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Erythrocyte Sedimentation Rate, C-Reactive Protein and CD4 Lymphocyte Count among Persons Living with HIV on Antiretroviral Therapy in Sokoto, North Western Nigeria

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Abstract

HIV infection is a worldwide public health challenge. Highly Active Antiretroviral therapy (ART) is a treat option which involves the use of multiple of antiretroviral (ARV) drugs to maximally suppress the HIV virus and stop the progression of HIV disease among persons living with HIV/AIDS (PLWHA). The aim of this study was to determine the effects of HIV on the Erythrocyte Sedimentation Rate (ESR), C-Reactive Protein (CRP) and CD4 lymphocyte count among antiretroviral naïve subjects in Sokoto. Ninety-six participants were recruited for this study (56 antiretroviral naïve subjects and 40 highly active antiretroviral therapy- experienced controls). Informed consent was obtained from all subjects. Ethical approval was obtained from the ethics committee of Maryam Abacha for women and children Sokoto and Specialist Hospital Sokoto. Five milliliters of blood were collected from each subject for the determination of ESR using Westergren method. The CRP and CD4 lymphocyte count were determined using ELISA and Cyflow technique respectively. Statistical Package for Social Science (version 25) was used for the data analysis. Results showed that there was a statistically significant increase in CRP in HAART- naïve subjects compared to that of HAART-competent controls ($p = 0.00$). The ESR was statistically higher among the ART naïve patients compared to Highly Active Antiretroviral Therapy (HAART)-experienced subjects ($p = 0.00$). The CD4 count was significantly higher among HAART-experienced controls compared to HAART- naïve patients ($p = 0.00$). The elevated ESR and CRP could be an indicator of inflammatory response as both parameters are positive acute phase reactants that tend to increase in inflammatory conditions. Although the CRP and ESR have a low index of specificity, sensitivity and are influenced by numerous disease factors, they can potentially provide clinicians with valuable information and additional focus when used in conjunction with other clinical and diagnostic data (clinical history and physical exam) for the diagnosis and monitoring of pathological conditions such as HIV.

Keywords: *ESR; CRP; Antiretroviral Therapy; Sokoto; Nigeria*

Introduction

The acquired immune deficiency syndrome (AIDS) is disease caused by the human immunodeficiency virus (HIV). At the early stages of infection, a patient may be asymptomatic or they may experience symptoms typical of influenza [1]. Characteristically, this phase may be followed by a prolonged period where patient may have no symptoms. On long-term, the disease interferes negatively with the cell mediated immunity in the patients. This predisposes patients to common infections like tuberculosis and other opportunistic infections, and tumors that rarely affect people whose immune systems are intact [1]. These symptoms that present in the significantly immunocompromised patients constitutes the acquired immunodeficiency syndromes (AIDS) [1]. Possible sources of HIV infection include unprotected sex (including anal and oral sex), transfusion of contaminated blood and blood products, sharing of contaminated sharps, and from an infected mother to her child during pregnancy, delivery and breastfeeding [2]. Infection by HIV can be prevented by practice of safer sex, implementation of effective and safe managements of sharps, treating HIV infected patient using HAART and by the practice of male circumcision [1]. Mother to child transmission of HIV can be prevented by enrollment of infected pregnant women into the Prevention of Mother to child transmission of HIC programme and providing antiretroviral medication for the infected mother. As at 2016, an estimated 36.7 million people were living with HIV 2016 with about 1 million HIV-associated deaths [3]. Between 2015 and 2016 an estimated 300,000 new HIV infection occurred globally with majority of those infected residing in sub-Saharan Africa [1].

Nigeria is one of the most affected country in Africa with over 140 million cases in 2006. The adult HIV prevalence in the most populous African Nation has increased steadily (1.8% in 1991 to 4.5% in 1996 to 5.8% in 2001) respectively for 1991, 1996 and 2001. Thereafter the prevalence decreased from 5.0% in 2003 to 4.4% in 2005. An estimated 6.6 million Nigerians (4.4% Nigerians) are living with HIV/AIDS. The disease has had a significant negative impact on the social and economic growth of Nigeria resulting in a reduction in life expectancy from 53 years in 1990 to 51 years in 2002 [4].

The erythrocyte sedimentation rate (ESR) is a haematology test that measure the rate of sedimentation of red cells in a sample of whole blood over a one-hour period. The test is non-specific and it often detects the presence of inflammation. The test is often performed be placing anticoagulated blood in a vertical Westergren tube, and the rate at which the red blood cells sediment in mm in an hour is recorded. The ESR is governed by factors such as the fibrinogen, content and the negative charge of the red cells (zeta potential). Inflammatory processes are often associated with raised fibrinogen level which is associated with adhering together to form stacks called rouleaux, which sediment faster, due to their increased density. Rouleaux formation has also be increased in patients with some lymphoproliferative disorders associated with increased production of one or more immunoglobulin. Increased ESR has been observed to be associated with conditions including: autoimmune diseases such as lupus erythematosus and rheumatoid, anaemia, infections, inflammation, kidney diseases, pregnancy and haematological cancers including lymphoma and multiple myeloma). The ESR measures the rate at which red cells sediment in anticoagulated blood sample in an upright tube in an hour expressed in mm/hour.

The ESR is related to plasma viscosity and the red cell count. Plasma viscosity is a more accurate test compared to ESR. It is essentially a measure of the albumin/globulin ratio. This test is affected in condition associated with the presence of acute phase reactant proteins which is also a major factor that affect the ESR. Another factor that affects the relatively simple and cheap ESR test is the serum fibrinogen level [5]. C-reactive protein is an acute-phase protein synthesized in the liver controlled by interleukin-6. CRP is thought to be involved in activation of complement through the classical complement activation pathway and often contributes to eradication of microorganisms through the process of opsonization and phagocytosis [6]. Inflammatory processes and non-inflammatory conditions can affect the ESR. Inflammatory conditions are associated with plasma proteins including fibrinogen and alpha globulin becoming positively charged as well as increase in the ESR [7]. ESR is considered as an indicator of disease progression [8]. Previous report indicated an insignificant fall in CD4 count with increasing ESR [9]. The clinical utility of ESR in the prediction of AIDS is being investigated in developing countries [10], it is however more relevant in developed economies where there is accessibility to CD4 count. The ESR cannot be used to forecast

acute infection in HIV [11]. However, it is common to observed a raised result often in triple figures in asymptomatic patients with normal CD4 counts. Studies involving the determination of ESR among persons living with HIV/AIDS is common in African settings [10]. Raised ESR is more informative and clinically more relevant in inflammatory disorders associated with immune activation, cytokines rush and TNF-alpha [12].

CRP is stable protein synthesized in the liver often in response to cytokine (IL-6) [13,14]. Immune activation has been demonstrated to be a significant contributor to HIV diseases progression in multiple studies [15]. It is expected that CRP levels should be increased in HIV patients because it is an acute phase reactant [16]. Immune activation has been implicated as a major factor that contributes to diseases progression in persons living with HIV/AIDS [15].

The management of HIV/AIDS normally includes the use of HAART involving the use of 2 - 3 antiretroviral drugs in an bid to control HIV infection. The use of multiple antiretroviral drugs that is active on different stages of the HIV life-cycle is vital in the effective management of HIV. The use of multiple drugs that act on different viral targets involved in the HIV life cycle is what is known as highly active antiretroviral therapy (HAART). HAART decreases the patient's viral load, maintains the CD4 mediated immune function and prevent the development of opportunistic infections that are often associated with risk of death in these patients [17]. Over the past two decades with the advent of highly active antiretroviral therapy (HAART), HIV has changed from being a deadly disease to becoming a manageable chronic illness. With the use of HAART in the management of PLWHA, the focus has now shifted to managing the long-term complication associated with HIV and improving the quality of life of HIV patients who are fortunate enough to have access to these lifesaving medications.

There is scarcity of data on ESR CRP and CD4 lymphocyte count among HIV -infected persons particularly in Sokoto, Nigeria. Finding from this study could provide a baseline data on the level of C-reactive protein and ERS among antiretroviral naïve patients in Sokoto.

Aim of the Study

The aim of this study was to determine the level of C-reactive (CRP) ESR and CD4 lymphocyte count among antiretroviral naïve subjects and HAART-experienced controls in Sokoto as well as to determine if there is any significant relationship between the CRP and ESR among antiretroviral naïve subjects and highly active antiretroviral therapy-experienced controls in Sokoto.

Materials and Methods

Sample collection

We collected five milliliters (5 ml) of blood from every subject into a clean plain and EDTA containers with strict aseptic technique for each participant. The sample was divided into two; one in plain container where serum was harvested by allowing the blood to clot and the level of serum CRP were measured and the remaining sample was introduced into EDTA container and used for ESR and CD4 count. ESR was determined using Westergren method, CD4 count was carried out using Cyflow technique. CRP was determined using hsCRP ELISA kit (Calbiotic, U.S.A.). Testing was done at School of Medical Laboratory Science in Haematology Department and Chemical Pathology in UDUTH Sokoto.

Study design

This study is a comparative study that evaluated the level of CRP, ESR and CD4 count among antiretroviral naïve subjects and HAART-experienced controls. This study recruited 96 participants made up of 56 antiretroviral naïve patients (subjects) and 40 HAART treatment- experienced (controls).

Study area

The study was carried out at School of Medical Laboratory Science Usmanu Danfodiyo University Sokoto, in department of Haematology and Chemical Pathology (UDUTH) in collaboration with the Maryam Abacha Hospital for Women and Children and Specialist Hospital Sokoto. Sokoto is city located in northwest geopolitical zone of Nigeria. The population of the state stood at 5.4 million as of 2017. The State is bordered by Republic of Niger, Kebbi and Zamfara State in the North, West/Southeast and the East respectively. Hausa and Fulani are the major ethnic groups in the state with other ethnic groups including: Igbo, Yoruba, Ebira, and Igala being in the minority. This study was conducted in Sokoto from Maryam Abacha for women and children hospital and Specialist hospital all in Sokoto using antiretroviral naïve patients and HAART. The site of the study has an enabling environment and material resources for the study to be carryout.

Inclusion criteria

All consenting legal adults with confirmed HIV positivity and ARV therapy naïve subjects visiting Maryam Abacha for Women and Children and Specialist Hospital Sokoto were consecutively recruited into the study.

Exclusion criteria

All non-consenting, non-legal adults, HIV-negative and ARV therapy- experienced individuals and those not managed at Maryam Abacha for Women and Children and Specialist Hospital Sokoto were excluded from participating as subjects in the study.

Informed consent

Written informed consent was sought and gotten from all the eligible participants who met the inclusion criteria.

Sample size determination

The HIV sentinel survey has shown that Sokoto state, the study area had a relatively low prevalence of 6.0% when compared with the other states in Nigeria [18].

The sample size was calculated based on Cochran [19] using the formula:

n = Least sample size

z = Standard normal deviation and probability.

P = Prevalence value from a previous study.

q = Share of failure (1-p)

d = Precision, tolerance limit, the minimum is 0.05.

Therefore $n = z^2pq/d^2$

Where z = 95%

P = 6.0% (0.06) [18]

q = 1-0.06 (= 0.94)

d = 5% (0.05)

Therefore n = $(1.96)^2$ (0.06) (0.94)/$(0.05)^2$

n = 86.6 approximately 87

Attrition was calculated as 10% of the total 87 subjects and added to the sample size.

10/100x87 = 8.7

87 + 8.7 = 95.7 approximately 96. Therefore, the calculated sample size is 96.

Sampling method

Stratified random sampling method was adapted to those subjects that met the inclusion criteria. The groups were divided into two strata; antiretroviral naïve patients (subjects) and highly active antiretroviral therapy patients (treatment experienced) (controls).

Questionnaire

A structured questionnaire was designed and administered to all participant involved to obtain their biodata, socio- demographic and medical history.

Statistical analysis

The data collected from subjects were analyzed using SPSS Version 25. The statistical differences of the data were analyzed using student t-test, Chi- square, Mean, and Standard deviation. Pearson correlation was employed in the determination of the relationship between sets of data. A p-value of ≤0.05 denoted statistical significance. Means was compared using student t-test for parametric data while Chi-square was used for comparing non-parametric data.

Ethical consideration

The ethical clearance to carry out this study was sought and obtained from Ethical Review Board of Maryam Abacha Hospital for Women and Children and Specialist Hospital all in Sokoto.

Results

In this study some acute phase reactants and CD4 count were determined among 56 antiretroviral- naïve subjects and 40 HAART- experienced controls in Sokoto North Western Nigeria. There were no statistically significant age, gender, residence, ethnicity and marital status-related differences in the HAART-naïve and experienced participants (X = 6.39,0.17, 0.12, 3.01 and 7.69, p = 0.27, 0.68, 0.39 and 0.21; p > 0.05) respectively. There was a statistically significant differences in the distribution of HAART-naïve and experienced participants based on occupational and educational status (X = 9.05 and 12.00; p = 0.01 and 0.01 respectively). Table 1 show the distribution of HAART-naïve and experienced participants based on socio-demographic factors.

	Group of participants				
Variable	**ART naive**	**HAART**	**Percentage% ART naive**	**X^2**	**p-value**
Age Group (Years)					
5 - 15	0	1	0	6.39	0.27
16 - 25	0	1	0		
26 - 35	29	21	51.8		
36 - 45	24	16	42.9		
46 - 55	3	0	5.4		
56 - 65	0	1	0		
Total	56	40	100		
Gender					
Male	16	13	28.6	0.17	0.68
Female	40	27	71.4		
Total	56	40	100		
Place of Residence					
Rural	2	2	3.6	0.12	0.73
Urban	54	38	96.4		
Total	56	40	100		
Tribe					
Hausa	47	33	83.9	3.01	0.39
Yoruba	1	2	1.8		
Igbo	3	4	5.4		
Others	5	1	8.9		
Total	56	40	100		
Occupation					
Civil servant	13	5	23.2	9.05	0.01
Self employed	19	26	33.9		
Non- employed	24	9	42.9		
Total	56	40	100		
Education status					
Primary	14	6	25	12.00	0.01
Secondary	12	17	21.4		
Tertiary	9	12	16.1		
Non- formal	21	5	37.5		
Total	56	40	100		
Marital status					
Monogamous	22	24	39.3		
Polygamous	14	2	25		
None	20	14	35.7		
Total	56	40	100	7.69	0.21

Table 1: *Sociodemographic characteristics of the study population.*

The C-reactive protein (CRP) and ESR levels were compared between ART- naïve subjects and HAART- experienced controls. The CRP and ESR were significantly higher in ART- naïve compared to HAART patients (18.11 ± 0.19 and 85.04 ± 4.37) compared to (14.42 ± 0.36 and 51.53 ± 7.65) (p = 0.00 and 0.00) respectively. Table 2 shows the comparison in the CRP and ESR levels between ART naïve and HAART experienced patients.

Parameters	Group of participants	N	Mean ± SEM	p = value
ESR	ART NAÏVE	56	85.04 ± 4.37	.000
	HAART	40	51.53 ± 7.65	
CRP	ART NAÏVE	56	18.11 ± 0.19	.000
	HAART	40	14.42 ± 0.36	

Table 2: *Comparison of CRP and ESR between ART-naive and HAART experienced patients.*

Key: ESR = Erythrocyte Sedimentation Rate; CRP = C Reactive Protein.

Table 3 shows the comparison of CRP and $CD4^+$ Count between ART- naïve subjects and HAART- experienced controls. The CRP was significantly higher among ART-naïve controls (18.11 ± 0.19) compared to HAART experienced (p = 0.000). The CD4 count was significantly higher (600.68 ± 54.26) among HAART experienced subjects compared to ART-naïve controls (161.00 ± 17.33) (p = 0.000).

Parameters	Group of participants	N	Mean	p = value
CRP	ART NAÏVE	56	18.11 ± 0.19	0.000
	HAART	40	14.42 ± 0.36	
$CD4^+$	ART NAÏVE	56	161.00 ± 17.33	0.000
	HAART	40	600.68 ± 54.26	

Table 3: *Comparison of CRP and $CD4^+$ count between ART Naive and HAART patients.*

Key: ESR = Erythrocyte Sedimentation Rate; CD4 = Cluster of Differentiation 4.

There was a relationship between increase in ESR level (85.04 ± 4.37) and decrease in CD4 count (161.00 ± 17.33) in ART naïve compared to a decrease in ESR (51.53 ± 7.65) and increase in CD4 count (600.68 ± 54.25) among the HAART-experienced patients (p = 0.00 and 0.00 respectively). Table 4 shows the relationship between ESR level and CD4 count in ART naïve and HAART-experienced patients.

Parameters	Group of participants	N	Mean	p = value
ESR	ART NAÏVE	56	85.04 ± 4.37	0.000
	HAART	40	51.53 ± 7.65	
$CD4^+$	ART NAÏVE	56	161.00 ± 17.33	0.000
	HAART	40	600.68 ± 54.25	

Table 4: *Comparison of ESR with $CD4^+$ lymphocyte count between antiretroviral naïve patients and HAART patients.*

Key: ESR = Erythrocyte Sedimentation Rate; CD4 = Cluster of Differentiation 4; HAART: Highly Active Antiretroviral Therapy.

Discussion

The ESR, C-reactive protein and CD4+ count of fifty-six antiretroviral- naïve subjects and forty antiretroviral-experienced controls who were recruited from Maryam Abacha and Specialist Hospital Sokoto was analyzed in this study. Findings from this study indicate that there are no gender-related differences in the number of ART naïve subjects and HAART-experienced controls. Finding from this study showed that patients within the reproductive ages had higher percentage of HIV compared to other groups. This finding is consistent with WHO report that African population has highest prevalence of HIV infection among reproductive ages compared to other regions of the world [20].

Finding from this study has shown that people residing in the urban settings have higher percentage compared to those living in the rural settings. This may be due to the fact that most people living in the rural areas don't have access to HIV diagnosis and healthcare. Previous report indicates that HIV diagnosis tends to be more and late in rural areas compared to urban areas [21].

Moreover, finding from this study has shown that level of education matters in terms of HIV-infection. From this study patient with low level of education tend to be more infected compared to other category of patients with higher education ($p = 0.01$). Our finding is consistent with a previous report in Kenya [22] which showed a relationship between level of education and infection with HIV/AIDS. HIV prevalence was observed to lower among subjects educated to tertiary level. More educated people were more knowledgeable on HIV/AIDS prevention and control methods compared to the less educated.

Result obtained from this study showed that majority of the subjects were in monogamous marriage compared to polygamous marriage and un-married. Previous report indicated that forced sexual intercourse with a spouse and family planning sterilization procedures among men carried out particularly in couples who have achieved the desired number of children have led to a high significant of such men not using condoms during sexual intercourse with their partner. This has been noted as a significant cause of HIV infection among married monogamous women whose husbands are living with HIV and AIDS [23]. These husbands often serve as a conduit population passing the virus to their innocent wives after becoming infected often through their illicit extramarital sexual relationship with other women. Similarly, a previous report in Ethiopia indicated that half of the study participants are married with 49.6% and 18.8% were single [24].

Finding from this has shown that non-employed patients have higher percentage of 42.86%, followed by those with self-employed 33.93%. A low percentage of subjects were civil servant. This study is in consistent with the previous study performed in Germany which indicated that there is a relationship between employment and HIV/AIDS [25]. Similarly, a previous study in Ethiopia indicates that majority of HIV/AID-infected persons (54%) earned monthly personal income (Independent) and 22.7% were unemployed and dependent [24].

Finding from this study has showed that a definite increase in CRP is associated with lower CD4 count among both ART naïve patients ($p = 0.00$). CRP was significantly higher among patient who are yet to commence HAART compared to HAART-experienced patients ($p = 0.00$). Higher CRP concentrations have been found to be connected with lesser CD4 counts and higher HIV viral RNA load among PLWHA [26]. A previous report indicated that there is a significant association between increased CRP level and quicker progression to AIDS and greater risk of mortality [27]. Similarly, another study found that an increased CRP concentration is associated with a greater risk of mortality [28]. The biological mechanism for the relationship of a persistently elevated CRP level with HIV treatment failure could be explained through its involvement in general inflammation [13], where persistent inflammation is known to increase risk factors for HIV disease progression [29].

Finding from this study has shown that there is significant increase in ESR in both ART naïve subjects and HAART competent controls (p = 0.00). This finding is consistent with the previous study carried out in Benin City which showed that there is significant increase of in ESR protein in non-ART patient and ART patients [30]. ESR tends to be elevated in infectious diseases and inflammatory conditions like HIV. The increase in ESR is linked to the increased synthesis of acute phase proteins by the causative organism. It is advocated that ESR can potentially be used as sensitive index of active phase protein changes which result from inflammation or tissue damage by the HIV [31]. Our finding is consistent with a previous report which showed that PLWHA have higher ESR values when compared to the rest of patients (p = 0.009) [32].

Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are both non-specific markers of inflammation and they are usually included in the initial diagnostic workup with potential for the detection of infections or systemic immune-mediated diseases [33,34]. Several physiological factors, including non-infectious disorders and resolution of inflammation can potentially contribute to abnormally raised ESR and low CRP levels or vice versa. Although these tests have a low specificity and sensitivity as well as being prejudiced by numerous disease factors, they can potentially offer the clinician with valuable clinically relevant information and focus particularly when used in combination with other clinical and diagnostic data (clinical history and physical exam) for the diagnosis and monitoring of pathological conditions such as HIV [35]. Elevated levels of ESR are due to a higher plasma protein levels (e.g. fibrinogen, gamma globulins) [36] and CRP is an acute phase protein released after tissue injury caused by infections or other sources of inflammation [13].

In HIV patients, the occurrence of increased levels of immunoglobulins is associated with the elevation of ESR (rather than a direct infectious trigger causing release of fibrinogen). Elevated ESR is a common finding in HIV-positive patients. It is worthwhile to determine HIV status in patients with unexplained high ESR for HIV particularly those with persisting HIV-related illness [37]. ESR was initially considered as an indicator of disease progression [38]. However, later studies disagreed and showed that only a negligible fall in CD4 count can be seen with rising ESR [39,40]. The use of ESR for the prediction of development of AIDS is being investigated in most African settings without easy access to CD4 monitoring. A previous report in Tanzania indicated that 27% PLWHA with an ESR > 120 mm/hr have a CD4 count greater than 200/mm^3 [41].

Antiretroviral therapy has played an important role in improving the quality of life and extending the life span of HIV positive patients. The drastic reduction in the prices of antiretroviral drugs has made it more affordable and relatively available to HIV-infected Nigerians. Our finding indicated that there is significant variation in the CD4 count between ART- naïve and HAART experienced patients (p = 0.00). This finding is also consistent with the previous work performed in Ethiopia which shows that the mean CD4 count for HAART patients is 1.2 times higher than that of HAART- naïve counterpart (p = 0.01) [24]. A previous report among 16 HIV-1 infected individuals who were on HAART and who were followed up for 12 months, the CD4 + T Cell count showed good response in a significant number of the subjects [42]. A previous report [43] which studied the short-term effect of HAART on the CD4 lymphocyte count of HIV-infected Nigerians indicated that 12 weeks treatment with HAART in HIV-infected subjects was associated with a mean increase in CD4 count of (39 cells/microL) in subjects compared to untreated controls who showed a mean decline of (12 cells/microL) (p = 0.05). Similarly, previous report among HIV-infected Nigerian and Chinese subjects indicated that HAART regime is associated with increase in CD4 Count [11, 44].

Conclusion

In conclusion, this study has shown that ESR and CRP were significantly higher among HAART-naïve HIV infected controls compared to subjects on HAART. The CD4 count was significantly higher among HAART -experienced subjects compared to HAART-naïve controls. Evidence has shown that although CRP and ESR have low specificity, sensitivity and are affected by many disease conditions, results of both tests can offer clinicians valuable information particularly when used in combination with other clinical, diagnostic result, history and physical examination for the diagnosis and monitoring of pathological disease such as HIV.

Recommendations

Based on these findings, we recommend that physicians giving care to HIV infected patients should routinely investigate the CRP, ESR and CD4 count among patients on HAART and those that are yet to commence treatment. These parameters could be used as evidence to help make decision on when to commence ART treatments among HAART-naïve patients.

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