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Plasma levels of fibrinolytic and coagulation biomarkers in HIV-infected individuals on highly active antiretroviral therapy: A case-control study in a Northern Ghanaian population

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Abstract

Background and Aim: Impaired coagulation and fibrinolysis have been implicated in thromboembolism in human immunodeficiency virus (HIV)-infected individuals. This study evaluated the plasma levels of plasminogen activator inhibitor-1 (PAI-1) and coagulation biomarkers in HIV-infected individuals on highly active antiretroviral therapy (HAART).

Methods: This matched case-control study from March to December, 2020 comprised 76 participants: 38 HIV-positive individuals on HAART and 38 apparently healthy HIV-negative individuals as controls. Blood samples were collected for prothrombin time (PT), activated partial thromboplastin time (aPTT), D-dimers, PAI-1, and soluble fibrin monomer complex (SFMC) estimations. The data were analysed using SPSS version 22.0 and statistical significance was set at $p < 0.05$.

Results: Activated partial thromboplastin time was significantly lower in HIV seropositive individuals on HAART compared with HIV seronegative controls (25.90 s vs. 29.0 s, $p = 0.030$); however, PT, SFMC, D-dimers, and PAI-1 were significantly higher among the HIV-seropositive individuals compared with the controls: PT: (16.29 s ± 2.16 vs. 15.15 s ± 2.60, $p = 0.010$), SFMC: [8.53 ng/mL (8.03–9.12) vs. 7.84 ng/mL (7.32–8.58), $p = 0.005$]), D-Dimer: [463.37 ng/mL (402.70–526.33) vs. 421.11 ng/mL (341.11–462.52), $p = 0.015$], and PAI-1: [12.77 ng/mL (10.63–14.65) vs. 11.27 ng/mL (10.08–12.95), $p = 0.039$]. PAI-1 showed a moderate positive correlation with D-Dimer ($r = 0.659$, $p < 0.001$) and SFMC ($r = 0.463$, $p = 0.003$) among HIV-positive individuals on HAART. There was a strong positive correlation between the plasma PAI-1 concentration and the HIV viral load ($r = 0.955$, $p < 0.001$).

Conclusion: HIV-seropositive individuals on HAART have deranged coagulation and fibrinolytic markers. Higher HIV viral load correlates strongly with elevated plasma levels of PAI-1 antigens. Periodic assessment of markers of coagulation and fibrinolysis be included in the management of HIV/AIDS in Ghana.

KEYWORDS
AIDS, D-Dimers, HAART, HIV, PAI-1

1 | INTRODUCTION

Highly active antiretroviral therapy (HAART) improves the quality of lives[1] by suppressing the viral replication and increasing the life span in people living with HIV/AIDS.[2] However, the increased life expectancy of HIV-infected individuals has resulted in a shift in the disease profile of HIV-infected individuals from AIDS related morbidities to conditions mostly associated with the aged in the general population including thromboembolism.[3]

Thromboembolism in HIV-infected individuals occurs as a result of defective coagulation, naturally occurring anticoagulants and/or fibrinolysis.[4] In recent years, there have been increasing reports of age-related morbidities such as thromboembolism in the HIV population. Up to 0.96% of clinical thromboembolic cases and about 17% in autopsy, have been reported in HIV-infected individuals after the introduction of HAART.[5] The risk of developing thrombotic events increases up to 10-fold in HIV-infected individuals on HAART compared to the general population,[6] buttressed by the increasing reports of coagulopathy in the people living with the condition.[7] HIV-infected subjects have significant changes in the plasma antigen and activity levels of procoagulant factors and anticoagulants, with some of these markers remaining abnormally elevated long after antiretroviral treatment.[8] HIV infection is a hypercoagulable state characterized by increase in procoagulants, coupled with decrease in the plasma concentrations of natural inhibitors.[9] This suggests a persistent abnormal coagulation (hypercoagulability) leading to the deposition of excess fibrin in chronic HIV infection.[10]

Physiologically, excess fibrin or unwanted clots are removed from the vascular system by the process of fibrinolysis.[11] Fibrinolysis is a highly regulated system which involves the degradation of the firm fibrin clots by plasmin into fibrin degradation products for onward removal by the reticuloendothelial system, and this provides a balanced haemostasis. Imbalance fibrinolysis either results in excessive, immature removal of clots leading to a bleeding disorder or vascular thrombosis.[4,11]

A major regulator of fibrinolysis is the plasminogen activator inhibitor-1 (PAI-1) which inhibits the activities of tissue plasminogen activator needed to convert plasminogen to plasmin to degrade the fibrin clots.[12] HIV-infection's interactions with the endothelial cells (major producer of PAI-1) causes endothelial dysfunction which consequently increases plasma PAI-1 antigen levels.[13,14] The interactions between HIV therapy (HAART) coagulation and fibrinolytic parameters are illustrated in Figure 1. Also, HIV/AIDS induces inflammatory response in infected persons and this increases plasma

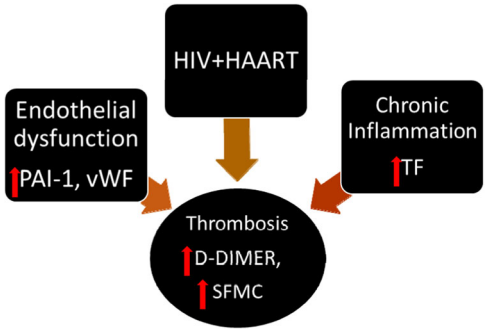

FIGURE 1 Diagram summarizing the pathogenesis of HIV-related hypercoagulability. HAART, highly active antiretroviral therapy; PAI-I, plasminogen activator inhibitor-1; SFMC, soluble fibrin monomer complex; TF, tissue factor; vWF, von Willebrand factor.

antigen levels of PAI-1 as the enzyme is an acute phase protein, rendering patients hypercoagulable.[15,16] Where there is hypercoagulabilty, impaired fibrinolysis further increases the thrombotic risks by several folds.[17]

The potential link between PAI-1 and thrombotic events, have been studied earlier, to assess plasma levels of PAI-1 as risk factor of developing thrombosis in HIV-infected individuals, but found conflicting results.[18–20] Whiles the Guzmán-Fulgencio et al.,[19] suggested a deranged fibrinolytic activity by observing elevated levels of plasma PAI-1 antigens among HIV infected subjects, the Dysangco et al.,[18] study found no significant difference in plasma levels of PAI-1 in HIV infected persons compared to normal HIV-seronegative individuals.

Moreover, there is scarcity of data on plasma levels of PAI-1 antigen and other biomarkers of coagulation in HIV-infected individuals in Ghana. Therefore, this study assessed the plasma concentrations of fibrinolytic and coagulation biomarkers in HIV-individuals on HAART.

2 | MATERIALS AND METHODS

2.1 | Study design and participants

A total of 76 participants were recruited in an age-matched case-control study from March to December, 2020 at the Sexually Transmitted Infections Clinic, Tamale Teaching Hospital, Ghana. A total of 38 HIV-infected individuals on HAART without any documented comorbidity were recruited as cases, while 38 healthy HIV-seronegative subjects were recruited as controls. Sociodemographic data (age, marital status, level of education, gender) were collected from all participants and clinical data (duration of HAART, type of HAART drug combination and viral load) collected from only the cases. The HIV viral load, HAART regimen and the duration on HAART were secondary data obtained from the clinical records using a data extraction sheet.

2.2 | Inclusion and exclusion criteria

The study participants included healthy HIV seronegative individuals and chronically stable HIV seropositive individuals on HAART, aged 18 years and above. Individuals with past history of thrombophilia, systemic diseases, diabetes mellitus individuals, coinfections, post-operative subjects, individuals on anticoagulants, acute infections, clinically staged 3 or 4 (in the course of HAART) and female individuals who were on oral contraceptives were excluded from this study.

2.3 | Sample size determination

The sample size for this study was determined using the formula:

where N is the sample minimum required size, Z_α is the confidence interval (CI) (at 95% CI, $Z_\alpha = 1.96$), Z_β is the expected power of the study (at the power of 80%, $Z_\beta = 0.84$), and δpooled is the average within-population standard deviation to standardize the difference in means.[21] The mean plasma levels of PAI-1 among apparently HIV patients and healthy controls (46 ± 4 vs. 18 ± 0.9), respectively.[22]

$\delta\text{pooled} = \sqrt{\frac{\delta_1^2 + \delta_1^2}{2}}$, where $\delta_1 = 4$ and $\delta_2 = 0.9$, representing the standard deviations for HIV patients and healthy controls as seen in the previous study.[22]

Thus:

$$N = 2\left[\frac{(1.96 + 0.84)4}{\delta\text{pooled}}\right]^2,$$

$$N = 2\left[\frac{(11.2)}{\delta\text{pooled}}\right]^2,$$

$$\delta\text{pooled} = \sqrt{\frac{4^2 + 0.9^2}{2}},$$

$$= \sqrt{8.405},$$
$$= 2.05,$$

$$\text{Hence,} \quad N = 2\left(\frac{11.2}{2.05}\right)^2,$$
$$N = 60.$$

From the above, a total of 60 participants were required for this study, but to take care of a possible 5% fallout, a total of 76 participants were recruited: 38 cases and 38 controls.

2.4 | Ethical consideration

Ethical approval was granted by the Committee for Human Research, Publication and Ethics of the Kwame Nkrumah University of Science and Technology, Kumasi, Ghana (CHRPE/AP/134/19). Permission was obtained from the management of the Tamale Teaching Hospital. Participants, either signed or thumb-printed to affirm informed consent, and were assured of confidentiality of their data.

2.5 | Sample collection and haematological analysis

From each participant, 5 mL of venous blood were drawn and dispensed into K_2EDTA and citrate test tubes, respectively. All samples were collected between the hours of 7:00 and 9:00 GMT. Blood samples were centrifuged at 3000*g* for 15 min and the plasma aliquoted. The aliquoted plasma samples were used for PT, aPTT and the enzyme-linked immunosorbent assay (ELISA) estimation of PAI-1, SFMC and D-dimers. All the samples were immediately analyzed

within 2 h. ELISA samples that could not be analyzed within 2 h were stored at −20°C until it was analyzed.

CLOT2B semi-automated analyzer using Fortress PT and aPTT reagents was used to estimate PT and aPTT (Netherlands, UK). CLOT2B operates on the principle of turbidometry. The sandwiched ELISA technique was used to measure plasma concentrations of PAI-1, D-dimers and SFMC using commercially prepared ELISA kits (BIOBASE, China). All procedures were carried out following the manufacturer's instructions for each analyte. The ELISA plates were washed using BIORAD WASHER while the plasma concentrations of the analytes were determined using microplate reader (MINDRAY MR-96A, C). All ELISA procedures were done at the Methodist Hospital Laboratory, Wenchi, Bono Region, Ghana.

2.6 | Data analysis

The results were analyzed using SPSS version 22.0. Chi-square test was used to compare differences in characteristics between categorical variables. All continuous data were tested for normality using the Kolmogorov–Smirnov and Shapiro–Wilk tests. Parametric data were analyzed appropriately using the Students' *t* test or one-way analysis of variance, while nonparametric data were analyzed using Mann–Whitney Utest and Kruskal–Wallis test. The Spearman's correlation was used to test the relation between two numerical data among the study groups. A $p < 0.05$ was considered statistically significant.

3 | RESULTS

3.1 | Sociodemographic characteristics and clinical data of the study participants

The average age of the study participants was 42 ± 11.2 years with majority (44/57.9%) of them between 30 and 49 years. The ratio of males to females was about 1:3, with females making up over 70% of the total study population. Number of participants on TDF + FTC + EFV, TDF + 3TC + EFV, and AZT + 3TC + NEV were 10 (26.3%), 16 (42.1%), and 12 (31.6%), respectively. Of the 38 HIV-seropositive participants, majority (20/52.6%) had high HIV load and only 6 (15.8%) had their HIV viral load undetected in the plasma (Table 1).

3.2 | Comparisons of plasma PT, aPTT, SFMC, D-dimers and PAI-1 between HIV-infected individuals on HAART and HIV-seronegative participants

Table 2 represents the coagulation system of HIV-infected individuals on HAART using PT, aPTT, and SFMC, as well as the antifibrinolytic agent PAI-1. The aPTT was significantly shortened among the HIV-positive individuals (25.90 s ± 5.91) compared with the HIV-negative controls (29.04 s ± 4.25), and this was statistically significant ($p = 0.010$), but PT was rather prolonged among the HIV-individuals than healthy controls (16.29 s ± 2.16 vs. 15.16 ± 2.60, $p = 0.043$). SFMC was significantly higher among the HIV-infected individuals, as compared to the negative controls [8.53 ng/mL (8.03–9.12) vs. 7.84 ng/mL (7.32–8.58), $p = 0.005$]. Plasma D-dimers concentrations were also significantly higher in the HIV-individuals on HAART compared with HIV-seronegative controls [463.37 ng/mL (402.70–526.33) vs. 421.11 ng/mL (341.11–462.52), $p = 0.015$]. Again, the median PAI-1 levels were higher in the HIV-positive individuals compared with the HIV-negative controls [12.77 ng/mL (10.63–14.65) vs. 11.27 ng/mL (10.08–12.95), $p = 0.039$] as shown in Table 2.

3.3 | Relationship between plasma levels of PAI-1, and PT, aPTT, SFMC and D-dimers among study participants

Table 3 presents the correlational analysis of PA1-1 with the markers of coagulation among the study participants. Among HIV infected

TABLE 1 Socio-demographic characteristics and drug regimen of study participants.

Characteristics	Frequency (*n*)	Percentage (%)
Age (years)		
Mean age (years) ± *SD*	42 ± 11.2	
Age group (years)		
20–29	9	11.8
30–39	24	31.6
40–49	20	26.3
50–59	18	23.7
>59	5	6.6
Gender		
Male	21	27.6
Female	55	72.4
Drug regimen		
TDF + FTC + EFV	10	26.3
TDF + 3TC + EFV	16	42.1
AZT + 3TC + NEV	12	31.6
HIV viral load		
Nondetectable (<50 copies/mL)	6	15.8
Low viral load (50–1000 copies/mL)	12	31.6
High viral load (>1000 copies/mL)	20	52.6

Note: *N* = number of participants, % = percentage of total number.
AZT = Zidovudine, EFV = Efavirenz, FTC = Emtricitabine, NVP = Navirapine, SD = standard deviation, 3TC = Lamivudine; TDF = Tenofevir.

TABLE 2 Comparison of plasma PT, aPTT, SFMC, D-dimers, and PAI-1 between HIV-*infected individuals on HAART and HIV-seronegative controls*.

Parameters	HIV-seropositive ($n = 38$)	HIV-seronegative ($n = 38$)	p-value
PT (s)	16.29 ± 2.16	15.16 ± 2.60	**0.043**
aPTT (s)	25.90 ± 5.91	29.04 ± 4.25	**0.010**
SFMC (ng/mL)	8.53 (8.03–9.12)	7.84 (7.32–8.58)	**0.005**
D-dimers (ng/mL)	463.37 (402.70–526.33)	421.11 (341.11–462.52)	**0.015**
PAI-1 (ng/mL)	12.77 (10.63–14.65)	11.27 (10.08–12.95)	**0.039**

Note: PT and PTT data are presented as mean ± *SD* and SFMC and D-dimers as median (interquartile ranges). A $p < 0.05$ was considered to be statistically significant. PT and aPTT were compared using unpaired Student *t* test, and SFMC, D-dimers and PAI-1 with Mann–Whitney *U* test.

Abbreviations: aPTT, activated partial thromboplastin time; ng/mL, nanogram per milliliter; PAI-1, plasminogen activator inhibitor-1; PT, prothrombin time; s, second; SFMC, soluble fibrin monomer complex.

TABLE 3 Correlation between PAI-1 and other coagulation markers (D-dimers, PT, SFMC, aPTT) among participants.

Biomarkers	HIV individuals on HAART PAI-1	HIV-negative subjects PAI-1
D-dimer (ng/mL)	$r = 0.659$[a]	$r = 0.174$
	$\mathbf{p < 0.001}$	$p = 0.297$
SFMC (ng/mL)	$r = 0.463$[a]	$r = 0.216$
	$\mathbf{p = 0.003}$	$p = 0.193$
aPTT (s)	$r = -0.120$	$r = -0.081$
	$p = 0.473$	$p = 0.629$
PT (s)	$r = -0.007$	$r = 0.110$
	$p = 0.966$	$p = 0.511$

Note: Spearman correlation test was used. A $p < 0.05$ was considered statistically significant.

Abbreviations: ng/mL, nanogram per milliliter; PAI-1, plasminogen activator inhibitor-1; PT, prothrombin time; PTT, partial thromboplastin time; r, correlation coefficient; s, second; SFMC, soluble fibrin monomer complex.

[a]Denotes significant relationship between PAI-1 and other coagulation markers.

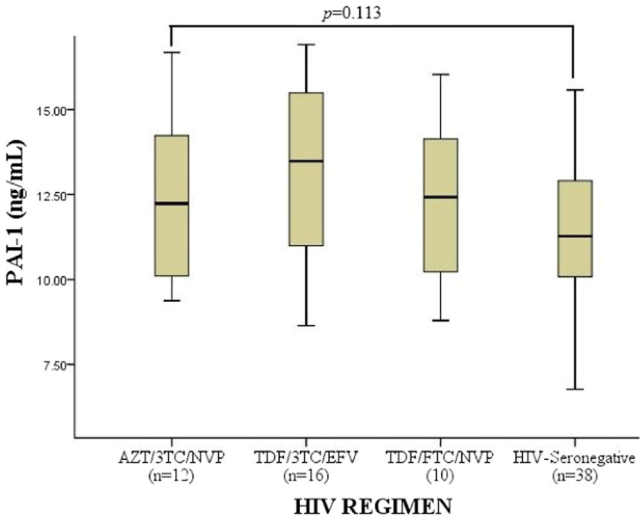

FIGURE 2 Comparison of plasma levels of PAI-1 among HIV-infected individuals on various HAART drug regimens to HIV-seronegative controls. Medians (IQR) were compared using Kruskal–Wallis test. A $p < 0.05$ was considered statistically significant. AZT, Zidovudine; EFV, Efavirenz; FTC, Emtricitabine; HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus; IQR, interquartile range; NVP, Navirapine; PAI-1, plasminogen activator inhibitor-1; 3TC, Lamivudine; TDF, Tenofevir.

individuals on HAART, PAI-I levels showed moderate positive correlation with D-dimer ($r = 0.659$; $p < 0.001$) and SFMC ($r = 0.463$, $p = 0.003$), but not with PT and aPTT. Among HIV-negative controls, PAI-1 did not show any statistically significant correlation with D-dimer, SFMC, aPTT and PT ($p > 0.05$) as shown in Table 3.

3.4 | Comparison of plasma levels of PAI-1 among HIV-infected individuals on various HAART drug regimens to HIV-seronegative controls

Figure 2 compares the plasma concentrations of PAI-1 in the HIV-seronegative controls with HIV-positive individuals on various HAART regimen. Although the plasma levels of PAI-1 were lower in the HIV-negative participants compared to those on the various drug combinations, the difference did not show statistical significance ($p = 0.113$)

3.5 | Correlation between plasma levels of PAI-1 and HIV viral load in HIV-infected individuals on HAART

Figure 3 shows the correlation between plasma levels of PAI-1 and viral load in HIV infected individuals on HAART. There was a strong positive correlation between the plasma PAI-1 concentration and the HIV viral load ($r = 0.955$, $p < 0.001$) as indicated in Figure 3.

3.6 | Assessment of the duration of HAART on plasma PAI-1, D-dimer, SFMC, PT, and aPTT

Table 4 illustrates the effect of HAART duration (categorized as: <1 year, 1–5 years, 6–10 years, and >10 years on the plasma concentrations of coagulation and fibrinolytic markers. Coagulation markers; PT ($p = 0.406$), aPTT ($p = 0.877$), and SFMC ($p = 0.225$,), and markers of fibrinolysis; PAI-1 ($p = 0.895$) and D-dimer ($p = 0.443$) were not statistically different when compared within the durations of HAART therapy among HIV-positive individuals (Table 4).

3.7 | Coagulation and fibrinolytic markers of the HIV participants stratified by viral load status

Table 5 indicates the association between HIV viral load and levels of the coagulation and fibrinolytic markers. PAI-1 levels were significantly higher in HIV-seropositive participants with viral load detected compared to those with undetected viral load, however, PAI-1 was relatively highest in those with high viral load: [viral load undetectable: 9.46 (8.76–9.82) versus low viral load: 11.17 (10.70–12.09) versus high viral load: 14.47 (13.38–16.03), $p < 0.001$]. However, PT, aPTT, SFMC, and D-dimer were not different within the HIV participants with undetectable, low and high viral loads, as seen in Table 5.

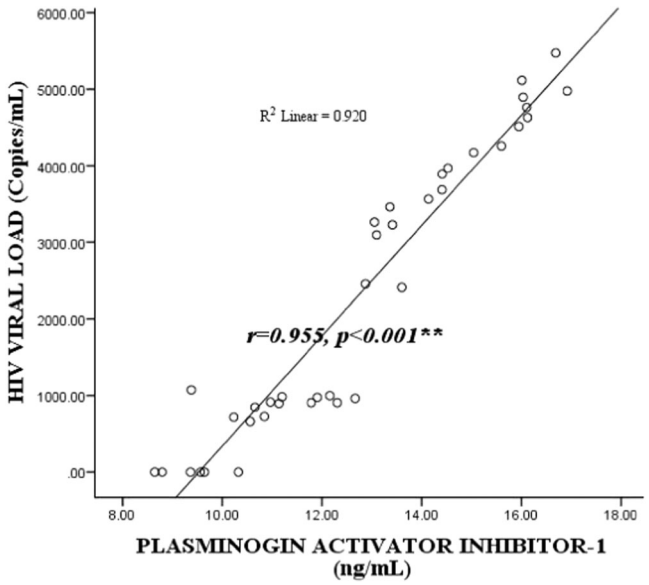

FIGURE 3 Correlation between plasma levels of PAI-1 and HIV viral load in HIV-infected individuals on HAART. A **p was significant at 0.01 level. Spearman correlation test was used to determine the association between the two variables. A $p < 0.05$ was considered significant. HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus, ng/mL, nanogram per milliliter.

4 | DISCUSSION

Cardiovascular and thrombotic disorders have become a major threat to people living with HIV infection after the introduction of the HAART. The current HAART combination effectively reduces viral load by mechanisms including transcription inhibition prolonging the lifespan of HIV infected patients. The hypercoagulable state of HIV/AIDS may result from the associated hyperactivation of procoagulants, reduced levels of naturally occurring anticoagulants[23] and hypofibrinolysis.[12] The associated hypofibrinolysis may be related to a possible elevation of a potent antifibrinolytic agent, PAI-1, induced by the viral disruption of the endothelium. This study assessed the plasma concentrations of fibrinolytic and coagulation biomarkers in HIV-individuals on HAART.

The average age of the study participants was 42 ± 11.2 years with majority within 30–49 years, and this is consistent with the study by Aisabokhale et al.,[24] in Nigeria. This age range forms the most active sexual activity group and are therefore vulnerable to acquiring sexually transmitted infections (STIs) such as HIV. The study had more than twice females as males infected with HIV who were receiving HAART. Earlier studies have reported higher females susceptibility rates to STIs including HIV compared to males, and this has been associated to the consequent changes in female genital mucosal epithelium, as well as the increased surface area of the female genitalia.[25,26]

The significantly increased plasma SFMC and D-dimers coupled with shortened aPTT observed in the HIV-infected individuals when compared with HIV-negative participants reflects hypercoagulability in HIV-infected individuals on HAART. HIV infected individuals on HAART have an increased tendency to clot formation as compared to the general population.[27] Elevated D-dimer which reflects excess clot

TABLE 4 Assessment of the HAART duration on fibrinolytic and coagulation biomarkers in HIV-infected individuals.

Duration (years)	D-dimer (ng/mL)	PAI-1 (ng/mL)	SFMC (ng/mL)	PT (s)	aPTT (s)
<1 year ($n = 8$)	**512.11** (450.92–560.54)	**13.39** (10.84–16.12)	**8.53** (7.80–9.45)	**17.15** (16.10–18.10)	**25.75** (20.45–35.70)
1–5 years ($n = 11$)	**462.98** (343.83–527.86)	**13.05** (9.65–14.52)	**8.37** (7.61–9.39)	**16.40** (13.90–17.15)	**23.10** (20.20–29.0)
6–10 years ($n = 8$)	**401.00** (335.44–521.34)	**11.65** (10.73–15.54)	**8.32** (8.10–8.61)	**16.65** (15.90–19.15)	**23.55** (21.25–25.65)
>10 years ($n = 11$)	**450.36** (414.55–522.85)	**11.79** (10.56–15.04)	**8.81** (8.11–9.66)	**14.70** (13.35–17.35)	**23.80** (22.50–34.50)
p-value	0.443	0.895	0.225	0.406.	0.877

Note: Data were compared using Kruskal–Wallis Test. A $p \leq 0.05$ was considered statistically significant.

Abbreviations: aPTT, partial thromboplastin time; ng/mL, nanogram per milliliter; PAI-1, plasminogen activator inhibitor-1; PT, prothrombin time; s, second; SFMC, soluble fibrin monomer complex.

TABLE 5 Coagulation and fibrinolytic markers of the HIV participants stratified by viral load status.

Parameters	Participants viral load			*p*-value
	Nondetectable (*n* = 6)	Low viral load (*n* = 12)	High viral load (*n* = 20)	
PT (s)	15.53 ± 2.41	15.35 ± 1.87	17.08 ± 2.03	0.054
aPTT (s)	25.95 ± 7.90	23.6 ± 5.78	27.26 ± 5.20	0.244
D-dimer (ng/mL)	493.30 (408.70–537.70)	467.30 (421.67–525.79)	428.32 (348.26–531.36)	0.539
SFMC (ng/mL)	9.04 (8.16–9.78)	8.77 (8.25–9.17)	8.27 (7.66–8.73)	0.101
PAI-1 (ng/mL)	9.46 (8.76–9.82)	11.17 (10.70–12.09)	14.47 (13.38–16.03)	<0.001

Note: PT and Aptt data were compared usuing unpaired Student *t* test, and D-dimer, SFMC and PAI-1 were also compared using Mann-Whitney *U* test. A $p \leq 0.05$ was considered statistically significant.

Abbreviations: aPTT, activated partial thromboplastin time; ng/mL, nanogram per milliliter; PAI-1, plasminogen activator inhibitor-1; PT, prothrombin time; s, second; SFMC, soluble fibrin monomer complex.

formation has also been reported in an earlier study by Aisabokhale et al.[24] Our findings of shortened aPTT was however contrary to the reports of a study by Thulasi Raman et al.[28] Their study reported prolonged aPTT in HV patients compared to HV-negative persons. The discrepancies in the findings could be attributed to the differences in the sampling techniques. The current study matched age and sex between cases and controls, and also excluded HIV positive patients with any known comorbidity.

This study also showed significantly higher plasma concentration of PAI-1 among the HIV-infected individuals on HAART compared to the healthy HIV-negative controls. This finding is consistent with an earlier study which reported significantly higher concentration of PAI-I in HIV infected individuals on HAART.[29] Inflammation with consequent vascular activation upregulates PAI-1 in HIV-infected individuals mostly through proinflammatory cytokines IL-6 and TNF-α.[30]

This study further establishes no difference in plasma levels of PAI-1 in HIV-infected individuals with regards to the various combinations of HAART therapy. Participants were found to be on the first-choice antiretroviral drug combinations. A study by Ifeanyichukwu et al.,[31] observed improvement in the coagulation profile in HIV infected individuals who were on the first line choice combination HAART. This suggests that these combinations of HAART could impact positively on the general haemostasis of people living with HIV/AIDS. HAART containing protease inhibitor-1 is the combination regimen of HAART that has been widely reported to be associated with increased plasma levels of PAI-1 in HIV-infected individuals.[29] This finding is consistent with the Ifeanyichukwu et al.,[31] and Seyoum et al.,[29] studies in Nigeria who also found no effect of HAART duration on circulating PAI-1 antigen levels. Shortly after the introduction of HAART, there is a sharp suppression of viral replication with immune function rebuilding, and this is sustained in consistent and effective therapy.[32] PAI-1 levels were also observed in another study in Nigeria, to reduce significantly shortly after the commencement of antiretroviral therapy.[33] This suggests that changes in viral load directly influences the plasma PAI-1 antigen levels in HIV-infected individuals.

In this study, HIV seropositive participants with high viral load had higher levels of PAI-1 antigens, coupled with a strong positive correlation between HIV viral load and the enzyme levels. This observation in the present study could be related to the induced inflammation and subsequent abnormal immune system activation following continues replication of HIV increasing the viral load.[34] Following inflammation, the resultant proinflammatory cytokine storm, including IL-6 and TNF-α directly influence endothelial and hepatic PAI-1 synthesis and increase plasma circulating levels of the protein.[34]

The significant positive correlation observed between PAI-1 and D-dimer in this study is consisted with a previous study by Jeremiah et al.[33] This may be due to the chronic inflammation associated with HIV infection, as both PAI-1 and D-dimer are inflammatory proteins.[35]

The study was limited by our inability to determine the various PAI-1 gene polymorphisms. It again did not include HAART-naïve HIV seropositive individuals. Also, the study did not assess inflammatory cytokines in the study participants.

5 | CONCLUSION

HIV seropositive individuals on HAART have deranged coagulation and fibrinolytic markers. Higher HIV viral load correlates strongly with elevated plasma levels of PAI-1 antigens. Periodic assessment of markers of coagulation and fibrinolysis be included in the management of HIV/AIDS in Ghana.

AUTHOR CONTRIBUTIONS

Charles A Derigubah: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Resources; Validation; Visualization; Writing—original draft; Writing—review & editing. **Charles Nkansah**: Formal analysis; Methodology; Software; Validation; Visualization; Writing—original draft; Writing—review & editing. **Kofi Mensah**: Methodology; Writing—original draft; Writing—review & editing. **Samuel K. Appiah**: Methodology; Writing—original draft;

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts interest statement.

DATA AVAILABILITY STATEMENT

The raw data used for the study has been deposited at http://flowrepository.org/experiments (ID: FR-FCM-Z66T).

TRANSPARENCY STATEMENT

The lead author Charles Nkansah affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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