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Fibrinolytic activity in HIV infected subjects at a tertiary health institution at Nnewi, Anambra state.

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Abstract

Human immunedeficiency virus (HIV) infection is a global pandemic of global concern, with thromboembolism and deregulated coagulation as cause of morbidity in infected individuals.

This present study was designed to evaluate fibrinolytic and haemostatic parameters in HIV positive subjects presenting at Nnamdi Azikiwe University between November 2022 and May 2023, with a view to identifying pattern of fibrinolytic markers in the study subjects. In this longitudinal study, a total of ninety (90) HIV seropositive subjects aged 18 – 60 were recruited by simple random sampling from Nnamdi Azikiwe University Teaching Hospital, Nnewi and followed-up 6-months post treatment. Ninety apparently (90) healthy HIV seronegative age matched subjects drawn from the same hospital community served as control. Informed consent and ethical approval were sought and obtained and blood samples were collected at baseline (before commencement of HAART) and at 3months, and 6 months post treatment. Euglobulin clot lysis time (ECLT) were assayed using visual method. D-dimer were assayed using enzyme linked immunosorbent assay. Antithrombin III were assayed using turbidimetric method. Data generated were analyzed using SPSS version 25. The result showed Euglobulin clot lysis time and anti-thrombin III were significantly lower in pretreatment subjects when compared with HIV seronegative subjects, 3-months and 6-months post treatment values (F 64.454; P<0.05) and (F 19.728; P<0.05) respectively. D-dimer in pretreatment group was significantly higher when compared with HIV

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seronegative subjects, 3-months and 6-months post treatment values (F 64.454; P<0.05) and (F 19.728; P<0.05) respectively. D-dimer in pretreatment group was significantly higher when compared with HIV seronegative subjects, 3-months and 6-months post treatment (F 62.513; P<0.05). This study shows dysregulated fibrinolysis in HIV which is corrected by ART. Delay in commencement of ART could result in thrombosis and cardiovascular problems in the subjects. This study therefore reports dysregulated fibrinolysis in treatment naïve HIV individuals.

Keywords: *Fibrinolytic; Euglobulin; D-dimer; Antithrombin; HIV; Seropositive*

1.0 Introduction.

The Human Immunodeficiency Virus (HIV) is a member of the genus Lentivirus (a subgroup of retrovirus), part of the family Retroviridae that causes the acquired Immunodeficiency Syndrome (AIDS), a condition in humans in which progressive failure of the immune system allows life threatening opportunistic infections and cancers to thrive [1].

HIV infection is common in Nigeria with about 1.4% National HIV prevalence [2]. The widespread prevalence of sexually transmitted diseases, the practice of scarification, unsafe blood transfusion and mother-to child transmission all may be facilitating factors in the transmission of HIV-1[3].

Sparse reports exist on the effect of human immunodeficiency virus infection and antiretroviral therapy (ART) on fibrinolytic activity especially in Nigeria literature. Derangement in fibrinolytic markers can result in thrombosis and cardiovascular problems [4]. Elevated levels of D-Dimer with reduced euglobulin clot lysis time are a key indicator of thrombotic events, indicating hyperfibrinolysis following activation of coagulation [4]. Plasminogen activator inhibitor-1 (PAI-1) and tissue plasminogen activator (tPA), markers of impaired fibrinolysis and increased cardiovascular risk are increased in patients with human immunodeficiency virus infection [5]. Euglobulin clot lysis time measures the overall fibrinolytic potential while D-dimer reflects the presence and level of fibrin degradation products. Shortened Euglobulin clot lysis time (Normal range 90-240mins) suggests hyperfibrinolysis while elevated D-dimer levels indicate a state of hypercoagulability or hyperfibrinolysis where the fibrinolytic system is overactive, potentially leading to a decreased clot formation and risk of bleeding and thromboembolism due to increased D-dimer in blood circulation. Cases of antithrombin III deficiency in patients with HIV as a result of complications associated with the disease such as liver disease, malnutrition or conditions that cause protein loss have been reported [6]. The objectives of the study are therefore to explore avenues for improved understanding of HIV infection. This will enhance the diagnosis and treatment of HIV infected persons by determining the effects HIV infection and antiretroviral therapy on some fibrinolytic markers.

2.0 Materials and method

2.1 Subjects

A total of ninety HIV seropositive (group B) subjects aged 18-60years were recruited for the study and followed-up after 3-months (group C) and 6-months (group D) post treatment with tenofovir (or abacavir for renal patients), lamivudine, and doutegranvir from the ART clinic of Nnamdi Azikiwe University Teaching Hospital, Nnewi in Anambra State Nigeria between November 2022 to May 2023. Eighty (80) subjects each were in their 3 months and 6 month's post treatment stages respectively. Ninety (90) apparently healthy subjects (group A) who visit the hospital for medical check- up served as control. Ethical approval was obtained from the ethics committee of Nnamdi Aziikiwe University Teaching Hospital, Nnewi before embarking on the study. Informed consent was also obtained from the subjects.

2.2 Methods

Five milliliters of blood were collected from all the participants for the analysis of the parameters. Exactly 3.6 milliliters of blood was added into 0.4 milliliter of 3.8% trisodium citrate container (1 part of citrate to 9 parts of blood) for euglobulin clot lysis time, D-Dimer assay and antithrombin III, while the remaining 1.4 milliliter of blood was dispensed into EDTA tube for HIV screening and confirmation.

The HIV seropositive subjects were identified based on HIV serial testing algorithm using Determine^{TM} HIV-1/2 Ag/Ab Combo (Abbott Rapid Diagnostics, Tokyo, Japan) for screening, followed by Stat-Pak (Chembio diagnostic systems, USA) for verification and Unigold (Trinity Biotech, USA) for tie-breaking in discordant results. The HIV- 1 and 2 Determine test is a qualitative membrane based immunoassay for the detection of antibody to HIV in the body based on the principle that membrane conjugate pad pre-coated with HIV antigen (selenium colloid-HIV antigen conjugate) reacts with HIV antibody in the plasma to form a mixture which migrates by capillary action through the solid phase and react with immobilized recombinant HIV antigen and synthetic peptide (enzyme) at the test line region or patient window site which with the help of the substrate, the attached enzyme will be hydrolyzed with colour change in the test line region. The HIV- 1 and 2 Chembio stat-pak test is a pouched qualitative membrane based immunoassay test device for the detection of antibody to HIV in the body based on the principle that nitrocellulose membrane conjugate pad pre-coated with HIV antigen (colloidal gold dye particles-HIV antigen conjugate) will react with HIV antibody in the plasma to form a mixture which migrates along the test strip by capillary action through the solid phase and react with immobilized recombinant HIV antigen on the test area producing a pink/purple coloured line. In the absence of HIV-1 and 2 antibodies, there is no coloured line development at the test area. The sample continues to migrate along the membrane and produces a pink/purple line in the control area containing immunoglobulin G antigens. This procedure controls the system to ensure that both specimen and reagents have been properly applied and have migrated through the device. The Unigold Recombinant HIV- 1 and 2 test is a qualitative membrane based immunoassay test device for the detection of antibody to HIV in the body based on the principle that membrane conjugate pad pre-coated with HIV antigen (proteins representing regions of the HIV virus) and a colour reagent will react with HIV antibody in the plasma to form a mixture which migrates along the test strip by capillary action through the solid phase and react with immobilized recombinant HIV antigen on the test area producing a pink/purple coloured line. In the absence of HIV-1 and 2

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antibodies, there is no coloured line development at the test area. The sample continues to migrate along the membrane and produces a pink/purple line in the control area containing immunoglobulin G antigens. This procedure controls the system to ensure that both specimen and reagents have been properly applied and have migrated through the device.

Euglobulin clot lysis time was measured using visual method described by Omoigberale *et al*, (2005) which relies on the principle that citrated plasma forms precipitate of euglobulin fraction with acetic acid which is harvested and re-suspended in buffer solutions and then clotted with calcium chloride. The time taken for the clot to lyse completely is the euglobulin lysis time. D-dimer concentration by ELISA technique as described by the manufacturer of the kit: Technoclone, Vienna, Austria which employs the sandwich enzyme linked immunosorbent assay technique. Antithromobin III concentration by turbidimetric method as described by the manufacturer of the kit: Monlab, Spain which relied on the principle that antithrombin III antibodies when mixed with samples containing antithrombin III, form insoluble complexes which cause an absorbance change, dependent upon the antithrombin III concentration of the sample which can be quantified by comparison from a calibrator of known antithrombin III concentration.

2.3 Statistical method

Result generated in this study were tabulated using excel. Statistical analysis was done using statistical package for social sciences (SPSS) version 25. The variables were expressed in mean and standard deviation. Student's t-test and analysis of variance (ANOVA) were used for comparison between and among groups respectively. A p-value of less than 0.05 ($p<0.05$) was considered statistically significant.

3.0 Result

The mean ± euglobulin clot lysis time; 183.23 ± 46.29 (mins) for HIV negative control subjects group A, 97.86 ± 27.34 (mins) for HIV pretreatment group B, 145.28 ± 40.33(mins) for 3-months post treatment group C, 136.73 ± 49.47(mins) for 6-months post treatment group D compared among the groups showed significant difference (F 64.454; $P<0.05$). The in between comparison showed that euglobulin clot lysis time in group B was significantly lower than the mean euglobulin clot lysis time in group A, C and D ($P<0.05$ in each case). The mean ± SD euglobulin clot lysis time in group A was significantly higher than the mean euglobulin clot lysis time in groups C and D ($P<0.05$ in each case). However, the mean ± SD euglobulin clot lysis time in group C compared with the value in group D showed no significant difference ($P>0.05$). The mean ±S D D-dimer; 307.66 ± 96.42(ng/ml) for HIV negative control subjects group A, 564.12 ± 169.34(ng/ml) for HIV pretreatment group B, 401.60 ± 108.64(ng/ml) for 3-months post treatment group C, 372.44 ± 140.09(ng/ml) for 6-months post treatment group D compared among the groups showed significant difference (F 62.513; $P<0.05$). The in between comparison showed that D-dimer in group B was significantly higher than the mean D-dimer in group A, C and D ($P<0.05$ in each case). The mean ± SD D-dimer in group A was significantly lower than the mean D-dimer in group C and D ($P<0.05$ in each case). However, the mean ± SD D-dimer in group C compared with the value in group D showed no significant difference ($P>0.05$). The mean ±SD Anti-thrombin III; 22.23 ± 2.98(mg/dl) for HIV negative control subjects group A, 17.24 ± 1.50(mg/dl) for HIV pretreatment group B, 22.49 ± 6.28(mg/dl) for 3-months post treatment group C, 21.52 ± 7.78(mg/dl) for 6-months post treatment group D compared among the groups showed significant difference (F 19.728; $P<0.05$). The in between comparison showed that Anti-thrombin III in group B was significantly lower than the mean Anti-thrombin III in group A, C and D ($P<0.05$ in each case). The mean ± SD Anti-thrombin III in group A showed no significant difference when compared with group C and D ($p>0.05$ in each case). Furthermore, the mean ± SD Anti-thrombin III in group C compared with the value in group D showed no significant difference ($p>0.05$).

Table 1.0: Comparison of some Fibrinolytic parameters among HIV negative control subjects, HIV pretreatment, 3-months post-treatment and 6-months post-treatment subjects (Mean ± SD)

Groups	ECLT (mins)	D-dimer (ng/ml)	Anti-thrombin (mg/dl)
A. Control (n=90)	183.23 ± 46.29	307.66 ± 96.42	22.23 ± 2.98
B. Pre treatment (n=90)	97.86 ± 27.34	564.12 ± 169.34	17.24 ± 1.50
C.3-months Post-treatment (n=80)	145.28 ± 40.33	401.60 ± 108.64	22.49 ± 6.28
D. 6-months Post-treatment (n=80)	136.73 ± 49.47	372.44 ± 140.09	21.52 ± 7.78
F(P) values	64.454(0.001)	62.513(0.001)	19.728(0.001)
A vs B P-value	0.001	0.001	0.001
A vs C P-value	0.001	0.001	1.000
A vs D P-value	0.001	0.006	1.000
B vs C P-value	0.001	0.001	0.001
B vs D P-value	0.001	0.001	0.001
C vs D P-value	0.058	0.023I	0.192

Significant at $P<0.05$

ECLT = Euglobulin clot lysis time

4.0 Discussion

In this study, HIV pretreatment subjects exhibited lower levels of euglobulin clot lysis time and anti-thrombin, and increased levels of D-dimer when compared with the HIV negative control subjects.

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Elevated levels of D-dimer (a biomarker of fibrin degradation), reduced euglobulin clot lysis time and antithrombin are key indicators of thrombotic events, indicating hyperfibrinolysis following activation of coagulation [6]. Impaired fibrinolysis is a risk factor for thromboembolism. The euglobulin clot lysis time measures overall fibrinolysis since the euglobulin fraction contains the important fibrinolytic factors fibrinogen, PAI-1, tissue plasminogen activator (tPA), plasminogen, and to a lesser extent alpha 2-antiplasmin and factor VIII. D-dimer are fibrin degradation products (FDPs) which are components of the blood produced by clot degeneration and indicates the presence of active blood clot formation and breakdown [7, 8]. Cases of antithrombin III deficiency in patients with HIV who experienced thrombotic events have been reported [6]. The observed increase in euglobulin clot lysis time and anti-thrombin level and decreased levels of D-dimer in 3-months and 6-months post treatment subjects when compared with the HIV pretreatment subjects may indicate effect of antiretroviral treatment.

5.0 Conclusions

In conclusion, the present study showed that HIV pretreatment subjects exhibited reduced euglobulin clot lysis time, lower level of anti-thrombin and higher levels of D-dimer. The study also indicates that these parameters returned to normal as patients undergo treatment. Based on these findings it is recommended that base line levels of these parameters are obtained prior to treatment to determine infected individuals at the risk of thromboembolism for proper management and to monitor the progress of treatment in HIV infected subjects.

Conflict of interests

Authors declared that no competing interests exist

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