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Hemostatic Profile and Associated Factors of Hemostatic Abnormality in Human Immunodeficiency Virus Infected Adults Attending Jimma University Specialized Hospital, Southwest Ethiopia: A Case-Control Study

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Abstract

Background: Human immunodeficiency virus infection has been proposed to inflict an insult on hemostatic system which involves endothelium, platelet and coagulation proteins. Information regarding hemostatic profile in human immunodeficiency virus infected patients is limited and contradicting too.

Method: A case control study was conducted from April to May 2014 in Jimma University specialized hospital, involving 96 HIV infected patients and 96 healthy controls that came consecutively to comprehensive chronic care center and voluntary counseling and testing (VCT) center respectively. Socio demographic and clinical data were obtained using structured questionnaire. For the purpose of hemostasis tests, 2.7ml of venous blood sample was collected in a 3ml citrated (3.2%) vacuum tube. Platelet count and CD4 count was determined from a 3ml EDTA sample. Mixing study was undertaken for prolonged coagulation tests. Data were analyzed using SPSS, version 20.

Result: The mean value of prothrombin time (PT), international normalized ratio(INR), activated partial thromboplastin time(APTT) and fibrinogen level was significantly higher in case group than control ($p< 0.001$, 0.01, <0.001 and <0.001) while mean platelet count was significantly lower in case group ($p<0.0001$). Mixing study showed correction of 35(87.5%) of 40 prolonged PT both in immediate and delayed test while 58(95.1%) of 60 prolonged activated APTT fail to correct in both situations. A CD4 count of less than 200cells/mm 3(AOR=8.8, 95% CI (1.8-42.4)) and HAART (AOR=3.4, 95%CI (1.2-10.1)) use were significantly associated with prolonged PT while a CD4 count of less than 200cells/mm3 (AOR=11.55, 95% CI (1.25-106)) was significantly associated with prolonged APTT.

Conclusion: There was a significant mean difference between case and control groups with respect to PT, APTT, platelet count and fibrinogen level. Direction of the finding points towards presence of inhibitors and factor deficiency which demands in depth investigation and corresponding intervention.

Keywords: Hemostatic profile; Associated factor; HIV; Ethiopia

Introduction

Studies are emerging that shows the interaction between coagulation and inflammation as a response to severe infection or trauma which results in a systemic activation of a coagulation system [1]. Likewise, Human Immunodeficiency Virus infection has been recognized as a prothrombotic condition by which the incidence of thrombotic events in HIV infected patients is rising as suggested in retrospective cohort studies (0.54%, which is 10 times than expected among people without HIV) [2].

Coagulation abnormalities that are described in HIV infection are acquired deficiency state of physiological anticoagulants: protein C [3], protein S [4] and heparin cofactor II [5] with deficiency of protein S being the most consistent observation [4]. Endothelial dysfunction is also evident in HIV infection, HIV replication being an important predictor of endothelial dysfunction [6]. It is also studied that higher frequency of tissue factor expression on monocyte in fresh blood sample from HIV infected persons than in samples from uninfected controls which probably contribute to an increased coagulation tendency [7]. Anticardiolipin antibodies (aCL) and lupus anticoagulant (LA) have also been reported in HIV-infected patients with a prevalence ranging from 7 to 94% and 0 to 72%, respectively [8].

An elevated D-dimer value which is indicative of increased blood coagulation, thrombin formation, and turnover of cross-linked intravascular fibrin, were evident in HIV infection and it is associated with an increased risk of cardio vascular disease according to the SMART (strategy for management of antiretroviral therapy) study [9]. Information regarding hemostatic screening tests which evaluates the integrity of intrinsic, extrinsic and common pathway of coagulation in HIV infected individuals is limited and contradicting. A study in Benin City, Nigeria revealed that prothrombin time (PT) and activated partial thromboplastin time (APTT) were significantly ($p<0.001$) higher in HIV seropositive individuals when compared to seronegative individuals [10]. The same is true for Tehran, Iran study only with respect to PT, but there was no difference between HIV positive and HIV negative individuals with respect to APTT [11]. According to Arildsen et al. a baseline APTT was marginally but not significantly lower in HIV-positive patients vs. controls (30 vs. 32 s,

respectively<0.07) while PT was similar in the two groups throughout the entire study period [12]. In addition to this, there is no study conducted in Jimma, Ethiopia. Thus, the aim of this study was to determine hemostatic profile in HIV infected individuals and compare it with HIV negative controls and to assess associated factors of hemostatic abnormality in HIV positive individuals in Jimma, Ethiopia.

Materials and Methods

Study setting and study participants

A case control study was conducted from April to May 2014 in Jimma University specialized hospital, comprehensive chronic care and training center and VCT center, Ethiopia. A 96 serologically confirmed HIV positive individuals and 96 unmatched HIV negative individuals with negative CRP test with no missing data were included in this study consecutively until the sample size is attained. Pregnant women and those individuals who are on anticoagulant therapy prior to data collection time were excluded in both groups.

Data collection and Laboratory testing

Socio demographic and clinical data were collected using structured questionnaire and checklist. Venous blood sample was collected using vacuum tube of 3 ml sodium citrate (3.2%) for PT and APTT test and 5ml K3EDTA for $CD4^+$ and platelet cell count. Platelet poor plasma was obtained from once-centrifuged (at 1500 g for 15 minute) sample of citrated tube for hemostatic tests. CELL-DYN 1800 (Abbott diag, USA) hematology analyzer was used to determine platelet number while a BD FACSCOUNT system(Becton Dickinson, USA) was used for $CD4^+$ cell count. PT and APTT were analyzed by making use of coagulation analyzer (Ares linear, Spain) while fibrinogen level was determined by PT derived method on the same coagulation analyzer. The APTT reagent was a rabbit brain cephalin with ellagic acid activator which is sensitive to inhibitors of blood coagulation such as lupus inhibitor while reagent of PT was lyophilized thromboplastin of rabbit brain and $CaCl_2$. Immediate and incubated plasma mixing test was undertaken for prolonged PT and APTT. Standard operating procedures and manufacturer instructions were strictly followed throughout the procedures and all reagents were prepared according to the manufacturer's instruction. Quality control run was undertaken for all laboratory tests in this study.

Statistical analysis

Data was coded, entered and cleaned using statistical software (epidata, version 3.1) and then exported to and analyzed with SPSS, version 20 for windows. Frequency and percentage of variables were determined in each group. The two groups were compared with respect to hemostatic profile using Mann-whitney U test. Multivariable logistic regression analysis was used to predict the outcome variable with a P value of less than 0.05 considered as statistically significant.

Ethical consideration

Ethical approval was obtained from Ethical Review Committee of Jimma University, College of Public health and Medical Science. Written informed consent was obtained from each participant after a clear explanation of the purpose, the procedure, benefits and possible discomfort of the study and the right to voluntary participation was given. Any information obtained from participants during the study was kept confidential and abnormal results were communicated to the physicians who were working in the comprehensive chronic care and training center for possible management of the study participants.

Result

Demographic and clinical data

A total of 192 individuals were involved on the study, 96 in each group. Sixty four (66.7%) of the case group were females while 56(58.3%) of control group were females. Majority of case and control groups were within the age range of 25-34, accounting 46(47.9%) and 44(45.8%) respectively (Figure 1). Among case group, 66(68.8%) were HAART initiated and the rest 30(31.2%) were HAART-naïve. Majority of case and control groups were within normal BMI range which accounts 62(64.6%) and 80(83.3%) respectively (Figure 2). Among females of case group, 3 use oral contraceptive while 16 females use oral contraceptive among control group. There were 2 individuals encountered trauma and 1 individual had surgery within the last three month prior to the study among case groups but none was reported in control groups. Current smoker [1] and former smokers [6] were found in case groups but none in control group.

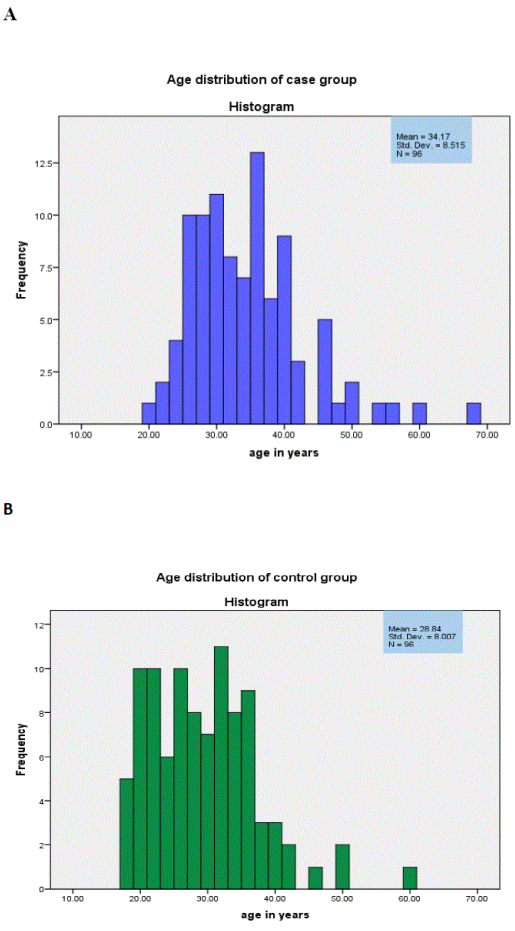

Figure1: Histogram of age distribution for case group (A) and control group (B).

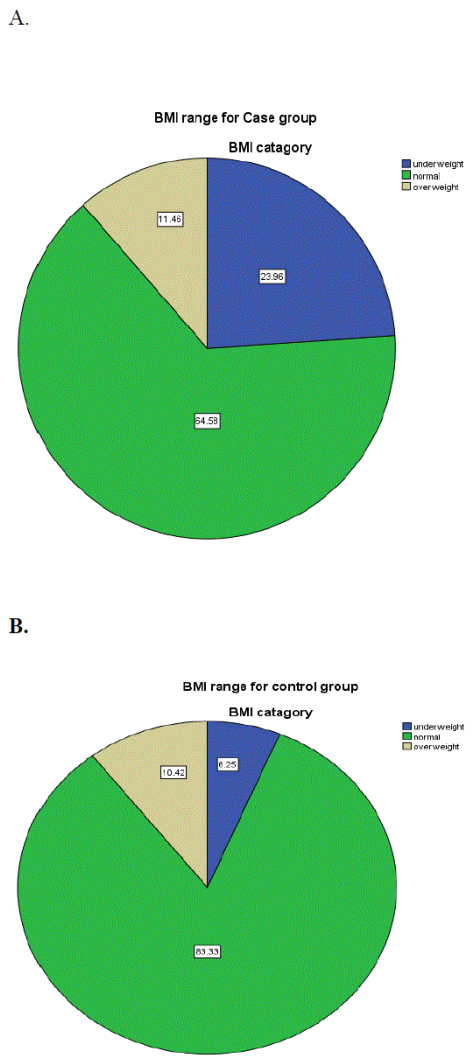

Figure 2: A Pie chart of BMI distribution among case group (A) and control group (B).

Hemostatic profile of study participants

Coagulation analysis showed that PT, APTT and fibrinogen level were higher in case groups than controls. Thrombocytopenia was found to be 1% in case groups and none in control groups (Table 1).There was also a significant mean rank difference between case and control groups with respect to PT, APTT and fibrinogen level (p= 0.004, <0.0001 and 0.001) respectively. Though it is within the normal range, the mean rank of platelet count was significantly low in case groups than controls (p=<0.0001) (Table 2). Figure 3 also depicts the difference between case and control groups with respect to different hemostatic parameters.

According to the mixing study, 40 prolonged prothrombin time results were tested with both immediate and delayed mixing study and 35(87.5%) were corrected to reference range in both immediate and delayed time frame. The reverse was true for APTT in which 61 prolonged results tested and 58(95.1%) were not corrected to reference range in both immediate and delayed mixing tests.

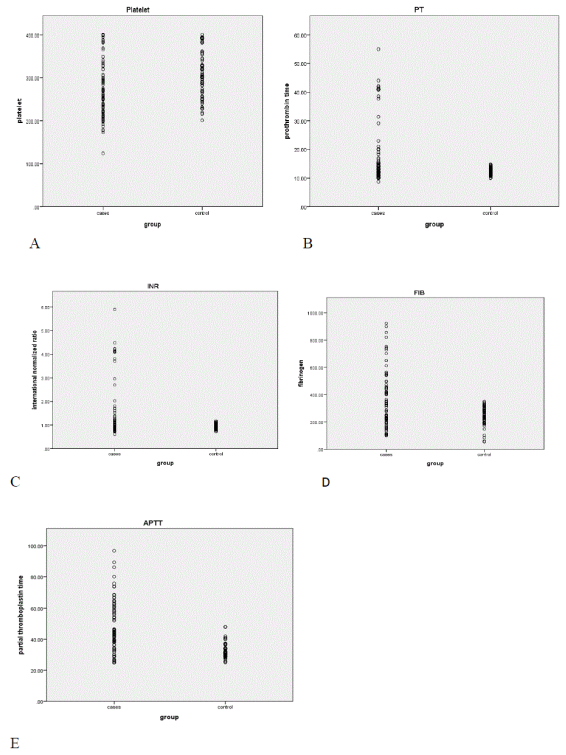

Figure 3: A dot plots for platelet (A), prothrombin time (B), international normalized ratio (C), fibrinogen (D) and activated partial thromboplastin time (E).

	Case group		Control group		
Hemostatic Parameters Status	No	(%)	No	%	Reference ranges
platelets					150-400 K/µl
normal	95	99	96	100	
low	1	1	0	0	
PT					10-13 second

normal	56	58.3	96	100	
prolonged	40	41.7	0	0	
APTT					25-36 second
normal	35	36.5	93	96.9	
prolonged	61	63.5	3	3.1	
Fibrinogen					
low	20	20.8	21	21.9	200-400mg/dl
normal	41	42.7	75	78.1	
high	35	36.5	0	0	

Table 1: Hemostatic parameters in study participants at JUSH chronic care center, southwest Ethiopia, from April to May, 2014.

Variable	Case group		Control group		Normal value
	Median	Interquartile range	Median	Interquartile range	
Platelet (K/µl)	257	100	315.5	78	150-400
PT (second)	13	4.8	12.3	1.7	10-13
INR	1	0.46	0.93	0.16	0.8-1.2
APTT(second)	42	26	31.3	4.15	25-36
Fibrinogen (mg/dl)	320	232	241.5	72.75	200-400
PT: Prothrombin Time; INR: International Normalization Ratio; APTT: Activated Partial Thromboplastin Time					

Table 2: Comparison of mean rank of coagulation parameters of case and control groups using Mann-Whitney U test at JUSH chronic care center, southwest Ethiopia, from April to May, 2014.

Factors associated with hemostatic abnormality

Association of predictors with PT and APTT was analyzed for HIV positive (case) group by making use of multivariate logistic regression. A blood pressure, HAART use, CD4 count, BMI, opportunistic infection and stages of the disease were the variables that were included in the adjusted models with P value ≤0.2 in a bivariate analysis. $CD4^+$ count of less than 200 cells/mm^3 (AOR=8.8, 95% CI (1.8-42.4)) and HAART initiation (AOR=3.4, 95%CI (1.2-10.1)) were significantly associated with prolonged PT (Table 3) while a $CD4^+$ count of less than 200cells /mm^3 (AOR=11.55, 95% CI (1.25-106)) was correlated with prolonged APTT (Table 4). There was no significant association for platelet count and fibrinogen level with any of the predictors which are assessed in this study.

Variables	Categories	COR(95% CI)	P-value	AOR(95%CI)	P-value
Sex	Male	0.63(0.26-1.52)	0.307		
	Female				
BP	Yes	0.42(0.11-1.68)	0.221	0.38(0.085-1.77)	0.222
	No				
OC	Yes	2.82(0.24-32.6)	0.408		
	No				
Age	18-24				
	25-34	1.46(0.26-8.39)	0.668		
	35-44	2.34(0.39-13.9)	0.350		

	45-54	3.13(0.38-25.6)	0.288		
	55-64	2.50(0.10-62.6)	0.577		
BMI	Underweight				
	Normal	0.78(0.30-2.06)	0.627		
	Overweight	0.41(0.08-1.95)	0.261		
HAART	Yes	3.29(1.24-8.7)	0.017	3.4(1.2-10.1)	0.028
	No				
OI	Yes	1.48(0.48-4.6)	0.496		
	No				
Disease stage	I				
	II	0.75(0.29-1.9)	0.55		
	III	1.79(0.37-8.8)	0.47		
	IV	1.0(0.2-4.96)	0.99		
CD4count	≥500				
	200-499	1.57(0.6-4.0)	0.34	1.2(0.4-3.2)	0.781
	<200	8.8(2.0-38.4)	0.004	8.8(1.8-42.4)	0.007

COR: Crude Odds Ratio; AOR: Adjusted Odds Ratio; BMI: Body Mass Index; BP: Blood Pressure; OC: Oral Contraceptive; OI: Opportunistic Infection; HAART:Highly Active Antiretroviral Therapy; *Reference row

Table 3: Association of predictors with prolonged PT at JUSH chronic care center, southwest Ethiopia, from April to May, 2014.

Variables	Categories	COR(95% CI)	P-value	AOR(95%CI)	P-value
Sex	male	0.94(0.39-2.52)	0.88		
	Female(ref)*				
BP	yes	0.53(0.16-0.78)	0.3		
	No(ref)*				
OC	yes	1.09(0.09-12.74)	0.94		
	No(ref)*				
Age **BMI** **HAART**	18-24(ref)* 25-34	0.97(0.19-4.86)	0.97		
	35-44	1.18(0.22-6.26)	0.84		
	45-54	121160(0)	0.999		
	55-64	121160(0)	0.999		
	underweight(ref)*				
	Normal	1.45(0.54-3.94)	0.46	0.45(0.15-1.37)	0.16
	overweight	0.37(0.08-1.62)	0.19	0.290.05-1.7)	0.17
	yes	0.32(0.11-0.88)	0.028	0.36(0.09-1.47)	0.16
	No(ref)*				
OI	yes	0.12(0.01-0.87)	0.037	7.66(0.47-125)	0.15

	No(ref)*				
Stage	I(ref)*	1.69(0.65-4.4)	0.28	1.17(0.39-3.5)	0.77
	II				
	III	4.8(0.54-42.6)	0.16	0.51(0.02-13)	0.68
	IV	4.8(0.54-42.6)	0.16	0.75(0.046-12.4)	0.84
CD4count	>500(ref)*				
	200-499	0.98(0.4-2.4)	0.96	1.25(0.4-3.6)	0.67
	<200	9.1(1.1-77.8)	0.044	11.55(1.25-106)	0.031

COR: Crude Odds Ratio; AOR: Adjusted Odds Ratio; BP: Blood Pressure; OC: Oral Contraceptive BMI: Body Mass Index; HAART: Highly Active Antiretroviral Therapy; OI= Opportunistic Infection; *Reference Row

Table 4: Association of predictors with prolonged APTT at JUSH chronic care center, southwest Ethiopia, from April to May, 2014.

Discussion

In this case control study, 192 individuals were involved, 96 in each group. An overall hemostatic abnormality in case groups was higher than the control groups. Prolonged PT was corrected to normal range in case group by mixing test whereas prolonged APTT of case group was not corrected to reference range by mixing test.

A large body of evidence suggest that there is hemostatic abnormality in HIV infected individuals, of which thrombocytopenia is widely spread and best documented [13,14], as well as prolonged APTT [15,16].This study showed significantly higher APTT (P=<0.0001) in case groups than the controls which is concordant with a study in Benin city, Nigeria that showed a significantly higher APTT (P<0.001) among case group [10] and a retrospective study in Korea with higher APTT in HIV positive patients than the reference range [17]. But this study was in contrary to the one done in Denmark which showed a slightly lower APTT at baseline of HIV-positive patients than the controls [12]. Measurement of APTT at baseline may mask the discordance in result of HIV-positive and negative individuals. Majority of the prolonged APTT were not corrected to reference range both in immediate and delayed mixing test in this study which is indicative of non-specific inhibitor [18]. Prolonged APTT, fail to correct both in immediate and incubated mixing with normal pooled plasma is a characteristic of presence of lupus anticoagulant, which is a frequent finding in HIV positive patients [19].

Our study revealed significantly higher PT in case groups than the controls (P=0.004) in such a way that HAART initiation is significantly correlated (P=0.028) with prolonged PT. This study was in agreement with a study done in Benin city, Nigeria which showed significantly higher PT (P<0.001) in HIV-seropositive individuals when compared to seronegative controls [10] and a study in Tehran, Iran which showed that PT in HIV positive group was significantly (P=0.003) higher than HIV negative group [11]. The value of PT was significantly higher (P<0.05) in a study carried out in FMC Owerri, and ananmbra state, Nigeria [20]. However, our finding was discordant with a study in Denmarkwhich showed no difference in terms of PT in both groups throughout the study period [12]. This variation may be explained by the fact that the duration after HIV infection in the former study is by far shorter than this study in which individuals initiated with HAART for a maximum of 3 month were involved in the former study which is a minimum of 9 month in our case with an average duration of 55.7 months. Majority of prolonged PT were corrected to reference range both in immediate and delayed mixing test which is suggestive of deficiency in one or more of extrinsic or common pathway factors since the effect of anti-phospholipid antibody is limited when it comes to PT [14]. The liver has a pivotal role in hemostasis by synthesizing clotting factors and there is evidence that antiretroviral drug-related liver injury is a common cause of morbidity and mortality. Of antiretroviral-related toxicity, liver toxicity is the most frequent complication according to Nunez et al. [21]. Impaired hepatic synthetic ability results in clotting factor deficiency which in turn leads to prolonged PT and APTT [22].

Fibrinogen level in our study is significantly (P<0.001) higher in case groups than controls which was in agreement with study in Netherlands which found higher plasma fibrinogen level in HIV positive patients than negative individuals [23] and Denmark who showed significantly higher (P=0.041) fibrinogen level in treatment-naïve patients than in controls [12]. However our study was different from the study in South Africa which showed no increase in fibrinogen level in HIV-infected subjects as compared to HIV-negative [24]. This difference may be attributed to relatively higher fibrinogen level in black South Africans of African ancestry [25] of the former study, though fibrinogen level is not determined in our locality. As an acute phase protein, fibrinogen level increases in HIV positive individuals that become risk factor when their concentration remains increased for a prolonged time according to Arildsen et al. [12].

Significant decrease in platelet count (P<0.001), though it was within the reference range, is observed in case groups than the controls. Among case groups thrombocytopenia was found to be 1% which is similar with the study in Britain Colombia center for excellence in HIV/AIDS which diagnosed thrombocytopenia in only 0.6% of 5290 HIV infected individuals [26]. But our study is lower than the one conducted in Gonder, who reported 5.9% thrombocytopenia among HAART-naïve HIV patients. High prevalence of thrombocytopenia during pre-HAART era [27], which is true for the previous study may explain the variation. Platelet specific antibody during HIV related ITP (Immune Thrombocytopenia) leads to increased platelet destruction via phagocytosis by macrophages in the spleen and subsequent thrombocytopenia [28]. Molecular mimicry between HIV-gp 160/120 and platelet gpIIb/IIIa may be another mechanism in the immune destruction of platelets in some cases of

HIV-related ITP [29]. Decreased platelet production [24] and infection of the megakaryocyte by HIV [30] is also a cause for thrombocytopenia in HIV infection.

Age of an individual was not significantly associated with both PT and APTT in this study. An increase in rate of venous and arterial thrombosis is associated with advanced age likely due to an increase in fibrinogen, factors VIII and IX, and other coagulation proteins, without a proportional increase in anticoagulant factors [31]. A longitudinal medical record review on 100 medical clinics in nine US cities shows a significant association of thrombosis with an age of 45 or more years [32]. Sex was not significantly associated with PT and APTT in our study. being male has higher risk of developing thrombosis in HIV-infected individuals by which all patients who developed thrombosis are male on the study according to [33]. In this study a CD4 count of less than 200 cells/mm^3 was significantly associated with prolonged PT which is concordant with a study conducted in Benin city, Nigeria which found a significant correlation (P<0.005) between prolonged PT and a CD4 count of less than 200 cells/mm^3 [10]. The same is true for a study in Tehran, Iran by which prolonged PT was significantly associated with a CD4 count of less than 200 cells/mm^3 [11].

A CD4 count of less than 200 cells/mm^3 is also significantly correlated with prolonged APTT which is in line with a study done in Benin city, Nigeria which revealed a significant association between a CD4 count of less than 200 cells/mm^3 and prolonged APTT [10].

Undertaking mixing study, a first line test to discriminate between causes of prolonged clotting time, is a one step forward move as compared to other studies which conducted hemostatic profile in HIV positive individuals. The importance of case-control study design is paramount in the absence of established reference range in our locality to compare hemostatic profile of case group with controls, which is also the strength of the study. As a limitation of this study, Fibrinogen level is determined by PT derived method which is not used without restriction though it may prove to be a useful screening test in a research environment for estimating fibrinogen levels among defined patient groups.

Conclusion

Our finding appreciates the difference in hemostatic profiles (platelet count, PT, APTT and fibrinogen level) of HIV-positive and negative individuals. Using plasma mixing study as a first line discriminating test between causes of clotting time prolongation, presence of non-specific inhibitor is more convincing. Deficiency of one or more of coagulation factors which is evidenced by prolonged PT (corrected to reference range by mixing with normal plasma) in HIV-infected patients should not be overlooked. There is also a significant increase in PT in HAART initiated HIV-positive individuals. Our study also showed a significant association between PT and APTT and a CD4 count of less than 200 cells/mm^3.

Confirmatory tests of immediate acting inhibitors, particularly lupus anticoagulants should be undertaken to confirm the exact cause of prolonged APTT. Investigation of specific coagulation factor/s is also warranted to identify the liable factor/s so as to provide rational care for the patient. The level and function of fibrinogen should also be determined with accurate assay method than the PT –derived method. In this regard, this study can be taken as baseline information for further studies which are aimed at investigating specific markers. Prospective studies are also required to correlate the screening tests with different clinical conditions so that these tests are used to predict particular clinical conditions especially in our setting where screening tests are the only available hemostasis tests. In line with the association of CD4count <200 cells/mm^3 with both prolonged PT and APTT, this study recommends early initiation of HAART to maintain the CD4 number higher.

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