Original Research Article

The Clinical Utility of Platelet and Platelet Biomarkers in the Management of HIV Infection

ABSTRACT

Background: Human immunodeficiency virus (HIV) infection is one of the world's public health challenges that affect the immune system as well as the haemostatic functions. **Aim:** This study assessed the platelet count, plateletcrit (PCT), platelet distribution width (PDW) and mean platelet volume (MPV) in HIV patients on ART and ART-naïve attending HIV clinics at AE-FUTHA – Nigeria. **Method:** This cross-sectional, descriptive and analytical study was conducted on HIV patients. Written informed consent was obtained from each participant/guardian and study protocol was approved by the hospital's Research/Ethics Review Committee. A total of 57 subjects (age; 17-38 years) were selected and grouped as follows; group I, age/sex-matched apparently healthy control (N=19), group II; HIV patients on ART (N=19) and group III; HIV patients ART-naïve (N=19). The HIV status of participants was determined using WHO serial testing algorithm and confirmed by Western blot. The platelet counts (PC)and platelet indices were determined using 5-part haematology analyzer (HCT Mindray BC 5150 Auto Hematology). Data obtained were analyzed using Statistical Package for Social Sciences (SPSS) version 22 and statistical significance was set at $p < 0.05$. **Results:** There were consistent significant decrease ($P<0.05$) in mean platelet counts ($10^{9/L}$); of 243.11±68.46, 191.53±76.58 and167.89±58.71 for control, HIV patients on ART and HIV patients ART-naïve respectively. There were significant differences in PDW, PCT and MPV among the three groups. The MPV showed consistence decrease in mean values when patient groups were compared with control. No significant relationship was observed between platelet count and PDW and MPV among the three groups. However, there was significant relationship between plateletcrit (PCT)) and platelet count of the apparently healthy participants. **Conclusion:** Platelet and platelet indices have prognostic utility in the management HIV patients and should therefore be assessed before enrolment for antiretroviral therapy and periodically during therapy.

Key words: Platelet count, platelet indices, Human immunodeficiency virus, Anti-retroviral therapy

Introduction

Human Immunodeficiency Virus (HIV); the virus that causes AIDS, is a major public health challenge affecting all age groups with medical and social implications. There is growing recognition that progression and management of HIV- infection is bidirectional not only affecting the immune system but also affects the coagulation system [1]. Platelet is of immense importance in haemostasis[2] and help to regulate the inflammatory events. Inflammation and haemostasis are intricately linked and are often activated concomitantly. Platelets activation is enhanced with the release of inflammatory mediators.

While the antiretroviral therapy has improved the overall disease-free survival of patients with HIV infection, studies indicate greater risk of thromboembolic event (VTE) and myocardial infarction [3]. The mechanism(s) to this is suggested to be due to possible thrombotic risk factors [6, 7]; hence this study.

Platelets and platelet indices; platetecrit (PCT), membrane platelet volume (MPV) and platelet distribution width (PDW) have been studied as inflammatory markers in many diseases [4-6]. In HIV infection; cardiovascular disease and thrombotic events are getting common and emerging as major cause of mortality and morbidity [8]. The role of activated platelets is suggested to be associated with this event.

Haematology autoanalyzer has long been used to assess haematological parameters especially the absolute values with little or no attention to the platelet indices (PI) which is now being recognized as surrogate markers of platelet activation. This allows for easy assessment of platelet indices in complete blood count with no extra cost. Therefore, the clinical implications of these markers should be taken into cognizance in the management of HIV infection.

The plateletcrit, (PCT), the mean platelet volume (MPV) and the platelet distribution width (PDW) are the parameters of complete blood count. Studies associating theses platelets markers to diseases indicate that they have diagnostic and prognostic utility [9-14]. Plateletcrit (PCT) just like haematocrit is the volume occupied by platelets in the blood as a percentage and calculated according to formula PCT = platelet count x MPV/10,000. Changes in PCT values has been found to be associated with clinical conditions; long lasting inflammatory conditions, ulcerative colitis and low PCT has be observed in thrombocytopenia and low-grade inflammatory condition, among others.

Mean platelet volume (MPV) represents an index of platelet function and changes when platelet production increases. An increase in “young” platelets usually influenced by cytokines, such as IL-3, IL-6 or TNF-α would possibly lead to an aggregation of large platelets which could lead to higher MPV values. The MPV is found to be elevated in patients suffering from type 2 diabetes mellitus, cancers, acute surgery conditions and acute appendicitis [12, 15, 16]. In Covid-19 which is characterized by heightened inflammation, dysregulated immunity, and thrombotic events; platelet number, size, and maturity have been associated with increased critical illness and all-cause mortality among hospitalized patient [18].

Platelet distribution width (PDW) reflects variability in platelet size and is considered a marker of platelet immune and coagulation functions and activation. A high PDW means that platelet size varies greatly, a clue that there is platelet activation and has been associated with vascular diseases, acute pancreatitis [19] and certain cancers and in distinguishing thrombocythaaemia from reactive thrombocytosis. Activated platelets have been found to enhance cancer progression and metastasis [20] by inducing tumour growth, epithelial-mesenchymal transition and invasion. The PDW has been found to be associated with patient's survival and as independent risk factor for prognosis of melanoma and breast cancer [21]. An increasingly body of evidence has identified the involvement of activated platelets in melanoma. Platelet-derived growth factor (PDGF) secreted by melanoma cell could stimulate the development of tumor stroma and angiogenesis.

The mean platelet volume (MPV) is currently being recognized as an inflammatory marker in several diseases [22-25]. The MPV changes when the platelet production increases and represents an index of platelet function. Studies associate clinical utility of MPV in appendicitis [24], pelvic inflammatory disease [25], rheumatoid arthritis, ankylosing spondylitis and emergency non-traumatic abdominal surgery [26].

In Nigeria under The AIDs Prevention Initiative (APIN), the use of highly active antiretroviral therapy (HAART) has resulted in a significant reduction in the morbidity and mortality related to AIDS [27]. HAART is defined as the concurrent use of a combination of three or more ARV drugs to suppress HIV replication and represents the current standard of care of antiretroviral therapy (ART) for HIV-infected patients [28]. In our centre the combination of Zidovudine + lamivudine + nevirapine is commonly used. This prevents treatment failure and with minimal side effects

Antiretroviral therapy (ART) as well as some other drugs is implicated in the alteration of platelet reactivity, and as a consequence, patients living with HIV may be at an increased risk of cardiovascular disease (CVD). Bogani *et al*., (2020) [29] observed that the levels of platelet activation were elevated in treatment-naïve HIV-infected patients, and these persist during successful ART and suggested further studies to assess the clinical relevance of monitoring the levels of platelet activation in HIV-infected patients on ART. It will be necessary therefore to study diagnostic and prognostic utilities of theses platelet indices in HIV infection.

METHODS:

Subjects and Sampling

This cross-sectional, descriptive and analytical study was conducted on HIV patients that presented at Alex Ekwueme University Teaching Hospital, Abakaliki between February 2021 to May; 2022. Written informed consent was obtained from each participant and study protocol was approved by the hospital's Research/Ethics Review Committee. Strict anonymity was observed throughout the study and sample size calculated using the method of Cochran (1977)[30].

A total of 57 subjects (age between 17 - 38 years) were recruited and grouped as follows; group I Age/sex-matched apparently healthy control (N=19), group II; HIV positive patients on ART (N=19) and group III; HIV positive patients ART-naïve (19). HIV patients with co-morbidity

and with any other inflammatory conditions were excluded. Two milliliters of blood were collected from each participant and adequately dispensed into EDTA bottle for haematological analysis. All analysis was done without preservation and not more than 1 hour after collection.

Measurements of variables:
Demographic characteristic of participants was captured using pretested questionnaire. The HIV status of participants were done using WHO serial testing algorithm (Determine, Unigold and Stat-Pak HIV 1/2 test kits used as the first, second and tie-breaker respectively) as reported by Akinbami *et al*., 2010 [31] and confirmed by Western blot. The platelet counts (PC), platelet distribution width (PDW), plateletcrit (PCT) and mean platelet volume (MPV) were determined using 5-part haematology analyzer (HCT Mindray BC 5150 Auto Hematology). Data were analyzed using Pearson correlation and Student T-test, adapted from Statistical Package for Social Sciences (SPSS) version 22 and Microsoft excel software. Statistical significance was set at $p < 0.05$.

RESULTS:

Table 1 shows the demographic characterization of participants. Majority of the participants 33 (57.7.9%) were females and out of these, greater proportion 12 (63.2%) were female that were HIV positive but not on ART, while majority of the male participants 9 (47.4%) were in the control group (HIV negative participants). Their age group shows that majority 30 (52.6%) were of age 24years or below, while 27 (47.4%) were above 24 years of age. There was no significant difference observed in the gender distribution (Chi square = 0.432, P = 0.806 >0.05) and age group (Chi square = 1.689, P = 0.430 > 0.05).

There were consistent and significance differences (P<0.05) in mean values of platelet counts from control (mean±SD = 243.11±4$\times 10^9/L$), HIV+ on ART (mean±SD = 191.53±76.58$\times 10^9/L$), and HIV+ ART-naive (mean±SD = 167.89±58.71$\times 10^9/L$)(Table 2). The comparison of platelet indices (PDW, PCT, and MPV) is presented in Table 3.There were significant differences in PDW, PCT and MPV among the three groups (P < 0.05). The MPV showed consistence decrease in mean values from control (mean±SD = 10.41±0.58fl), HIV+ on ART (mean±SD = 9.70±0.94 fl), and HIV+ ART-naive (mean±SD = 8.11±0.92 fl) respectively.

The relationship between platelet count ($\times 10^9/L$) and platelet indices (PDW, PCT, MPV) is presented in Table 4. No significant relationship (P>0.5) was observed between platelet count and PDW and MPV (P > 0.05) among the three group of participants. However, there was significant relationship between plateletcrit (PCT)) and platelet count of the apparently healthy participants (control group), (R = 0.512, t = 2.396, P = 0.030< 0.05). Male/female and age relationship (Tables 5 & 6) between platelets and platelets indices showed no significant difference.

Table 1: Socio-demographic characteristics of the participants

Characteristics	Control (n=19)	HIV+ on ART (n=19)	HIV+ ART-naive (n=19)	Total (n = 57)	Chi Square	P-Value
Sex						
Male	9 (47.4)	8 (42.1)	7 (36.8)	24 (42.1)	0.432	0.806
Female	10 (52.6)	11 (57.9)	12 (63.2)	33 (57.9)		
Age Group (Years)						
<=24	10 (52.6)	8 (42.1)	12 (63.2)	30 (52.6)	1.689	0.430
Above 24	9 (47.4)	11 (57.9)	7 (36.8)	27 (47.4)		
Mean (SD)	24.74±4.34	26.16±6.87	24.32±5.55	25.07±5.64		

Table 2: Comparison of Platelet count ($\times 10^9/L$) of the participants according to the control, HIV+ on ART and the HIV+ ART-naïve.

Group	Range	Mean	Std. Dev	F	P-Value
Control (n = 19)	166-422	243.11	68.46	6.023	0.004*
HIV+ on ART (n = 19)	128-471	191.53	76.58		
HIV+ ART-naive (n = 19)	96-333	167.89	58.71		
Total (N = 57)	96-471	200.84	74.18		

* Significant

Table 3: Comparison of platelet indices (PDW, PCT, MPV) of the participants according to the control, HIV+ on ART and HIV+ ART-naive

Group	Range	Mean	Std. Dev	F	P-Value
PDW (%)					
Control (n = 19)	15.0-16.6	15.93	0.32	30.181	0.000*
HIV+ on ART (n = 19)	15.4-16.6	15.93	0.41		
HIV+ ART-naive (n = 19)	8.9-16.2	12.19	2.91		
Total (N = 57)	8.9-16.6	14.68	2.45		
PCT (ml/l)					
Control (n = 19)	1.48-2.53	1.92	0.33	5.566	0.006*
HIV+ on ART (n = 19)	1.49-4.10	2.51	0.76		
HIV+ ART-naive (n = 19)	1.47-3.70	2.07	0.52		
Total (N = 57)	1.47-4.10	2.17	0.61		
MPV (fl)					
Control (n = 19)	9.2-11.5	10.41	0.58	38.016	0.000*
HIV+ on ART (n = 19)	8.6-11.4	9.70	0.94		
HIV+ ART-naive (n = 19)	6.8-9.5	8.11	0.92		
Total (N = 57)	6.8-11.5	9.41	1.27		

* Significant

Table 4: Relationship between Platelet count ($\times \mathbf{10^9/L}$) and platelet indices (PDW, PCT, MPV) of the participants according to the control, HIV+ on ART and the HIV+ ART-naïve.

Dependent Variable = Platelet count ($\times \mathbf{10^9/L}$)				
Red Cell Indices	R	Predicting Equation	t	P-Value
PDW (%)				
Control (n = 19)	0.200	$= 3.552 + 2.601(PDW)$	0.842	0.412
HIV+ on ART (n = 19)	0.175	$= 4.889 + 2.616(PDW)$	0.733	0.473
HIV+ not on ART (n = 19)	0.248	$= 56.90 - 0.241(PDW)$	1.057	0.305
PCT (ml/l)				
Control (n = 19)	0.204	$= 50.004 - 2.606(PCT)$	-0.858	0.403
HIV+ on ART (n = 19)	0.350	$= 53.711 - 2.947(PCT)$	-1.542	0.141
HIV+ not on ART (n = 19)	0.512	$= 48.357 + 2.780(PCT)$	2.396	0.030*
MPV (fl)				
Control (n = 19)	0.046	$= 48.474 - 0.334(MPV)$	-0.191	0.851
HIV+ on ART (n = 19)	0.483	$= 15.516 + 3.200(MPV)$	2.277	0.036
HIV+ not on ART (n = 19)	0.451	$= 42.700 + 1.387(MPV)$	2.085	0.053

* Significant

Table 5: Comparison of the sex matched relationship between platelet count ($\times 10^9/L$) and platelet indices (PDW, PCT, MPV) of the participants according to the control, HIV+ on ART and the HIV+ ART-naive

Group	Platelet Indices	Gender Female R	P-Value	Male R	P-Value
	PDW (%)				
Control (n = 19)		0.482	0.159	0.035	0.922
HIV+ on ART (n = 19)		0.359	0.278	-0.201	0.633
HIV+ not on ART (n = 19)		-0.408	0.188	0.453	0.307
	PCT (ml/l)				
Control (n = 19)		0.018	0.961	0.039	0.922
HIV+ on ART (n = 19)		-0.254	0.450	-0.148	0.726
HIV+ not on ART (n = 19)		0.402	0.196	0.498	0.314
	MPV (fl)				
Control (n = 19)		0.489	0.152	-0.613	0.079
HIV+ on ART (n = 19)		-0.027	0.938	-0.147	0.729
HIV+ not on ART (n = 19)		-0.294	0.353	-0.710	0.074

* Significant

Table 6: Comparison of the age matched relationship between Platelet count ($\times 10^9/L$)and platelet indices (PDW, PCT, MPV) of the participants according to the control, HIV+ on ART and HIV+ARTnaive.

Group		Age <=24years		25 years & above	
	Platelet Indices	R	P-Value	R	P-Value
	PDW (%)				
Control (n = 19)		0.395	0.258	-0.178	0.647
HIV+ on ART (n = 19)		-0.094	0.825	-0.451	0.164
HIV+ not on ART (n = 19)		-0.143	0.658	-0.032	0.946
	PCT (ml/l)				
Control (n = 19)		0.362	0.465	-0.284	0.458
HIV+ on ART (n = 19)		-0.291	0.484	0.024	0.944
HIV+ not on ART (n = 19)		0.381	0.248	0.231	0.619
	MPV (fl)				
Control (n = 19)		0.346	0.328	-0.615	0.078
HIV+ on ART (n = 19)		0.599	0.116	-0.582	0.060
HIV+ not on ART (n = 19)		-0.143	0.658	-0.692	0.085

* Significant

DISCUSSION:

Thrombocytopenia and platelet dysfunction are frequent complications of viral infections [32] suggestive of evidence that interaction of platelets with viruses is an important pathophysiological phenomenon. Mechanisms of platelets destruction involve; immunological platelet destruction, inappropriate platelet activation and consumption and impaired megakaryopoiesis. Thrombocytopenia and platelet dysfunction has been observed in HIV infection [33] and other diseases [26, 34].

In this study, we evaluated the platelet count and platelet indices in HIV positive individuals on ART and HIV positive ART-naïve individuals. The mean platelet count decreased consistently and significantly from control to ART-naïve individuals respectively. This is in line with our previous study [31] and that of other researchers [32, 33, 35] suggestive of possible immunological shortening of platelet life span, splenic sequestration and suppressed megakaryopoiesis.

Platelet indices: plateletcrit (PCT), mean platelet volume (MPV) and platelet distribution width (PDW) have been widely studied and found to have diagnostic and prognostic utility [9, 19,22, 36]. This study observed significant differences in MPV, PCT and PDW when the two patient groups were compared with control. The MPV decreased significantly from apparently health control to HIV+ ART-naïve. This is in line with the work of previous researchers suggesting further the clinical implication in HIV infection [37, 38]. Though decreased MPV was observed in this study; the work of Klovaite et al., (2011)[37] observed high MPV in myocardial patients. The study (ibid) also observed association of high MPV with worse survival outcome in Sudanese HIV-infected patients in disagreement with the present study. The work of Mena et al., (2011)[39] also is in disparity with our study with finding of fundamental increment in MPV during course of asymptomatic HIV infection. Low but not high MPV was previously reported [40] in a large cohort group of HIV-infected women. The report is in line with our findings, despite larger sample size, ethnic/racial differences and gender diversity. Improving MPV in survival anticipation in HIV was also documented [41].

Mean platelet volume has been found to be early indication marker for activated platelets. Studies suggest that bigger platelets are more metabolically and enzymatically more dynamic than little platelets and arrange complex angiogenic reactions through various mechanisms [37]. Low MPV observed in some diseases associated with bone marrow depression therefore may be because the fact that the size of immature thrombocytes is larger than that of senescent thrombocytes. Hence low MPV generally marks marrow depression, including aplastic anaemia, whereas higher MPV generally denotes high destruction in diseases such as immune thrombocytopenic purpura, preeclampsia, viral infection, and sepsis. An increase in “young” platelets usually influenced by cytokines, such as IL-3, IL-6 or TNF-α would possibly lead to an aggregation of large platelets which could lead to higher MPV values. In parity with our study the MPV elevation has been found in patients suffering from type 2 diabetes mellitus, cancers, acute surgery conditions and acute appendicitis [11, 14, 15]. In Covid-19 which is characterized by heightened inflammation, dysregulated immunity, and thrombotic events; platelet number,

size, and maturity have been associate with increased critical illness and all-cause mortality among hospitalized patient [17].
Anti-retroviral therapy (ART) has been known to improve immunity and haematopoiesis [42] and from this study it appears that improvement on MPV and PDW levels will improve anticipated risk and of help in the management of HIV infection and AIDS.

CONCLUSION:

The platelet count, PDW and MPV decreased significantly in HIV patients compared with apparently healthy control group. The HIV patients not on ART presented with lower mean values in MPV, PDW and PCT indicating that HIV and ART have effects on the platelets and platelet indices and should be used as markers in the management of HIV infection.

RECOMMENDATION:

HIV-positive subjects should therefore be assessed for platelet and platelet indices before enrolment for antiretroviral therapy and periodically during therapy given the significant changes of theses markers in HIV infection. Prognostic utility of these markers in the management of HIV infection is therefore advocated.
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