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Gender-Based Differences in Hematological and CD4+ T-Lymphocyte Counts among HIV-Patients in Ido-Ekiti

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ABSTRACT

The aim was to determine gender-based differences in some hematological and immunological parameters among Human Immunodeficiency Virus (HIV)-patients on treatment and treatment naïve in Ekiti. Differences in prevalence and severity of HIV/AIDS infection between males and females remain complex and controversial; this may vary with time in the same location during the course of the epidemic. A total of 400 HIV infected participants were recruited for the study. Four milliliters (4ml) of blood samples were collected into K_2 EDTA bottles for the analysis of hematological and immunological parameters. Two hundred and seventy seven (277) were females (146 on highly active antiretroviral therapy (HAART) and 131 HAART naïve) while 123 were males (54 on HAART and 69 HAART naïve). Hematological and immunological parameters were statistical significantly higher in HAART patients. Female are at higher risk of HIV infection compared to their male counterparts, this study demonstrated that significant hematological and immunological differences exist between male and female initiating HAART and HAART naïve.

Key word: Sex, HIV-Patients, Hematological and Immunological Parameters.

ABBREVIATIONS: PCV- Packed Cell Volume, PLT- Platelets, WBC- White Cell Count, LYM- Lymphocytes, NEU- Neutrophlis, MXD- Mixed, SD- Standard Deviation, HAART- Highly Active Antiretroviral Therapy.

INTRODUCTION

Worldwide, Nigeria has the second highest number of new HIV infections reported each year and an estimated 3.7% of the population is living with HIV. Although HIV prevalence is much lower in Nigeria than in other African countries (Federal Republic of Nigeria, 2012). However, differences in prevalence and severity of HIV/AIDS infection between males and females remain complex and controversial; this may vary with time in the same location during the course of the epidemic, and vary greatly by place of residence. Gender differences with respect to HIV/AIDS depend on patterns of disease transmission, as well as on the stage of the epidemic. Approximately half of the people living with HIV are women (Ackermann and Klerk, 2002). The highest HIV prevalence found among women is in countries where the epidemic has become generalized; many women are infected with HIV by their long-time trusted partners or husbands. Women are at a greater physiological risk of contracting HIV than men, because women have a greater mucosal surface area exposed to pathogens and infectious fluid for longer periods during sexual intercourse and are likely to face increased tissue injury. Young women are at particularly high risk due to immaturity of the opening of the womb (cervix), which has not acquired sufficient thickness to act as an effective barrier, thereby facilitates greater exposure of target cells to trauma and pathogens in the vagina (Ackermann and Klerk, 2002) Women living with HIV have mainly become

infected in heterosexual relationships and often in a marriage context. However, Females often experience the impact of HIV more severely than men, due to a combination of biological, social, cultural and economic factors which contribute to women's vulnerability to HIV. Hematological abnormalities are common complications of human immunodeficiency virus infection. These abnormalities increase as the disease advances. In both antiretroviral-treated and untreated individuals, different types of hematological abnormalities are common (Gange et al., 2003; Muluneh and Fessahaye, 2009; Dikshit et al., 2009).

Anemia is the most common hematological abnormalities in HIV patients. Several factors play a role in the development of anemia in patients with HIV, including chronic disease, opportunistic infections, nutritional deficiencies and toxicities from medications. As HIV disease progresses, the prevalence and severity of anemia also increases (Belperio and Rhew, 2004; Volberding, 2002). Thrombocytopenia is another frequent hematological complication of human immunodeficiency virus infection which can occur at any stage of HIV infection. Chronic infection with HIV is now well-characterized causes of chronic immune thrombocytopenic purpura (Liebman, 2008). The possible mechanisms that have been reported are immune-mediated destruction of platelets by antibodies, cross-reacting antibodies that are directed toward HIV proteins, particularly gp120 and p-24. This type of platelet destruction is called immune thrombocytopenic purpura (ITP) which is characterized by very low platelet counts with normal hematocrit and white blood cell count (Dikshit et al., 2009; Akinbami et al., 2010; Kouri et al., 1993). Neutropenia is also common leucopenia occurring in HIV infected individuals HIV infection suppresses the bone marrow and leads to decreased levels of granulocyte colony-stimulating factor, the factor that stimulates production of white blood cells in the bone marrow and affects the granulocyte-macrophage lineage, resulting in leucopenia. Also myelosuppressive drugs or other opportunistic infections including cytomegalovirus, tuberculosis, histoplasmosis and leishmaniasis may cause leucopenia. Furthermore, HIV infection can directly result in lymphopenia as the infection progresses, leading to a decrease in CD4± lymphocytes (Dikshit et al., 2009; Kouri et al., 1993).

The CD4±T lymphocyte count is the determination of the concentration of CD4± T lymphocyte in the blood. It is a measure of the immune system which indicates the stage of disease progression in an individual with HIV-infection, a lower count indicating a more advanced stage of the disease. World Health Organization recommended that most treatment initiation decisions be guided by CD4 measurement and clinical staging (Balter, 2003; Hanson et al., 1995). Stein et al. (1992) reported that, there is a good correlation between CD4 count and development of various complications in HIV/AIDS (Stein et al., 1992). It is clear that late starters of highly active antiretroviral therapy with CD4 count <200 cells/µl have significantly poor response to therapy and a worse prognosis when compared with early starters with higher CD4± T cell count (Cheisson et al., 2000; Ledergerber et al., 1999; Kilaru et al., 2004). General treatment guidelines for the treatment of HIV-infected patients in many countries have adopted three approaches for the initiation of antiretroviral therapy. Early intervention in asymptomatic patients involves the commencement of antiretroviral therapy once the CD4 count is less than < 500 cells/µl. A less intensive approach is to recommend antiretroviral therapy when the CD4 count falls to 350 cells/µl. In other countries where patients have limited financial resources, treatment decisions are typically delayed until the CD4 count becomes less than 200 cells/µl (Tarwater et al., 2001; British HIV Association, 2000; Mellors et al., 1997). McGrath et al. (2015) reported that time to initiate ART eligibility was significantly shorter for men, highlights the need to develop gender oriented strategies throughout HIV care in the African context, they reported that men are more likely to present for care with slightly lower CD4 cell counts than women and there is a need to find ways to get men into care earlier (McGrath et al., 2005).

According to UNAIDS, more than 3.9 million HIV patients were receiving antiretroviral therapy (ART) in sub-Saharan Africa at the end of 2009. This represents 37% of those in need of treatment and an increase of one million patients in one year (World Health Organization, 2010). Early initiation of ART in the course of disease is associated with better survival (Sterne et al., 2009; Kitahata et al., 2009) and better long-term immune reconstitution (De Beaudrap et al., 2009; Garcia et al., 2004). Introduction of highly active antiretroviral therapy (HAART) in developed countries in the late 90s has been associated with a remarkable decrease in AIDS-related mortality. This decrease in mortality has changed the perspective of HIV infection from that of a rapidly fatal to a chronic manageable infection. Clinical benefits of HAART are due to its effectiveness in decreasing disease progression in HIV infected patients by sustained suppression of viral replication (Ledergerber et al., 1999). The aim of this study is to determine the gender-based differences in some hematological and immunological parameters among HIV-patients on treatment and treatment naïve in Ekiti.

MATERIALS AND METHODS

Study Design

A total of 400 HIV infected patients were recruited to participate in the study, 200 were treatment-naïve, 69 and 131 were male and female, respectively; also 200 were on treatment; 54 and 146 were male and female, respectively. 4ml blood were collected into di-

potassium ethylenediaminetetracetic acid (K_2 EDTA) vaccutainer bottles for the analysis of hematological and immunological (CD4) parameters. The study is a cross-sectional study, HIV infected individuals who are on treatment and treatment-naïve were recruited into the study from those who attended HIV clinic at Federal Teaching Hospital, Ido-Ekiti, Nigeria (FTH) between August 2013 and February 2014 were enrolled for the study.

Ethical Considerations

Ethical clearance and Permission for the conduct of the study was obtained from the Ethics Committee, Federal Teaching Hospital, Ido-Ekiti. After informing study participants of the objectives of the study and assuring them of confidentiality of their data, written informed consent was taken from all the participants.

Hematological Parameters Analysis Using Hematology Analyzer (Sysmex Automated Hematology Analyzer Model KX-21N, Manufactured by Sysmex Co-Operation Kobe, Japan)

Three parts differential hematology analyzer was used which consist of lymphocyte count (LYM), neutrophil count (NEU), sum of eosinophil, basophil and monocyte as mixed (MXD).

Procedure

Sysmex machine was inspected (for instrument, reagents, waste bin and printer paper) before switch on the machine from power source, machine was calibrated before used and control sample was run along each batches of sample analysis. Well mixed EDTA blood sample was used for the analysis of complete blood count, blood sample was aspirated through the sample probe one after another by pressing start switch, sample was analyzed, rinsed and display the result on the LCD screen of the machine also printed the results out. After the analysis, machine was shut down by aspirating cell clean which washed and rinsed the machine before finally shutdown and switch off from the power source (Esan, 2014).

CD4 Count Was Analyzed Using Flow Cytometry (Cyflow Counter)

Calibration of Cyflow Counter

Research samples for CD4 count were prepared and run on the Partec cyflow counter (Partec flow cytometer, GMBH, Munster, Germany) according to the manufacturer's instructions. Partec flow cytometer (Cyflow counter) was first calibrated to ascertain optimal equipment performance by using count check beads of already known concentration following daily cleaning procedure. Samples from normal subjects were tested along with research samples to ensure reagent control and quality of results. A well calibrated cyflow counter must give count check beads reagent control within ±10% of reagent concentration. CD4 monoclonal antibodies were used within the expiry dates. Values within ±10% of known results validated the potency of the CD4 monoclonal antibodies used for our research procedure.

Cyflow Counter Count Check Beads Calculation

A specific count check bead used during analysis of our research samples had known concentration of 23,470 cells/ml. The equipment displayed absolute CD4 count value of the count check bead as 966 cells/µl, and the pre-set dilution factor is 42, and then calculated concentration of the count check beads in cells/ml from the flow.

$$\text{Cytometer} = \frac{(\text{CD4 count in cells}/\mu\text{l}) \times 1000}{42}$$

$$= \frac{966 \times 1000}{42}$$

$$= 23{,}000 \text{ cells/ml.}$$

% deviation from the known concentration is calculated from the formula as follow;

$$\%\ \text{deviation} = \frac{\text{calculated concentration of the count check beads} - \text{known concentration of count check bead}}{\text{known concentration of count check bead}} \times 100$$

$$\%\ \text{deviation} = (23{,}000-23470)/23470 \times 100\%$$
$$= -2.0\%.$$

Since the calculated value of count check beads concentration fell within -10% of known value, the equipment was successfully calibrated.

Principle and Procedure of Flow Cytometry for CD4 Count

The cyflow counter operation is based on the simultaneous measurement of multiple physical characteristics of CD4 count in a single file as it flows through the cyflow counter. The counter separated the CD4± T cell from the monocytes- CD4 bearing cells and noise using a gating system. We prepared the samples and analyzed them for CD4 count according to the manufacturer instructions. 20 µl of well-mixed whole blood sample was added to 20µl of CD4 MAB

Table 1. CD4 counts and some hematological parameters of HIV positive patients on HAART and HAART Naïve.

Parameters	HAART Naïve		HAART	
	MEAN±SD	t-value (significant)	MEAN±SD	t-value (significant)
CD4	152.72 ±177.22	12.19 (0.00)	543.73 ±295.79	25.99 (0.00)
WBC	4.08± 2.63	25.86 (0.00)	5.08 ±1.85	38.77 (0.00)
PCV	32.24± 6.29	72.47 (0.00)	35.37± 5.35	93.54 (0.00)
PLT	164.29± 150.38	15.45 (0.00)	251.91 ±73.87	48.23 (0.00)
LYM	37.06± 14.57	35.98 (0.00)	46.73± 12.25	53.99 (0.00)
NEU	51.32 ±15.49	46.84 (0.00)	41.53± 12.87	45.65 (0.00)
MXD	11.18 ±7.37	21.06 (0.00)	11.85 ±8.48	19.25 (0.00)

Table 2. Sex difference in CD4 counts and some hematological parameters of HIV positive patients on HAART Naïve.

SEX	CD4	WBC	PCV	PLT	LYM	NEU	MXD
Male N=69	163.16 ±257.01	5.13 ±3.38	33.81 ±6.86	176.07 ±205.47	38.98 ±13.46	48.82 ±13.91	11.99±9.98
Female N=131	147.23 ±115.14	31.41 ±5.83	31.41 ±5.83	158.09 ±111.46	36.05 ±15.07	52.64 ±16.16	10.75±5.51
F (P-Value)	0.87 (0.35)	1.38 (0.24)	1.55 (0.22)	2.98 (0.08)	1.23 (0.27)	3.07 (0.08)	1.32 (0.25)

Table 3. Sex difference in CD4 counts and some Hematological parameters of HIV positive patients on HAART.

SEX	CD4	WBC	PCV	PLT	LYM	NEU	MXD
Male N=54	523.74 ±314.13	4.94 ±2.03	37.39 ±6.35	251.85 ±69.84	46.99 ±13.18	41.62±13.28	11.19±7.49
Female N=146	689.12 ±289.49	5.13 ±1.79	34.62 ±4.73	263.93 ±75.54	47.64 ±11.93	41.49 ±12.76	12.09±8.83
F (p-value)	4.23 (0.02)	0.20 (0.65)	6.19 (0.01)	0.13 (0.72)	1.52 (0.22)	0.00 (0.99)	0.92 (0.34)

(monoclonal antibody) in a Rhören tube. This was incubated for 15 min in the dark. 800 µl of CD4 no-lyse buffer was added (carefully without introducing bubbles) and the mixture was analyzed on Partec cyflow counter and results recorded in cells/µl.

Statistical Analysis

Results obtained were analyzed using student t-test to compare the means. Analysis was performed using computer database software from the statistical package for social sciences (version 16.0 SPSS). A P-value of < 0.05 was considered statistically significant in all clinical comparisons at 95% confidence interval.

RESULTS

A total of 400 HIV infected patients was categorized into two, 200 HAART naïve treatment and 200 on HAART treatments were involved in this study. The mean ± SD of CD4, WBC, PCV, PLT, LYM, NEU and MXD were 152.72 ±177.22, 4.08± 2.63, 32.24± 6.29, 164.29± 150.38, 37.06± 14.57, 51.32 ±15.49 and 11.18 ±7.37, respectively in patients on HAART naïve patients and 543.73 ±295.79, 5.08 ±1.85, 35.37± 5.35, 251.91 ±73.87, 46.73± 12.25, 41.53± 12.87 and 11.85 ±8.48, respectively for HAART patients. All the parameters analyzed were statistical significantly higher in HAART patients except in NEU when compared with HAART naïve patients as shown in Table 1. Out of 400 HIV infected patients that participated in this study, 277 were females (146 on HAART and 131 HAART naïve) and 123 were males (54 on HAART and 69 HAART naïve). Mean±SD of CD4, WBC, PCV, PLT, LYM, and MXD were higher in male compared to female except NEU in HAART naïve patients. However, in HAART patients, Mean±SD of CD4, WBC, PLT, LYM, and MXD were higher in female compared to male except PCV and NEU as shown in Tables 2 and 3.

DISCUSSION

In this present study, female had height prevalence of HIV infection with high frequency of HIV Patients on HAART compared to male, similar to previous studies by Bamlaku et al. (2014) Denue et al. (2013) Yakubu et al. (2014) and Ibrahim et al. (2015) they reported high prevalence of HIV infection among female (Bamlaku et al., 2014; Denue et al., 2013; Yakubu et al., 2014; Ibrahim et al., 2015). This study supported the fact that Women are at a greater physiological risk of contracting

HIV than men because women have a greater mucosal surface area exposed to pathogens and infectious fluid for longer periods during sexual intercourse (Ackermann and Klerk, 2002) especially when exposed to unprotected heterosexual intercourse. Hormones such as progesterone are reported to be playing a role in a woman's biological vulnerability to HIV infection. Observational evidence suggests that progesterone containing injectable contraception depot medroxyprogesterone acetate (DMPA) may be putting women at higher risk of HIV acquisition (Baeten et al., 2007; Ramjee and Wand, 2012; Heffron, 2012; Wand and Ramjee, 2012). Studies show that pregnant women are at a higher risk of HIV infection than lactating or other women, possibly due to physiological changes that a woman undergoes during pregnancy (Chersich and Rees, 2008). High levels of estrogen and progesterone either during pregnancy or from exogenous sources could cause changes in the structure of the genital mucosa or cause immunological changes, such as an increase in mucosal lymphoid aggregates or hormone-induced over expression of co-receptors associated with HIV infection. Supporting evidence suggests that women have a window of vulnerability approximately seven to ten days after ovulation in their menstrual cycle in which the potential for viral infectivity in the female reproductive tract is increased.

This is due to the suppressing influence of sex hormones on the innate, humoral and cell-mediated immune systems which this takes place in the upper and lower female reproductive tract, and overlaps with the up-regulation of co-receptors for HIV uptake and the recruitment of potentially infectable cells (Wira and Fahey, 2008). This present study supported fact that women are tested for HIV earlier than men and had their earlier access to treatment and clinical care compared to men, because of the increasing availability of antenatal testing as part of ongoing expansion in voluntary counseling and testing (Bharucha et al., 2005; WHO, 2007). Early access to treatment and clinical care in female improve their health condition compared to their male counterparts at enrollment into care. In this study, patients on treatment shows greater improvement in immunological and hematological parameters compared to treatment naïve patients in both sexes, this confirmed the earlier report by Kumarasamy et al. (2008) that, both men and women showed consistent improvement in the HIV patients on initiating HAART (Kumarasamy et al., 2008).

CONCLUSION

Females have been found to be prone to high risk of HIV infection when compared with their male counterparts. Hence, this study demonstrated that there exist significant differences in the values of hematological and immunological features between males and females in relation to HAART and HAART naïve.

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