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Effect of HIV Infection and Antiretroviral Therapy Duration on Reticulocyte Count and Red Cell Indices

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Authors' contributions

This work was carried out in collaboration between all authors. Authors COO and GIA designed the study, wrote the protocol, managed the literature review and wrote the first draft of the manuscript. Author MI managed the statistical analysis and computations. Authors COO and SNI managed the analysis of the study, while authors OMO and AOO performed manuscript revision. All authors read and approved the final manuscript.

Original Research Article

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ABSTRACT

Aim: To determine the Red cell indices and Reticulocyte count values in HIV-positive patients under antiretroviral treatment and those not under antiretroviral treatments with varying durations of HIV infection and antiretroviral treatments.
Study Design: Case-control study.
Place and duration of Study: The study was carried out at Nnamdi Azikiwe University Teaching Hospital Nnewi, Nigeria from March to August 2013.
Methodology: 181 subjects were recruited consisting; Sixty (30 males and 30 females) HIV subjects under antiretroviral therapy (ART) with an HIV infection and ART duration of <1–5 years, >5 –8 years and >8–17 years; Sixty (25 males and 35 females) HIV subjects

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not under ART (non-ART) with an infection duration of <1–3 years, >3–6 years and >6–11 years; and Sixty-one (31 male and 30 female) apparently healthy seronegative control subjects. The Reticulocytes count, Packed cell volume (PCV), Haemoglobin (HGB), Red blood cell count (RBC), Mean cell volume (MCV), Mean cell haemoglobin (MCH), Mean cell haemoglobin concentration (MCHC) and Human Immunodeficiency virus (HIV) status of the study subjects were determined.

Results: MCV and MCH for ART and non-ART subjects were significantly increased compared with control group (P<.05) and the differences with varying durations of HIV infection and antiretroviral therapy were not significant (P>.05). Moreover, there was a significant decrease in the mean HGB, RBC, MCHC of ART and non-ART compared with control (F=8.51; 133.85; 33.32; P<.05 respectively) and their differences with varying durations of infection and antiretroviral therapy were not significant (P>.05). MCV were significantly higher in ART compared with non-ART (P<.05).

Conclusion: There is no significant variation in Red cell indices and Reticulocyte count values in HIV patients with differences in duration of HIV infection and antiretroviral therapy.

Keywords: Reticulocyte; mean cell volume; mean cell haemoglobin; mean cell haemoglobin concentration; antiretroviral therapy.

ABBREVIATIONS

ART: Patients on antiretroviral therapy; Non-ART: Patients not on antiretroviral therapy; HGB: Haemoglobin; RBC: Red blood cell count; PCV: Packed cell volume; Retics: Reticulocyte count; MCH: Mean cell haemoglobin; MCV: Mean cell volume; MCHC: Mean cell haemoglobin concentration

1. INTRODUCTION

Haematological abnormalities are among the most common complications of HIV infection and involve all lineages of blood cells [1]. Besides immunological complications of HIV disease, haematological abnormalities have been documented as strong independent predictors of morbidity and mortality in HIV infected individuals [2]. Human Immunodeficiency virus (HIV) is a *lentivirus* that causes Acquired Immune deficiency Syndrome (AIDS) [3] a condition in humans in which progressive failure of the immune system allows life-threatening opportunistic infections and cancers to thrive. HIV infects vital cells in the human immune system such as helper T cells (specifically CD4+T cells), macrophages and dendritic cells [4]. There is currently no cure or effective HIV vaccine. Treatment consists of highly active antiretroviral therapy (HAART) which slows progression of the disease and as of 2010 more than 6.6 million people were taking them in low and middle income countries [5]. There are several classes of antiretroviral agents that act on different stages of the HIV life-cycle. HAART decreases the patient's total burden of HIV, maintains function of the immune system, and prevents opportunistic infections that often lead to death. Adverse effects of antiretroviral drugs vary by drug, ethnicity, individual, and interaction with other drugs, including alcohol. Thus the centre for disease control and prevention (CDC) advocates for evaluation of ART safety before subjects are considered for administration [6]. Hypersensitivity to some drugs may also occur in some individuals [7]. HAART may increase chemically reactive species in circulation, possibly by producing more oxidized metabolites deriving from the interaction between ROS and infected-cell

biomolecules [8]. Although specific mechanisms of ART-associated toxicities are largely unknown, Day and Lewis [9] showed that all of these processes may be mediated at a fundamental level by free radical-induced cellular damage, also referred to as oxidant stress. It is worth noting that patients who rigorously follow antiretroviral therapy (optimal HAART adherence) have significantly higher oxidative status than those who do not closely follow the therapy (poor HAART adherence).

Anaemia is a very common finding in patients with HIV infection, particularly in individuals with more advanced HIV disease. In a study of patients receiving no myelo-suppressive therapies, 8% of asymptomatic HIV-seropositive patients, 20% of those with symptomatic middle-stage HIV disease, and 71% of those with Centers for Disease Control (CDC)-defined AIDS were anaemic [10]. HIV infection alone, without other complicating illness, may produce anaemia in some patients. A study of serum immune-reactive erythropoietin in HIV-infected patients in various stages of illness showed that levels of the hormone failed to rise commensurately with increasing anaemia, suggesting that insufficient amounts of erythropoietin may be one cause of anaemia in this setting [10]. Zidovudine (AZT) therapy is probably the most common cause of anaemia in HIV-infected patients [11], with a fall in haemoglobin that is accompanied by a progressive rise in erythrocyte mean corpuscular volume that has now become familiar to physicians treating patients with AZT. Red cell indices like mean cell volume (MCV), Men cell haemoglobin (MCH) and Mean cell haemoglobin concentration (MCHC) are utilized in the morphologic classification of anaemia. [12] the mean cell volume gives information on red cell size and is increased in macrocytic anaemia and decreased in microcytic anaemia; Mean cell haemoglobin is a measure of the amount of haemoglobin in an average red cell and is reduced in hypochromic anaemia and increased in macrocytic anaemia while Mean cell haemoglobin concentration (MCHC) is a measure of the concentration of haemoglobin in 1 litre of packed red cells and is reduced in hypochromic and microcytic anaemia. Reticulocytes are immature red cells normally present in small numbers in the blood (up to 2%). A reticulocyte count assesses bone marrow activity (whether there is an effective erythropoietic response when there is a reduction in the number of red cells due to haemolysis or haemorrhage). It is also of value in monitoring the erythropoietic response of an anaemic patient following treatment [12]. This study was therefore aimed at determining the Red cell indices and Reticulocyte count values in HIV positive patients on antiretroviral treatment and those not on antiretroviral treatments with varying durations of HIV infection and antiretroviral treatments.

2. METHODS

2.1 Study Site

This study was carried out at Nnamdi Azikiwe University Teaching Hospital (NAUTH) Nnewi, Anambra State, a tertiary health institution serving patients of high, middle and lower socio-economic status. It houses a major HIV/AIDS Centre (IHVN Clinic) serving patients from all parts of the state and beyond, with a registered HIV-positive patients population of over 6000.

2.2 Subject Recruitment

One hundred and eighty one (181) subjects were recruited by simple random sampling and categorized into three groups comprising; Sixty adult HIV-positive subjects under antiretroviral therapy (ART)-Lamivudine, Zidovudine, Nevirapine (30 males and 30 females),

Sixty adult HIV-positive subjects not under antiretroviral therapy (25 males and 35 females) and Sixty-one adult Sero-negative control subjects (31 males and 30 females) respectively.

2.3 Sample Collection

Five millilitres (5mls) blood sample was collected aseptically from the veins by venepuncture and aliquoted as follows; three millilitres (3mls) was drawn into bottles containing di-potassium salt of Ethylenediamine tetra-acetic acid (K_2-EDTA) at a concentration of 1.5mg/ml of blood and used for red cell indices and Reticulocyte count while two millilitres (2mls) was drawn into plain sample bottles. Serum was obtained after clotting by spinning at 3000rpm for 10 minutes and used for HIV testing.

2.4 Statistical Analyses

The data obtained was analysed using Statistical Package for Social Sciences (SPSS) version 20). Data were expressed as mean±SD. The significance of differences in mean values between groups were analysed using t-test, while significance of the differences in mean values among different group was evaluated using one-way ANOVA. $P<.05$ was considered statistically significant.

2.5 Laboratory Methods

2.5.1 HIV testing

The tests were carried out according to the manufacturer's instruction.

2.5.2 Determine HIV 1/2 assay

The abbot Determine™ HIV ½ is an in vitro test kit, visually qualitative immune assay for the detection of antibodies to HIV-1 and HIV-2 in human serum, plasma or whole blood.

2.5.3 Principle of the test

Determine HIV ½ is an immune chromatographic test for the qualitative detection of antibodies to HIV-1 and HIV-2. Sample migrates through the conjugate pad, it reconstitutes and mixes with the selenium colloid-antigen conjugate. This mixture continues to migrate through the solid phase to the immobilized recombinant antigens and synthetic peptides in HIV-1 or HIV-2. If HIV ½ were present in the sample, the antibodies bind to the antigen-selenium colloid and to the antigen at the patient window side. If antibodies to HIV-1 and/or HIV-2 are absent. The antigen selenium colloid flows past the patient window and no red line are formed at the patient window site. To ensure assay validity, a procedural control bar is incorporated in the assay device.

2.6 Chembio HIV ½ Stat-Pak™ Assay

2.6.1 Principle of test

The Chembio HIV ½ STAT PAK™ assay employs a unique combination of a specific antibody-binding protein, which is conjugated to colloidal gold dye particles and HIV ½ antigens which are bound to the membrane solid phase. The sample is applied through the

sample well followed by the addition of running buffer. The buffer facilitates the lateral flow of the released products and promotes the binding of antibodies to the antigens. If present, the antibodies bind to the gold conjugate antibody-binding protein. In a reactive sample, the dye-conjugate immune complex migrates through nitrocellulose membrane and is captured by the antigens immobilized in the test (T) area. The sample migrates along the membrane and produces a pink/purple colour on the control (C) area containing immunoglobulin antigens. This control serves to demonstrate that specimens and reagents have been applied properly and have migrated through the device.

2.6.2 Measurement of red cell indices

By automation using Sysmex automated haematology analyser KX 21N model manufactured by Sysmex Corporation Kobe, Japan.

2.6.3 Principle of test

The aspirated blood samples is measured to a predetermined volume, diluted at the specified ratio and then fed into each transducer chamber which has a minute aperture which also contains the electrodes in which direct current flows. Blood cells suspended in the diluent sample pass through the aperture causing direct current resistance to change between the electrodes and the blood cell size is detected as electric pulses. Blood cell count is calculated by counting the pulses and the histogram determined by the pulse sizes.

2.6.4 Procedure

The sample in EDTA bottle was placed in the Spiral Mixer and allowed to mix very well. Whole blood mode was activated in the LCD screen, the sample no (code) was inputted via the key board and then the enter key is entered. Then the sample was mixed very well again, the cap was removed and inserted into the probe and the START button was pressed. The LCD screen displayed ANALYSING; the sample was removed and re-capped. The unit executes automatic analysis and displays the result on the LCD screen.

2.7 Reticulocyte Count Estimation [13]

2.7.1 Principle of test

Reticulocytes which are immature erythrocytes (red cells) are recognized by violet-blue stained granules of Ribosomal RNA (reticulin) they contain when an isotonic solution of supravital stain (one that stains living material) such as New Methylene blue or Brilliant cresyl blue is incubated with a few drops of blood and a thin blood film preparation made and examined microscopically. The reticulocyte count is expressed as a percentage, or preferably in absolute numbers when total RBC count is available.

2.7.2 Procedure

Two drops of Brilliant cresyl blue and three drops of EDTA anti coagulated blood was mixed in a test tube and incubated at 37℃ for 15 minutes. The tube was gently tapped to re-suspend the cells and a blood film was made using a drop of the mixture in the same manner as for peripheral smear. The blood film was air-dried and examined microscopically. In counting the cells, 10×objective (with reduced condenser iris diaphragm) was used to check the distribution of the cells and an area were the red cells do not overlap was selected

and oil immersion was added. The area was examined using 100x (oil immersion) objective and 1000 red cells were counted systematically with the number of reticulocytes noted. The absolute reticulocyte count was then calculated.

2.8 Calculations

Reticulocyte percentage=Number of reticulocytes counted x 100/ number of red cells + Retics counted

Absolute reticulocyte count=% Reticulocyte count x Red blood cell count

3. RESULTS AND DISCUSSION

Table 1 shows that the mean±SD of haemoglobin (HGB) was significantly lower in both ART and non-ART when compared with the corresponding values in the control (P<.05). Similarly the Red blood cell count (RBC) in ART and non-ART were significantly lower compared with the control (P<.05). In addition, there was a significantly higher Mean cell volume (MCV) in ART and non-ART, compared with the control (P<.05). Moreover, the Mean cell haemoglobin (MCH) in ART and non-ART were significantly higher than the control (P<.05). Similarly the mean cell haemoglobin concentration (MCHC) for ART and non-ART were significantly lower than the control (P<.05). However, there was no significant difference in the reticulocytes (RETICS) and packed cell volume (PCV) for ART and non-ART compared with the control (P>.05).

Table 2 shows that the mean±SD of RETICS, PCV, Hb, RBC, MCV, MCH and MCHC for ART durations of <1–5 years, >5–8 years and >8–17 years showed no significant difference when compared (P>.05).

Table 3 shows that there was no significant difference in the mean values of RETICS, PCV, HGB, RBC, MCV, MCH and MCHC for HIV durations of <1–5 years, >5–8 years and >8–17 years in ART subjects (P>.05).

Table 4 shows that there was no significant difference in the mean values of RETICS, PCV, HGB, RBC, MCV, MCH and MCHC for HIV durations of <1–3 years, >3–6 years and >6–11 years in non-ART subjects (P>0.05) respectively (P>.05).

Table 5 shows that the mean±SD of HGB for ART male was significantly higher compared with their female counterpart (P<.05). Similarly, the mean values of PCV, HGB and RBC were significantly higher in the male controls compared to the female controls, while MCHC was significantly higher in female controls compared with male controls (P<.05). However, there was no significant difference in the mean values of RETICS, PCV, RBC, MCV, MCH and MCHC for ART male when compared with their female counterpart (P>.05). Moreover, no significant difference was also observed for non-ART male when compared with the mean values of non-ART female (P>.05).

Table 1. Mean±SD of parameters compared among HIV positive under ART, not under ART and HIV negative control subjects

Category of patients	RETICS ($X10^9$/L)	PCV (%)	HGB (g/dl)	RBC ($X10^{12}$/L)	MCV (fl)	MCH (pg)	MCHC (%)
(A)ART(n=60)	30±12	37.55±5.14	11.85±1.76	4±1	97.54±9.47	30.88±4.09	31.57±1.84
(B) Non-ART(n=60)	31±11	38.00±7.69	11.97±2.37	4±1	91.25±13.05	29.05±4.98	31.71±1.85
(C) Control(n=60)	33±14	39.10±4.77	13.21±1.86	6±1	63.51±5.48	21.47±1.93	33.82±1.39
F(P) Values	1.30(.27)	1.07 (.34)	8.51(.00*)	133.85 (.00*)	206.45(.00*)	100.44(.00*)	33.32 (.00*)
A vs. B:P-values	.74	.93	.94	.07	.01*	.08	.91
A vs. C: P-values	.28	.20	.00*	.00*	.00*	.00*	.00*
B vs. C: P-values	.64	.61	.00*	.00*	.00*	.00*	.00*

**Significant at P<.05Key:F (P) value = Mean ± SD of parameters compared among HIV-positive under ART, not under ART and HIV negative control subjects using ANOVA.A vs. B: (P) value = Mean ± SD of parameters compared between HIV-positive under ART and not under ART using t-test. A vs. C: (P) value = Mean ± SD of parameters compared between HIV-positive under ART and HIV negative control subjects using t-test. B vs. C: (P) value = Mean± SD of parameters compared between HIV-positive not under ART and HIV negative control subjects*

Table 2. Mean±SD of parameters compared for the HIV positive under ART based on duration of antiretroviral therapy

Parameters	<1 – 5years (n=23)	>5–8years (n=25)	> 8–17years (n=12)	F-values	P-values
RETICS ($X10^9$)	29.17±10.25	30.36±13.10	28.42±13.83	0.12	.89
PCV (%)	38.40±4.51	37.22±5.94	36.62±4.61	0.55	.58
HGB (g/dl)	12.06±1.66	11.74±1.91	11.66±1.70	0.28	.76
RBC ($X10^{12}$)	3.90±0.57	3.87±0.66	3.88±0.68	0.01	.99
MCV (fl)	99.14±9.20	97.01±9.26	95.58±10.71	0.62	.54
MCH (pg)	31.23±4.09	30.74±4.05	30.49±4.46	0.15	.86
MCHC (%)	31.42±2.07	31.60±1.70	31.79±1.76	0.16	.85

Significant at P<.05

Table 3. Mean±SD of parameters compared for the HIV-positive under ART based on duration of HIV infection

Parameters	<1 – 5years(n=17)	>5–8years (n=26)	> 8–17years (n=17)	F-values	P-values
RETICS ($X10^9$)	25.94±7.86	33.35±13.29	27.24±12.44	2.49	.09
PCV (%)	37.52 ±4.39	38.56±5.76	36.04±4.71	1.25	.30
HGB (g/dl)	11.87±1.63	12.16±1.86	11.35±1.70	1.11	.34
RBC ($X10^{12}$)	3.81±0.54	3.96±0.67	3.85±0.64	0.31	.73
MCV (fl)	99.28±9.82	98.33±8.39	94.61±10.53	1.20	.31
MCH (pg)	31.46±4.18	31.16±3.81	29.86±4.46	0.75	.48
MCHC (%)	31.61±2.08	31.62±1.78	31.45±1.78	0.05	.95

**Significant at P<.05*

Table 4. Mean±SD of parameters compared for the HIV-positive not under ART based on duration of HIV infection

Parameters	<1 – 3years (n=17)	>3–6years (n=26)	> 6–11years(n=17)	F-values	P-values
RETICS ($X10^9$)	31.39 ±11.83	30.89±10.16	30.50±11.81	0.03	.97
PCV (%)	36.33±5.64	41.57±10.43	36.41±4.92	3.23	.05
HGB (g/dl)	11.45±1.97	13.03±3.02	11.56±1.51	2.96	.06
RBC ($X10^{12}$)	4.10±0.75	4.62±1.40	4.00±0.87	2.00	.14
MCV (fl)	90.20±13.83	91.31±11.15	94.41±14.69	0.39	.68
MCH (pg)	28.75±4.99	28.84±4.16	30.33±6.54	0.39	.68
MCHC (%)	31.83±1.98	31.44±1.30	31.84±2.38	0.28	.76

**Significant at P<.05*

Table 5. Mean±SD of parameters compared in HIV positive under ART, not under ART and HIV negative control subjects between genders

Parameters	ART		P-value	Non-ART		P-value	Control		P-value
	Male (n=30)	Female(n=30)		Male(n=25)	Female(n=35)		Male(n=31)	Female(n=30)	
RETICS	30.50±12.81	28.53±11.36	.99	31.12±9.13	31.06±12.50	1.00	31.19±11.57	35.20±16.13	0.87
PCV	38.93±5.80	36.18±4.02	.29	39.48±6.21	36.95±8.52	.78	42.27±3.58	35.84±3.47	.00*
HGB	12.50±1.95	11.20±1.27	.04*	12.25±1.93	11.77±2.66	.96	14.52±1.35	11.86±1.24	.00*
RBC	4±1	4±1	.38	4±1	4±1	1.00	7±1	6±0	.00*
MCV	97.27±9.38	97.81±9.71	1.00	94.98±11.91	88.59±13.34	.39	63.23±5.25	63.80±5.78	1.00
MCH	31.32±3.92	30.43±4.26	.96	29.85±4.36	28.47±5.36	.88	21.70±1.94	34.31±1.20	.94
MCHC	32.11±1.55	31.02±1.96	.18	31.47±1.84	31.88±1.86	.96	21.24±1.92	33.31±1.39	.04*

**Significant at P<.05*

4. DISCUSSION

Haematological abnormalities are among the most common complications of HIV infection and involve all lineages of blood cells; thus anaemia, thrombocytopenia and leucopenia are common findings [1]. In this study, Haemoglobin and Red blood cell count were found to be decreased in HIV-positive subjects (ART and non-ART) compared to the control Table 1. This is in consonance with the findings of some previous authors [13,14,15,16]. This finding could be as a result of decreased RBC production or ineffective erythropoiesis. Generalized effect of HIV/AIDS on haematopoietic and mature blood cell has been reported with a possibility of infecting the haematopoietic precursor cell and inhibiting their differentiation and development to mature blood cells [17]. The changes in the mean values of both parameters were not significant with longer duration of infection and antiretroviral treatment Tables 2–4.

Mean cell volume gives information on red cell size, it is increased in macrocytic anaemia and decreased in microcytic anaemia [12]. Mean Cell Volume (MCV) was higher in HIV-positive subjects (ART and non-ART) when compared with the control values Table 1. This supports previous findings [15]. Earlier studies [11] observed a fall in haemoglobin values accompanied by a progressive rise in erythrocyte mean corpuscular volume (MCV) for patients treated with Zidovudine which is one of the combination of drugs administered to the ART subjects. This could account for the significant increase in MCV in ART subjects compared to non-ART subjects coupled with a non-significant decrease in Haemoglobin and packed cell volume Table 1. However there was no significant increase in MCV with longer duration of HIV infection and antiretroviral therapy Tables 2–4.

Mean cell haemoglobin is a measure of the amount of haemoglobin in an average red cell and it is reduced in hypochromic anaemia and increased in macrocytic anaemia [12]. Mean Cell Haemoglobin (MCH) was significantly increased in HIV subjects (ART and non-ART) compared with control Table 1. This correlates with previous finding [15] and disagrees with yet another finding [14]. Also the differences in duration of HIV infection and antiretroviral therapy did not affect the MCH in the subjects Tables 2–4.

Conversely, Mean Cell Haemoglobin Concentration (MCHC) was significantly reduced in HIV subjects (ART and non-ART) than controls Table 1 and agrees with the findings of some authors [13-15]. Mean cell haemoglobin concentration (MCHC) is a measure of the concentration of haemoglobin in 1 litre of packed red cells and is reduced in hypochromic and microcytic anaemia [12]. Duration of HIV infections and antiretroviral therapy were not observed as a source of significant variation in MCHC Tables 2–4.

Reticulocytosis usually occurs when there is an increase in erythropoietic activity [12]. In this study, there were no significant changes in reticulocyte count in the ART and non- ART subjects even with longer durations of HIV infection and antiretroviral therapy compared with the control subjects Tables 1–4.

PCV, HGB and RBC were significantly higher in male controls than the females and MCHC was significantly higher in female controls than the male controls, while HGB was significantly higher in male under ART compared with the female subjects. These may be explained by the normal sex variations of these parameters. However no significant difference was observed when values for Reticulocyte count, RBC, PCV, HGB, MCV, MCH and MCHC were compared between the male and female non-ART subjects Table 5.

5. CONCLUSION

The result of this research work showed that there were significant variations in mean values of red cell indices in ART, non-ART and seronegative control subjects. These differences were not a function of the duration of HIV infection and length of antiretroviral therapy. However, reticulocyte count values were not significantly affected by duration of HIV infection and antiretroviral therapy.

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CONSENT

The authors declare that 'written informed consent was obtained from the patient before being recruited for this research.

ETHICAL APPROVAL

The authors hereby declare that all experiments was examined and approved by the Nnamdi Azikiwe University Teaching Hospital ethics committee (NAUTHEC).

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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