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The Effect of cART on Platelets/Lymphocytes Ratio and Viral Load Indices in HIV+ Subjects Initiating Therapy in a Tertiary Hospital in Port Harcourt, Nigeria

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Abstract: *Background:* In other to enhance immune response and remove completely the danger of disease associated with AIDS, commencement of combination Antiretroviral Therapy (cART) is advocated. Common among HIV positive subjects are diseases such as cardiovascular conditions among others which happen when there is distortion in the gut mucosa, existence of co-infections, and long-term cART effect which gives room to vicious cycle that impairs on immune activities and inflammation. Inflammatory predictors which reveal the danger of morbidity and mortality are raised in HIV disease. A novel marker for inflammation – Platelet/Lymphocyte ratio (PLR), is a prognostic tool for assessing inflammation, atherosclerosis and platelet activation. *Aim:* This study was aimed at assessing prospectively, cART effect on the PLR and coagulation indices in HIV positive subjects presenting to commence cART in Rivers State University Teaching Hospital. *Methods*: Six milliliters of venous blood was collected from each participants into EDTA bottles at entry into the study, after 3 months and 6 months on cART respectively for Full Blood Count using a 3-part Sysmex XP300 and HIV Viral Load using RT-PCR Cobas TaqMan version 1.5 *Results*: A total of 40 subjects were recruited, with a mean age of 36.20 years, 14 (35%) of them were males. Mean PCV, Platelet: Lymphocyte ratio and HIV VL at Month 0 were 31.65±7.30%, 7.82±2.90 and 215767.85 ± 360338.04cp/ml respectively. There was a statistically significant increase ($p < 0.001$) in the haematocrit by the 6^{th} month on cART, the reduction in Platelet: Lymphocyte count and of HIV VL by the 6^{th} month was also significant ($P<0.001$). Interestingly, PLR positively correlated with the VL at baseline (0.3676), however, there was a negative correlation at 3 months (-0125) and 6 months (-0.028). *Conclusion*: From this work it is clear that all the cases in this regard, confirm the fact that cART remarkably drops the viral load and inflammation in HIV positive subjects; nevertheless, it also shows that a low-level inflammation continues which probably leads to chronic inflammatory state, morbidity and mortality in this group of subjects.

Keywords: Platelet/Lymphocyte Ratio (NLR), Combined Antiretroviral Therapy (cART), Human Immunodeficiency Virus (HIV), Viral Load (VL)

1. Introduction

Human Immune Virus (HIV) replication is brought to minimal when antiretroviral therapy is properly combined with the overall intention to normalize immune activities and get rid of AIDS associated diseases. Nevertheless, health is not fully recovered. HIV positive subjects are likely to come down with cardiovascular conditions, neurocognitive disease, osteoporosis, liver disease, kidney conditions and some neoplasm unlike patients without HIV [1]. Generally, both AIDS and non related AIDS patients suffer from raised inflammatory and coagulation bio-indices linked to spontaneous danger in morbidity and death. [2-4]. Numerous works abound revealing that ART causes rise in incidence of cardiovascular disorders [5]. CD4 count act as an indicator of clinical effects in HIV positive subjects, though its function

is not linked to immune dysfunction or inflammatory conditions in HIV positive subjects on cART [6, 7].

Platelet/lymphocyte ratio (PLR) is a recently discovered prognostic tool in telling abnormal values in counts of platelet and lymphocyte caused by inflammation and prothrombotic conditions. The 95% reference range of PLR in normal male and female are 36.63 – 149.13 and 43.36 – 172.68 respectively. PLR has been comprehensively enumerated in malignant cases followed by immune alteration and thrombosis that could be analyzed using components of white blood cell and their ratios. Abnormal values in counts of platelet and lymphocyte have been shown by numerous researchers in the determination of intensity of systemic inflammatory issues and revealing abnormal health states. As a predictive tool, PLR may rise in count when it is unsteady. It can be interpreted using hematologic factors. a high PLR reflects inflammation, atherosclerosis and platelet activation.

Replication in HIV produces hypercoagulation and raises the values of D-dimer. In HIV patients who have not been exposed to therapy, HIV replication associates strongly with D-dimer values [3, 8] meanwhile commencement of cART depletes D-dimer values [9, 10]. Inflammation connected to HIV weakly relates to coagulation states in most researches.

Potentially, D-dimer levels are prognostic tools used to predict venous and arterial thrombosis not limited to HIV subjects [2] as well as in HIV subjects [11-14]. D-dimer levels are often regulated by the effects of pathophysiological activities like damage of the endothelium and vascular abnormality. Raffetti *et al*. [15] propounded that there is a strong connection between PLR mortality in a good number of HIV subjects with solid cancers. Nevertheless, much has not been done on the ability of PLR to predict inflammation and the cause of death in HIV related activities. This research strives to assess the consequences of anti-retroviral therapy on PLR, to know whether there is an important link existing between the HIV viral load and PLR and ascertain if the consequence is maintained for up to 6 months into cART.

There is an obvious link between PLR aggregation and inflammation pathways. They are seen as tools used to predict death related cases in disease conditions. PLR is also linked to cardiovascular issues and death in people with myocardial infarction and serious cases of neoplasm [16].

PLR is known to contribute to many disease conditions [17, 18]. During inflammation cytokines are produced which raise great amount of platelets [19]. These platelets come in great and different sizes [20, 21].

Vascular ischemic is caused largely by thrombocytosis while thrombocytopenia is linked to raised levels of inflammatory predictors in plasma according to Zetterberg *et al*. [22] and to the danger of acquiring AIDS and non-AIDS issues like cancer and cardiovascular issues according to Li *et al*. [23]; Wang *et al*. [24]. Whether platelet values are low or high, a strong link exists between it, HIV and non-HIV cases, basically cancer associated HIV conditions [25].

For about 10 years running, PLR has become a global predictor of different malignant, prothrombotic, and metabolic conditions [23, 24]. Its unsteady nature may be explained in line with the basic numerous immune dysfunction.

Alterations in the values of PLR, has a strong link with systemic dysfunction, especially NLR. In other to establish systemic inflammation before clinical judgment can be made, PLR is preferred to platelet or lymphocyte values.

2. Materials and Methods

2.1. Study Design

The study was carried out in three phases viz, Baseline: Samples were taken from study subjects who have just been confirmed HIV positive and enrolled in ART clinic. Subjects commenced ART treatment after sample collection. Follow-up 1 with ART: Samples were collected after three months of ART commencement. Follow-up 2 with ART: Samples were collected after six months of commencement. In course of the study, 40 subjects' samples were analysed at different times: baseline (before ART commencement), 3 months (after ART commencement) and 6 months (after ART commencement) for viral load, haematological parameters and fibrinolytic markers bringing it to a total of 120 samples.

2.2. Study Area

The research was done in Rivers State University Teaching Hospital, Port Harcourt, Rivers State, Nigeria. Geographically, the location of Rivers State is Latitude 4°31′ - 5°31′ and longitudinally, it maintains 6°30′- 7°21′. Rivers State University Teaching Hospital, Port Harcourt is a 346 bed specialist hospital owned by the Government of Rivers State.

2.3. Study Population

The study lasted for a period of six months within which the sum total of forty naive anti-retroviral therapy HIV positive subjects attending RSUTH were enrolled. 14 males and 26 female aged 20-45 years. These patients were prospectively assessed for their viral load and haematological parameters, within a period of 6 months of follow up which comprised of baseline, three months and six months respectively. In other to obtain demographic characteristics, questionnaire was administered to every patient enrolled into the study and before their blood was collected their informed consent was sought and got.

2.4. Eligibility Criteria

The criteria used to include largely depended on confirmed cases of HIV positive subjects, only ART naive patients who were recently diagnosed and confirmed positive to HIV, only subjects within the age bracket of 20-45 and Patients enrolled into Art clinic after confirmation of HIV status. The criteria used for exclusion depended on unconfirmed HIV positive subjects, those (patients) who are not willing to be enrolled into ART clinic after ascertainment, Patients not up to 20 years, HIV positive subjects above 45 years and those who have commenced ART.

2.5. Ethical Consideration

Ethical clearance to conduct academic research was obtained from ethical committee of the Rivers State Ministry of Health.

2.6. Blood Sample Collection and Processing

A total amount of 6ml of blood was taken from each patient through venous puncture, 4.0 mL was put into EDTA anticoagulant bottle for viral load testing and 2.0 mL was put into another EDTA bottle for haematological investigations.

2.7. Determination of Viral Load Values Using the Cobas® Ampliprep/cobas® taqman® 96 (Real Time PCR) Procedure

Procedures for Start up were carried out and loading of reagents into the COBAS® AmpliPrep Instrument. Samples were brought to room temperature after removal from storage. Consumables were loaded on the COBAS® AmpliPrep Instrument. Orders were made and sample racks were loaded into the COBAS® AmpliPrep Instrument. Activation of the start button of the COBAS® AmpliPrep Instrument was made. Results were reviewed and accepted by using the AMPLILINK software.9.

2.8. Determination of Haematological Parameters by Sysmex Xp-300 Haematology Auto-Analyser, Model NO: XP-300 KOBE Japan

The haematological parameters investigated include haematocrit, haemoglobin, red blood cells, platelets, white blood cell, neutrophils, MXD (The MXD comprise of Basophils, Eosinophils and Monocytes generated by a three-part automated haematology analyzer).

2.9. Principle

Automated analyzer was used for estimation of full blood count by means of whole blood. Whole blood was aspirated through the probe of the sample into the sample rotor valve; 6µl of blood calculated by the sample rotor valve was moved to the white blood count (WBC) transducer chamber including 1.99 ml of diluent. The solution reacts for about 10 secs, red blood cells (RBC) were hemolyzed and platelet gets smaller with WBC membrane remaining same. In same vein, hemoglobin was changed into red colored met-hemoglobin. Approximately 1.0 ml was transferred to the HGB flow cell from the diluted/hemolyzed sample in the WBC transducer chamber. 500µl of the sample in the WBC transducer was aspirated by the aperture. The pulses of the blood cells when passing through the aperture are determined by the DC detection method. In the HGB flow cells, 555nm wavelength beam irradiated from light emitting diode (LED) was added to the sample in the HGB flow cell. Concentration of this sample measured as absorbance. This absorbance was evaluated with that of the diluent only that was estimated prior to the adding of the sample, hence measuring HGB (Hemoglobin level). CELLPACK is normally used to dilute the effect of the blood sample earlier to 1:26.

2.10. Procedure

After allowing samples to mix for 10 minutes in the mixer, the power switch was turned on. Self-check, automatically performance of auto-rinsed and background check were made. Introduction of control samples were made into the instrument through the probe. While sample were introduced through the probe with a gentle tap on the start button for easy up take of sample. A double buzzer sound was heard (beep, beep), and analysing was displayed and the immediate removal of the sample. Test result was displayed on the LCD screen.

Data generated was analyzed using calculations of simple percentages and Pearson correlation analysis to determine the Relationship between Platelet/Lymphocyte ratio and Fibrinolytic markers.

3. Results

3.1. Demographic Characteristics of the Study Population

A total of 40 patients were recruited, with a mean age of 36.20 years, 14 (35%) of them were males and 26 (65%) were females. Details are shown in Table 1.

Table 1. *Social Demographic Characteristics of the Study Population.*

Variable	Frequency (n)	Percent (%)
Sex		
Males	14	35.0
Females	26	65.0
Age Group		
≥25	3	7.5
26-35	11	27.5
≤36	26	65.0
Mean Age: 36.20		

The relationship between PLR and PAI-1 is shown on Table 2 below; it indicates a moderate negative correlation, which implies that an increase in platelet/lymphocyte ratio leads to a decrease in Plasminogen Activator Inhibitor – 1 (PAI-1).

Table 2. *Relationship between Platelet/Lymphocyte ratio and PAI-1.*

Variable	Correlation- coefficient	P-Value
Platelet/Lymphocyte Ratio PAI	-0.492	<0.001

The relationship between PLR and D-dimer is shown on Table 3. It is indicative of a weak positive correlation, which implies an increase in platelet/lymphocyte ration leads to an increase in D-dimer.

Table 3. *Relationship between Platelet/lymphocyte ratio and D-dimer.*

Variable	Correlation- coefficient	P-Value
Platelet/lymphocyte Ratio D-dimer	0.249	0.006

Table 4. *Platelet/Lymphocyte Ratio over the Study Period.*

Variable	Mean ±SD	95% C.I. Lower Upper	F-Value	P-Value
Month 0	7.823±2.900	6.896	26.250	<0.001
		8.751		
Month 3	5.648±1.439	5.182		
		6.109		
Month 6	4.721±1.053	4.384		
		5.058		

Platelet/lymphocyte ratio reduced over the study period as shown in Table 4.

3.2. Comparison of the Viral Load over the Study Period

Comparison of the viral load over the study period showed that viral load-significantly reduced in the sixth month when compared with the third month and month 0, as shown in Table 5.

Table 5. *Comparison of the viral load over the study period.*

Variable	Mean	Standard Deviation	95% C.I. Lower Upper	F-Value	P-Value
Month 0	215767.850	360338.040	100526.15	14.293	<0.001
			331009.55		
Month 3	705.650	684.220	486.83		
			924.47		
Month 6	29.330	17.869	23.61		
			35.04		

Table 6. *Hematological parameters of the respondents over the period.*

Variable	Mean ±SD	95% C.I. Lower Upper		F-Value	P-Value
HCT					
Month 0	31.650 ±7.303	29.314	33.986	20.920	<0.001
Month 3	36.435 ±4.291	35.063	37.807		
Month 6	38.960 ±2.707	38.094	39.826		
Hb					
Month 0	9.630 ±2.236	8.915	10.345	30.644	<0.001
Month 3	11.295 ±1.132	10.933	11.656		
Month 6	12.195 ±0.590	12.006	12.384		
RBC					
Month 0	4.073 ±1.050	3.737	4.409	10.637	<0.001
Month 3	4.554 ±0.810	4.292	4.815		
Month 6	4.945 ±0.617	4.748	5.143		
PLT					
Month 0	269.030 ±45.895	254.350 2	83.700	4.846	0.010
Month 3	254.38 ±42.004	240.940	267.810		
Month 6	239.00 ±41.370	225.770	252.230		
WBC					
Month 0	5.015±1.015	4.678	5.352	8.709	<0.001
Month 3	4.535±1.020	4.209	4.861		
Month 6	4.138±0.716	3.909	4.366		
N					
Month 0	47.03±12.099	43.160	50.900	22.554	<0.001
Month 3	39.49±7.439	37.110	41.860		
Month 6	33.93±5.344	32.220	35.630		
L					
Month 0	38.265±11.559	34.568	41.962	25.662	<0.001
Month 3	46.243±6.652	44.115	48.370		
Month 6	51.215±4.661	49.724	52.706		
IXD					
Month 0	13.490±2.093	12.821	14.159	21.533	<0.001
Month 3	14.592±1.020	14.266	14.919		
Month 6	15.565±0.767	15.320 1	5.810		

The result shows that HCT, Hb, RBC, L, IXD levels were significantly higher in the sixth when compared with previous months. Also, PLT, WBC, N had a significantly lower levels in the sixth month.

4. Discussion

The study revealed that an increase in platelet/lymphocyte ratio leads to an increase in PAI-1 which is suggestive of a sign of impaired fibrinolytic activity [26]. While an increase in platelet/lymphocyte ratio leads to an increase in D-dimer which is a pointer to thrombotic event. Reduced PAI-1 is a sign of impaired fibrinolytic activity. Findings from this study, strongly agrees with that of Raffetti *et al*. [15] whose study revealed the estimated values of PLR both at baseline and in course of follow-up, were indicative of high mortality in their study population as well as other studies carried out in patients who were not positive to HIV, revealing the importance of inflammation as prognostic marker in death.

This study also revealed reduction in Platelet/lymphocyte ratio over the study period. However, high and low values of PLR as a biomarker may be the outcome of thrombocytosis and thrombocytopenia. Both of which links to raised conditions, not connected to AIDS according to Li *et al* [23] and Wang *et al*. [24].

This study also correlates with that of Eugenia *et al*. [27] which revealed that value of PLR did not appreciate, but rather maintained low levels in the follow-up period. It was also revealed in their work that values of PLR significantly dropped when therapy was changed. This continued for 1 year, whereas this study showed that PLR continued to drop during follow up period which lasted for 6 months. Reasons for this may, in part, be due to the impact of cART on the progenitor cell line in the bone marrow, which invariably affect their roles as well as functions of the cells they produce, in this case, platelets and lymphocytes. The continued fall in PLR also shows that the body at some point begins to acclimatize with therapy. It could also be that these blood cells dropped in values while responding to the endothelial dysfunction initiated due to cART commencement.

Finally, comparative analysis of viral load over study period revealed remarkable decrease in viral load levels in the sixth month when compared with the third month and at month 0. This aligns with the research performed by Moore - Igwe *et al*. [28], whose experimental subjects gained total viral suppression. Viral suppression is therefore achievable, only in as much as antiretroviral patients will comply completely with therapy through advanced adherence counselling.

Generally, findings from the studies have shown that the correlation between viral load and PLR is significantly positive. The implication of this is that there is a steady balance in the level of viral load and the value of PLR since it is apparent that when viral load is high, the value of PLR rises also. Nevertheless, viral load level and the predictor of inflammation (PLR) reduced immediately cART was introduced. This is premised on solid impact of cART on platelet and lymphocyte producing cells (haematopoietic cells) in the bone marrow by changing their usual role. Nevertheless, the bone marrow becomes normal as the body responds to medication. Hence, PLR positively correlated with the VL at baseline (0.3676), however, there was a negative correlation at 3 months (-0125) and 6 months (-0.028). The PLR did not significantly reduce in the 3rd and 6th month of evaluation after initiation of cART, this suggests persistent inflammation in this group of patients.

There was a statistically significant increase ($p < 0.001$) in the haematocrit by the 6th month on cART. There is firm agreement with the findings of Moore-Igwe *et al*. [29]. The use of antiretroviral drugs (ARVDs), in one of the earlier works done, was reported that therapy boosted the haemoglobin level, which however, has the ability to improve the quality of life despite the side effects [30, 31]). Blockman radically departs from the above opinion by noting in his work that both HIV positive subjects on ARVDS therapy and those not on ARVDS therapy had their heamatocrit value reduced such that they developed mild anaemia [32].

5. Conclusion

From this work it is clear that all the cases in this regard, confirm the fact that cART remarkably drops the viral load and inflammation in HIV positive subjects, nevertheless, it also shows that a low-level inflammation continues which probably leads to chronic inflammatory state, morbidity and mortality in this group of patients.

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