Research Article

Haematological Profile of Patients on Antiretroviral Therapy in a Nigerian Teaching Hospital

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ABSTRACT

Background: Haematological parameters are important monitoring tool for assessing prognosis and treatment in Human Immunodeficiency Virus (HIV) infected patients. Therefore, examining these parameters for abnormalities are absolutely imperative. **Objective:** This research was conducted to examine the effects of ARV drugs on haematological indices of HIV–infected patients under treatment. **Research approach:** The study was conducted in President's Emergency Plan for AIDS Relief Clinic of the University of Benin Teaching Hospital, Benin City, Nigeria between October, 2012 and April, 2013. The blood samples of 275 HIV–infected patients on antiretroviral (ARV) drugs and 109 patients yet to receive ARVs were analysed for haematological parameters with automated blood analyser. **Findings:** A higher incidence of anaemia, thrombocytopenia and lymphocytopenia were observed in those patients that were yet to commence ARV drugs. Leucopoenia and neutropenia were prominent among HIV–infected patients on ARV drugs. Microcytic anaemia was more frequent in patients that were about to start drugs, while macrocytic anaemia was identified among HIV–infected patients on ARV drugs. **Conclusion:** All types of anaemia except life threatening were found in patients receiving ARV drugs. The anaemia, leucopoenia and neutropenia found in patients on ARV drugs were associated with first–line Tenofovir–based regimen. **Research Value:** Further research is needed to ascertain the safety of Tenofovir–based therapy in managing HIV–infected patients.

Key words: Human immunodeficiency virus, Anaemia, Leucopenia, Neutropenia, Cytopenia, Antiretroviral drugs.

INTRODUCTION

Human Immunodeficiency Virus (HIV)/ Acquired Immune Deficiency Syndrome (AIDS), continues to be a major global public health concern,[1] with a prevalence of about 36.9 million in 2014. In terms of HIV burden however, Nigeria is second to South Africa worldwide with 3.4 million people living with the disease.[2] Haematological parameters (such as haemoglobin, white blood cells, red blood cells, neutrophils, lymphocytes and platelets) are important monitoring parameters for assessing treatment and prognosis in HIV/AIDS.[3,4] Antiretroviral (ARV) drugs represent major advancement in managing HIV infection. However, the use of these drugs could either negatively or positively affect haematological parameters, depending on the choice of combinations. In the early 2000s, adverse reactions began to appear and started to challenge the goals of ARVs.[5] Although many drugs used for the treatment of HIV–related disorders are myelosuppressive, severe cytopenia is most often associated to the utilization of zidovudine.[6] These complications are generally marked with cytopenias involving anaemia, neutropenia, leucopenia, lymphocytopenia and thrombocytopenia.[7] The prevalence of the cytopenia especially anaemia majorly serves as a predictor of advancement to AIDS or death.[8] The study[9] reported decline in the haematocrit values of HIV-infected patients on ARV drugs and those that were yet to receive ARVs. A previous research conducted in the United Kingdom also showed that cytopenia is a prevalent abnormality of HIV infection, and more than 70% of the

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patients developed anaemia, sometimes requiring transfusion.[10] Anaemia, ranging between 1.3% and 95% is the first frequent haematological complications in the HIV–infected patients on ARV drugs. This is followed by thrombocytopenia, the second most frequent haematological complication of HIV infection which affected 3% to 40% of individuals with the infection. Neutropenia is also common in HIV–infected individuals and may occur in 10% to 30% of the patients.[11,12]

A study[13] in Ethiopia revealed that prevalence of anemia was of great magnitude in those patients who are yet to start ARV drugs, while leucopenia and neutropenia were prominent in patients on ARV drugs. Study in Ghana[14] reported the incidence of 63% anaemia, and 16.7% lymphocytopenia in those patients that were yet to start ARV drugs, while 46% anaemia and 5.3% lymphocytopenia were recorded for those patients on ARV drugs. Furthermore, the findings in New Guinea[15] showed that anaemia, leucopenia, eosinophilia, thrombocytopenia, neutropenia and monocytosis were prevalent among HIV–infected patients. These different reports provide a framework for conducting further studies on haematological profile of HIV-infected patients on antiretroviral therapy and those that are yet to commence ARV drugs in President's Emergency Plan for AIDS Relief (PEPFAR) Clinic at University of Benin Teaching Hospital, Benin City, Nigeria.

MATERIALS AND METHOD

Study site

The study was conducted in the PEPFAR Clinic, University of Benin Teaching Hospital (UBTH), Benin City, Nigeria which provides medical services to over three million citizens of Edo State of Nigeria. Ethical aapproval to conduct the study was obtained from Ethics and Research Committee of UBTH before the enrolment of subjects (Protocol Number: ADM 22/A/VOL.VII/833 on 10th September, 2012). Permission to work with the patients was obtained from the Consultant and Coordinator in charge of the Clinic.

Population of study

The population of study were HIV–infected patients diagnosed and established to be positive, using the Determine HIV 1 and 2 Test Kit (Alere Medical Company Limited, Chiba, Japan) and STAT– PAK HIV 1 and 2 Test Kit (Chembio Diagnostic System Inc, USA).

Experimental design

The experimental design was a cross–sectional, prospective, randomized controlled study. The study time spanned between October, 2012 and April, 2013. Adult HIV–infected patients attending the PEPFAR Clinic, were included in the study, who have been on a combination therapy of ARV drugs for at least one year, and those that were yet to receive ARV drugs. Patients excluded were children, pregnant women and cigarette smokers. A total of 384 HIV-infected patients who met the inclusion criteria were randomly selected among the population of 14,610 HIV-infected patients receiving care in the facility of study. The 384 patients recruited were divided into two equal groups that were well–matched in sex and age.

Group 1: 275 HIV–infected patients on ARV drugs;

Group 2: 109 HIV–infected patients yet to be placed on ARV drugs (control group).

Haematological analysis

Written informed consent was obtained from the patients before blood sample collection. Three millilitre of whole blood was obtained from each patient for haematological assay, using automated blood analyser–sysmex KX–21N (Sysmex Corporation, Kohe, Japan). The blood samples collected were evaluated within 24 hours for haemoglobin (Hgb), White Blood Cell count (WBC), Total Lymphocyte Count (TLC), Red Blood Cell count (RBC), neutrophils count, Mean Cell Volume (MCV), platelet count, Mean Cell Haemoglobin Concentration (MCHC), and Mean Cell Haemoglobin (MCH). The blood collected were mixed and fed to the automated machine which aspirated 50 µl of the blood. The reagents supplied by the manufacturer were used for the analysis. The machine displayed the analysis results of the haematological parameters on the Liquid Crystal Display (LCD) screen.

Haematological complications in HIV patients

Haematological disorders were determined in the patients using World Health Organization criteria. Anaemia was defined when Hgb concentration is less than 12.0 g/dl and 13.8 g/dl in females and males respectively. Leucopenia was considered as WBC count less than 2.75×10^3 cells/µl, lymphocytopenia as lymphocyte count of $< 0.8\times10^3$ cells/µl, neutropenia as neutrophils count $<1.0\times10^3$ cells/µl and thrombocytopenia as platelet count $<125\times10^3$ cells/µl for females and $< 156\times10^3$ cells/µl for males.[16]

Statistical analysis

Descriptive analysis and Student't' test were performed using the SAS software program version 9.2.[17] Results are presented as means ± Standard deviation (SD), while $P\leq0.05$ was considered significant.

RESULTS

It was observed that the patients were receiving a combination of three to four ARV drugs. Almost all the patients (91.5%) were on first line regimen (Table 1). The most widely used first–line regimen was lamivudine + zidovudine + nevirapine combination. Also, less than 10% of the patients were on second–line combination therapy, which includes lamivudine + tenofovir + lopinavir/ritonavir and lamivudine + zidovudine + lopinavir/ritonavir. The zidovudine backbone regimen (82%) constituted the main drugs of choice and the rest (18%) were on tenofovir backbone. Furthermore, 79.7% of the patients were on ARV drugs for duration of three to five years. The average time on ARV drugs was 3.7 years (range from 1-5 years) (Table 1). A higher incidence of thrombocytopenia (14.3%), anaemia (26.6%) and lymphocytopenia (6.6%) were found in patients who were yet to commence ARV drugs as compared to patients on drugs (6.6%; 17.5% and 2.7% respectively) (Figure 1). Higher frequency of leucopoenia (27.6%) and neutropenia (13.5%) were also observed in patients on ARV drugs as compared to those that were about to start ARV drugs (21.4% and 6.3% respectively).

There were statistically significant ($P<0.05$) differences in all the haematological parameters except the lymphocyte and platelet counts of the patients on ARV drugs, as compared with those that were yet to receive medication (Table 2). The levels of Hgb, RBC, MCV, MCH and MCHC of patients on ARV drugs however, were higher relative to those who were not on drug therapy The values of WBC, neutrophil and platelet counts of patients that were about to commence drugs were higher than those on drugs. Anaemia was more prominent (26.6%) in patients that were yet to start drugs compared with 17.5% observed in patients on therapy between 1 and 5 years. All grades of anaemia were found in patients receiving ARV drugs but none was life threatening. Less severe forms of anaemia (mild and moderate) occurred in those that were yet to commence therapy (Table 3).

As shown in Table 4, microcytic anaemia occurred most frequently in HIV–infected patients not yet on treatment, while macrocytic anaemia was found in patients on treatment. Table 5 shows the haematological profile of patients in relation to their ARV drugs. A significant difference in neutrophil levels of patients on CPE and those on TRN was observed. Also, there were statistically significant variations in the values of RBC, MCV and MCH of those on TRA and patients managed with five other combination regimens. Among the six ARV drug combination therapy used in the management of these patients, TRN; Lamivudine + Tenofovir + Nevirapine regimen was found to have lowest values of platelets, neutrophils, WBC, lymphocytes, RBC as well as Hgb. Furthermore, those patients on Zidovudine based regimens (CPN, CPE, and CPA) were found to have higher values of haemoglobin concentration of greater than 12 g/dl. However, patients receiving Tenofovir back bone regimens (TRA, TRE and TRN) were observed to have haemoglobin concentrations below normal reference value of 12 g/dl for females and 13.8 g/dl for males.

DISCUSSION

It has been observed that Lamivudine + Zidovudine + Efavirenz combination recommended by World Health Organization as first line therapy was commonly used for treating HIV patients in the facility of this study. This regimen is tolerable, feasible, less toxic and less pill burden. This result is in line with[18] in Cameroon who reported that 95% of patients were on first line regimen which includes Nevirapine, Lamivudine, Efavirenz, Stavudine and Zidovudine, while very few (5%) were on second line ARV regimen.

The values of haematological parameters obtained for the patients (yet to start treatment) were also similar to those observed by[19] in Thailand. Contrarily, previous findings [20] in Cameroon, in Osogbo,[21] Nigeria and Italy[22] revealed that therapeutic combination of Lamivudine + Zidovudine + Efavirenz is less prescribed and rather used as a second line therapy. The higher incidence of anaemia was also found in patients that were yet to receive drugs as compared to patients on ARV drugs was similar to findings[9] in Benin City, Nigeria, where the occurrence of anaemia was higher among ARV drugs–naive patients than patients on ARV drugs. The rationale for the decrease in incidence of anaemia in patients on ARV drugs as compared to those that were yet to receive medication indicated the efficacy of ARV drugs in managing HIV infection. ART has also been shown to promote blood cells production.[9]

Anaemia which was the commonest haematological disorder among patients that were yet to be on drugs may be due to several factors ranging from nutritional deficiencies, opportunistic infections and chronic nature of the disease.[23,24] HIV infection causes decrease in the production of RBCs by suppressing the Erythroid Colony Forming Unit (CFU–E).[24] Again, a diminished production of erythropoietin has been observed in HIV–infected patients that were yet to be placed on drugs.[25] Decreased value of MCV found in patients that were yet to start ARV drugs as compared to patients on ARV drugs was in line with the findings of,[26] who reported that the majority of the patients about to start ARV drugs presented with microcytic hypochromic anaemia, common in most chronic diseases. The microcytic

Table 1: Treatment variables of HIV–infected patients on ARV drugs

Variables	Frequency (n=275)	(%)
ARV drugs combination		
Lamivudine + Zidovudine + Nevirapine (CPN)	194	70.6
Lamivudine + Zidovudine + Efavirenz (CPE)	19	6.9
Lamivudine + Zidovudine + Lopinavir/Ritonavir (CPA)	12	4.5
Lamivudine + Tenofovir + Efavirenz (TRE)	24	8.5
Lamivudine + Tenofovir + Nevirapine (TRN)	15	5.5
Lamivudine + Tenofovir + Lopinavir/Ritonavir (TRA)	11	4.0
Duration of ARV therapy (Years)		
1-2	55	20.3
3-4	81	29.3
5	139	50.4

Table 2: Haematological parameters of HIV–infected patients

Parameter	Patients on ARV drugs Mean ± SD	Patients not yet on ARV drugs Mean ± SD	P–value
Hgb (g/dl)	11.75±1.80	10.94±2.06	0.001
WBC (10^3/µl)	4.78±1.32	5.13±1.53	0.049
Lymphocyte count (10^3/µl)	2.16±0.77	2.16±0.87	0.970
Neutrophil count (10^3/ µl)	1.93±0.93	2.37±1.15	0.001
RBC (10^6/µl)	4.21±0.79	3.75±0.62	0.001
MCV (fl)	95.02±10.18	83.48±7.67	0.001
MCH (pg)	31.72±4.55	26.06±3.46	0.001
MCHC (g/dl)	33.26±1.71	31.27±2.11	0.001
PLT (10^3/µl)	230.60±67.67	238.58±102.25	0.414

Table 3: Anaemia among HIV–infected patients based on haemoglobin concentration

Haemoglobin g/dl	Patients on ARV drugs with anaemia n=48 (17.5%)	Patients not yet on ARV drugs with anaemia n=29 (26.6%)
Mild (9.5-11.9)	40 (82.3)	22 (77.7)
Moderate (8.0-9.4)	6 (12.8)	7 (22.3)
Severe (6.5-7.9)	2 (4.9)	0
Life threatening (<6.5)	0	0

Table 4: Types of anaemia in HIV–infected patients by mean cell volume

Mean cell volume (Femtoliter)	Patients on ARV drugs 48 (17.5%)	Patients not yet on drugs 29 (26.6%)
Microcytic anaemia (<80)	13 (27.8 %)	22 (77.3%)
Macrocytic anaemia (>100)	35 (72.2%)	7 (22.7%)

hypochromic anaemia was caused by the infections of the gastrointestinal tract that may be responsible for chronic blood loss, with eventual iron deficiency anaemia.[27]

The incidence of anaemia among patients on ARV drugs (17.5%) in this study was high as compared to the findings in Cameroon[18] which reported 3.8% among HIV–infected patients on ARV drugs for the median onset of five months. The difference in the results could be attributed to the fact that the patients in present study were on ARV drugs for a median time of 3.4 years (range 1-5 years). However, the present study corroborates with earlier reports.[28-30] In the present study, mild to severe anaemia was found in a few patients on ARV drugs especially among those on Tenofovir

Table 5: Haematological parameters and antiretroviral drugs of patients on ARV drugs

Parameter	CPE	CPN	CPA	TRA	TRE	TRN	P–value
Haemoglobin (g/dl)	12.03 (a)	12.14 (a)	12.06 (a)	11.89 (a)	11.66 (a)	10.77 (a)	0.392
White blood cells (10^3/µl)	4.89 (a)	4.69 (a)	5.35 (a)	5.34 (a)	4.88 (a)	4.50 (a)	0.203
Lymphocyte count (10^3/µl)	2.10 (a)	2.18 (a)	2.08 (a)	2.29 (a)	2.15 (a)	1.99 (a)	0.893
Neutrophil count (10^3/µl)	2.02 (ab)	1.85 (ab)	2.48 (b)	2.42 (b)	2.07(ab)	1.51 (a)	0.013*
Red blood cells (10^6/µl)	3.94 (ab)	3.67 (a)	3.85 (ab)	4.18 (b)	3.83 (ab)	3.65 (a)	0.005*
Mean Cell Volume fl	93.55 (ab)	96.26 (b)	93.59 (ab)	88.15 (a)	94.23 (ab)	91.70 (ab)	0.017*
Mean Cell Haemoglobin (pg)	30.96 (ab)	32.28 (b)	31.56 (ab)	28.81 (a)	31.12 (ab)	30.02 (ab)	0.017*
Mean Cell Haemoglobin Concentration (%)	32.95 (a)	33.43 (a)	33.67 (a)	32.58 (a)	32.84 (a)	32.60 (a)	0.086
Platelets (10^3/µl)	236.14 (a)	228.87 (a)	241.33 (a)	233.22 (a)	237.60 (a)	220.23(a)	0.948

NB: Means having the same letter(s) are not significantly different at 0.05 level of significance. Values with different letter(s) indicates significant difference at P<0.05; C; Zidovudine, P; Lamivudine, N; Nevirapine, E; Efavirenz, R; Lamivudine, A; Lopinavir/ Ritonavir, T; Tenofovir.

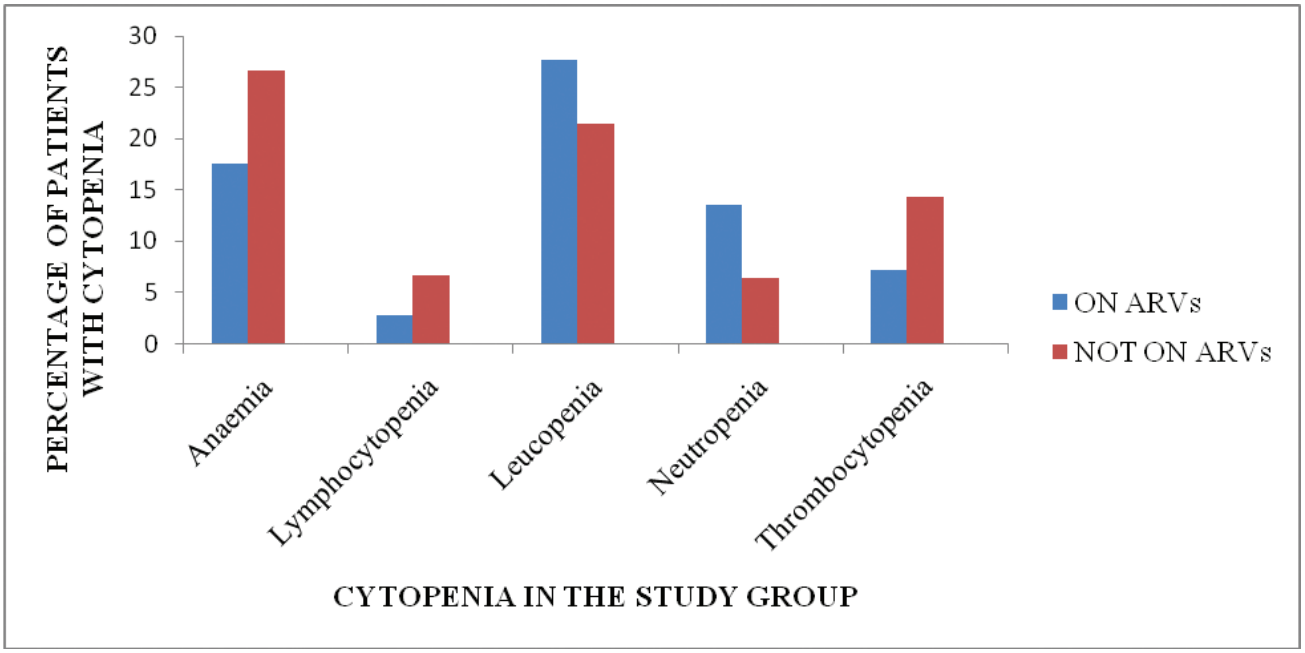

Figure 1: Haematological abnormalities in HIV/ AIDS patients on ARV drugs and not yet on ARV drugs.

based regimen. This was contrary to the findings[14,31] which reported that anaemia in HIV infected patients was caused by zidovudine based regimen. Leucopoenia and neutropenia were the most prominent haematological abnormalities among patients on ARV drugs. These were similar to previous reports.[32,33] The likely cause of these haematological disorders in this study could be due to the use of Tenofovir + Emtricitabine + Nevirapine combination.

The findings in Sokoto,[34] Nigeria also revealed that Stavudine + Lamivudine + Nevirapine regimen was responsible for leucopenia and neutropenia.[29] It was also reported that the primary culprit in drug–induced neutropenia was Zidovudine. Furthermore, lymphopoenia was less common in patients on ARV drugs as compared to those that were yet to be on the drugs, this was attributed to the ability of these drugs to boost the immune system and reduce the risk of opportunistic infections. Also, the study[35] reported that treatment with ARV drugs in HIV–infected patients usually resulted in sustained platelet increases, this was contrary to the present study whereby the platelet level of patients on therapy was lower than the patients not yet on drugs.

CONCLUSION

Anaemia, leucopoenia and neutropenia were found in a few patients on ARV drugs for one to five years, and this was associated with first–line Tenofovir–based regimen. Further research is needed to determine the safety of Tenofovir–based therapy in managing HIV–infected patients.

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CONFLICT OF INTEREST

The author declares no conflict of interest.

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