 28	44 (17.6)	21 (42.0)	0.00
29 - 39	107 (42.8)	21 (42)	0.92
40 - 49	59 (23.6)	5 (10.0)	0.03
50 - 59	33 (13.2)	3 (6)	0.15
≥60	7 (2.8)	0 (0)	0.23
Total	250 (100%)	50 (100)	
Mean Age = 37.00	37.86	32.28	0.00
Median = 35.00	37.00	30.00	0.00
Mode = 32.00	32	24	
Gender			
Male	93 (37.2)	46 (92)	0.00
Female	157 (62.8)	4 (8)	0.00
Total	250 (100)	50 (100)	

Table 2. Haematological variables of study subjects.

Variables with cut off values	Patients	Controls	P-value
	n (%)	n (%)	
Hb			
<10 g/dl	73 (29.2)	0 (0)	0.000
≥10 g/dl	177 (70.8)	50 (100)	0.000
Hct			
<30%	69 (27.6)	0 (0)	0.000
≥30%	181 (72.4)	50 (100)	0.000
WBC			
<2/nl	20 (8)	0 (0)	0.030
≥2/nl	230 (92)	50 (100)	0.000
Platelet count			
<100/nl	6 (2.4)	0 (0)	0.260
≥100/nl	244 (97.6)	50 (100)	0.000

Table 3. $CD4^+$ ve T lymphocyte Count of patients and controls.

$CD4^+$ T lymphocytes count/ul	Patients	Controls	P-value
Minimum	4	255	0.00
Maximum	1324	1736	0.00
Mean	293	750	0.00

had a count between 200 to 499 cells/μl and 44 (17.6%) had CD4 count ≥ 500 cells/μl. Anaemia was most prevalent 53 (48%) in HIV infected patients who

Table 4. $CD4^+$ ve T lymphocyte counts and haematological changes among patients.

Haematological Parameters				Total
	<200 N = 110	200 - 499 N = 96	≥500 N = 44	
Hb < 10 g/dl	53	18	2	73
Hct < 30%	50	18	1	69
Wbc < 2/nl	16	3	1	20
Platelets < 100/nl	3	3	0	6

were severely immunocompromised with absolute CD4 count < 200 cells/μl, while leucopenia and thrombocytopenia were 14.5% and 2.7% respectively. The mean haemoglobin (Hb) level of subjects was 10.9 g/dl and 13.05 g/dl (p = 0.000) for the patients and the controls respectively. The mean haematocrit of the patients and controls were 33.32% and 40.43% (p = 0.000) respectively, while the mean white cell count was 4.735/nl among the patients and 4.611/nl in the controls (p = 0.881). The mean platelet count for the patients and controls were 205.280/nl and 253.792/nl (p = 0.000) respectively as in Table 5. The mean erythrocyte sedimentation rates (ESR) of the subjects were 81.88 mm/hr and 9.46 mm/hr for patients and controls respectively (p = 0.000, Table 5).

4. Discussion

This current study assessed the baseline Haemoglobin (Hb) levels, the haematocrit (Hct), total white cell and platelet counts, erythrocyte sedimentation rates and $CD4^+$ T lymphocyte counts in HIV-positive antiretroviral therapy (ART) naïve patients and HIV-negative blood donor controls. We observed that anaemia (at Hb of <10 g/dl) was prevalent among the HIV patients but none in the blood donor controls (29.2% vs. 0%, p = 0.000). Our finding was higher than the previous reported prevalence values of anaemia of 4.2% [10] but lower than 50.5% [5], 63% [21] 77.9% [11], 80% [12], 48% [13] among ARV naive HIV positive patients in various previous studies using the cut off value of 10 g/dl. In our study, haematocrit (Hct) was found to be less than our study cut off value of 30% in 69 (27.6%) of patients and none of controls (p = 0.000). Our finding of anaemia prevalence with a study definition of less than 30% was lower than 36.7% [22], 79.9% [8] among ART naive HIV positive patients in previous researches. We found a statistically significant difference in the mean haematocrit of the patients and controls; 33.32% and 40.43% (p = 0.000) respectively. This finding of the differences in the mean haematocrit values of the patients and controls corroborates a previous report by De Carvalho *et al.* in Pretoria, South Africa [7]. These documented findings confirm the previous reports that anaemia is common in HIV infection [10] [11]. In this current study, we found that anaemia 53 (48%) was most prevalent in HIV positive patients who were severely immunocompromised with absolute $CD4^+$ T cells count < 200 cells/μl. This finding confirms previous reports that there is a higher prevalence of anaemia among HIV

Table 5. Mean haematological parameters and $CD4^+$ ve T lymphocyte count of study subjects.

Variables	Patients	Controls	P-value
	n = 250	n = 50	
Hb	10.9	13.05	0.000
Hct	33.32	40.43	0.000
Wcc	4573	4611	0.881
Platelets	253,792	205,280	0.000
$CD4^+$ ve T lymphocyte	293	750	0.000
ESR	81.88	9.46	0.000

positive patients with $CD4^+$ T cells count < 200 cells/μl [10] [13] [15] [23]. Anaemia reportedly occurs especially when CD^{4+} ve T cells level is <200 cells/μl and is also independently associated with increased risk of death [23] [24]. Anaemia has been found to be the most commonly encountered haematological abnormality in HIV infections and an important indicator of progression to AIDS [10] [11] [24]. The aetiopathogenesis of anaemia in HIV infection includes impaired haematopoiesis, immune-mediated mechanisms, opportunistic infections, lymphoma, myelotoxic effect of antiretroviral drugs such as zidovudine [25] [26]. In advanced HIV infection, bone marrow hypoplasia occurs [27]. The documented opportunistic infections that cause anaemia through intercurrent bone marrow suppression or induce cytopenias include mycobacterium avium complex, parvovirus B19 and cytomegalovirus [28]. The most frequent types of anaemia in HIV infections are reportedly normochromic normocytic and hypo chromic microcytic [5] [8] [12] [13] [29]. Also, we found that leucopenia (Total WBC of <2.0/nl) was higher among HIV positive patients than the negative controls (8% vs. 0%, p = 0.00). This finding is comparable with previously reported prevalence values of leucopenia of 6% [11], 10% [12] but higher than 4.9% [5] and lower than 20.8% [13] among ART naïve adult HIV positive patients. Chukwuezi *et al.* in a previous study also reported that HIV positive individuals showed decreased total white cell count compared to seronegative individuals [30]. The prevalence of leucopenia among the severely immunocompromised ($CD4^+$ T cell < 200 cells) HIV positive patients in our study was 14.5%. Parinitha *et al.* in India have reported a comparable value (16.8%) of leucopenia in severely immunocompromised ART naive HIV positive patients while Munyazesa *et al.* in Rwanda reported a lower value of 8.4% among women [10] [13]. Leucopenia increases the incidence of opportunistic infections in affected individuals and has been described as the second most common haematological abnormality in HIV infection [8]. The causes of leucopenia in HIV infection include inhibition of leucopoiesis by the virus, marrow infiltration by infectious organisms, neoplasia, adverse drug effects, autoimmune neutropenia and hypersplenism [16].

In the current study, thrombocytopenia was observed as higher among HIV

patients than the blood donor controls (2.4% vs. 0%, p = 0.001) at a cut off of 100/nl. This obtained prevalence value is in keeping with previous reports of 2.5% [11], 3.4% [5] but lower than 18% [13] in HIV positive adult patients by previous researchers. Among the severely immunocompromised patients with $CD4^+$ T cell count less than 200 cells, we obtained a thrombocytopenia prevalence of 2.72%. A previous research in India reported a higher thrombocytopenia value of 21.7% in severely immunocompromised treatment naïve HIV positive patients [13]. Thrombocytopenia may be an early manifestation of HIV infection and a result of increased platelet destruction or a decreased production which may be immune-mediated [17] [31]. The mean platelet count in the current study was significantly higher in the HIV positive patients than in the HIV negative (253.79 nl v 205.28 nl p = 0.000).This may be because the majority of the patients had normal platelet count 244 (97.6%) confirming previous reports [8] [32].

HIV-associated cytopenias are common and tend to increase in magnitude and severity with worsening disease [33]. However, the use of antiretroviral drugs in HIV infection has been documented to boost the immune status of the body and improve the haematological parameters such as the haemoglobin (Hb) levels, the haematocrit, white cell and platelet counts [34] [35].

We found the mean Erythrocyte Sedimentation rates (ESR) was significantly higher among the patients than the controls (81.88 vs 9.46 mm/hr, p = 0.000). This finding corroborates previous research reports with mean ESR of HIV positive patients being statistically significantly higher compared with negative controls [8] [12] [13]. Previous studies have reported the ESR as an important predictor for the development of AIDS [8] [12]. The higher ESR in HIV positive patients may be due to inflammatory changes, decreased erythrocyte count and therefore the haematocrit [15]. Previous studies in Nigeria have reported the upper limit of normal ESR in healthy individuals as 5.0 and 12 mm/hr in adult male and females repectively [36] [37] [38] Abdulqadir *et al.* in a previous study in Nigeria documented that HIV positive pregnant women had a mean lower haematocrit and absolute white cell count but higher ESR than HIV negative pregnant women [39].

We also found a statistically significant difference in the mean absolute $CD4^+$ T cell counts in patients and controls which were 293 cells/μl and 750 cells/μl respectively (p = 0.000). These figures are comparable with previous documented findings [8] [30]. In the current study, the recorded minimum $CD4^+$ T cell counts were 4 and 255/μl for the patients and the controls respectively (p = 0.000). Previous studies have also reported lower $CD4^+$ T cell counts in HIV positive patients [5] [8] [23] [30]. The absolute $CD4^+$ ve T cell count is the most commonly used marker to determine HIV progression, patient's disease evaluation and to define appropriate time to initiate antiretroviral therapy and prophylactic antimicrobial therapies [20]. The laboratory staging of HIV-infection is also based on this marker. Oladepo *et al.* in a previous widespread and comprehensive National study in Nigeria reported the normal reference range of abso-

lute $CD4^+$ T cells among healthy adults as from 365 - 1571 cells/μl [40]. Aina *et al.* also reported a reference range of 547 - 1327 for adult men and women in Nigeria [41]. A previous study by Rahmana *et al.* has documented a significant increase in the number of anaemia, leucopenia, lymphopenia and thrombocytopenia with decreasing $CD4^+$ T cell counts [5].

Our study is limited by its single centre and hospital-based design among adults as a result of which the findings may not necessarily be generalised. A multicenter study with a much larger sample size is desirable to fill the required gaps.

In conclusion, this current study reveals that anaemia, leucopenia and thrombocytopenia were all more associated with HIV-positive serostatus than in controls. The $CD4^+$ T lymphocyte values are much lower with much higher ESR values among the HIV positive patients than the controls.

We recommend that at enrolment of HIV positive patients into care and treatment, they should have very comprehensive work up and attending physicians should be meticulous in the review of test results. A diligent review and interpretation of results would help in correct decision making of care and initiation of appropriate antiretroviral therapy. This would improve the care and services to the people living with HIV/AIDS thereby prolonging life.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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